bmjmedicine

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Journal:	*BMJ Medicine*
Manuscript ID	bmjmed-2021-000040
Article Type:	Specialist review
Date Submitted by the Author:	29-Oct-2021
Complete List of Authors:	Young, Megan; Imperial College London, Faculty of Medicine Crook, Harry; Imperial College London, Faculty of Medicine Scott, Janet; University of Glasgow, Centre for Virus Research Edison, Paul; Imperial College London, Faculty of Medicine; Cardiff University, School of Medicine
Keywords:	Covid-19, Virology

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COVID-19: Virology, variants, and vaccines

Megan Young[1†], Harry Crook[1†], Janet Scott[2], Paul Edison[1,3,*]

[1] Faculty of Medicine, Imperial College London, London, UK.
[2] Medical Research Council-University of Glasgow Centre for Virus Research, University of Glasgow, UK
[3] School of Medicine, Cardiff University, Cardiff, UK.

† Both authors contributed equally to the manuscript

*Corresponding author:
Dr Paul Edison, MD, MRCP, PhD, FRCP, FRCPI,
Clinical Senior Lecturer and Professor
Clinical Senior Lecturer, Imperial College London and Honorary Professor, Cardiff University, UK
Division of Neurology, Faculty of Medicine, Imperial College London
Level 2, Commonwealth Building,
Hammersmith Campus, Imperial College London,
Du Cane Road, London, W12 0NN, UK

Tel: +442075941081
E-mail: paul.edison@imperial.ac.uk

No authors have any competing interests.

Abstract

Objectives – In this review, we aim to provide an overview of the severe acute respiratory syndrome 2 (SARS-CoV-2) virus covering viral transmission, genetic susceptibility along with the structure of the virus and different mutations. We outline how certain mutations of SARS-CoV-2 variants may increase transmissibility and disease severity. We also aim to examine the current state of vaccine development, highlighting the effectiveness of vaccines along with giving evidence for the use of boosters.

Design – This review was performed by searching for relevant articles within PubMed and Embase databases, as well as preprint databases MedRxiv and BioRxiv, due to the novelty and rapidly evolving nature of the field. Further manual searching for additional articles and data was performed.

Results - A total of 227 articles were included in the final manuscript. The SARS-CoV2 virus is highly pathogenic to humans, which infects host cells by binding its Spike protein with the angiotensin-converting enzyme-2 receptor and replicates using host cell machinery. Certain SARS-CoV-2 variants have significantly increased transmissibility and disease severity. The WHO currently report four VOC, two VOI, and fifteen VUM. Currently, there are 23 approved vaccines in use in 194 countries, with seven having gained emergency use listing approval from the WHO. These vaccines have been shown to be tolerable and effective. As of 19th October 2021, there are 194 vaccines in pre-clinical development and 124 in clinical development. There are lessons to be learned from this pandemic and previous ones, in order to be better prepared for the next one.

1. Introduction

There are seven coronaviruses known to infect humans, which all belong to the alpha- and beta- coronavirus subgroups, including the common coronaviruses 229E (alpha), NL63 (alpha), OC43 (beta), and HKU1 (beta). (1). Over the last three decades, three notable beta-coronaviruses, severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002, Middle East respiratory syndrome coronavirus (MERS-CoV) in 2011, and most recently, severe acute respiratory syndrome 2 (SARS-CoV-2) in 2019, have emerged and caused severe respiratory illness resulting in debilitating disease and worldwide fatalities. SARS-CoV-2 infection has caused more than 4.8 million deaths in approximately 18 months and caused a multisystem illness in several million people (2). The pathogen responsible for the current Coronavirus 2019 (COVID-19) pandemic is SARS-CoV-2. The SARS-CoV-2 virus genome shares 96% similarity with the bat coronavirus BatCoV RaTG13 and a 98% amino acid identity to the Pangolin-CoV (3, 4). Clearly, SARS-CoV-2 was able to infect both human and bats, although speculation about the origin of the virus is still debated.

All viruses, including SARS-CoV-2 change and mutate over time, with most changes having little to no impact. However, some changes may alter its pathogenic or transmission potential and could therefore hinder the effectiveness of vaccines and therapeutic strategies. SARS-CoV-2 variants that have a significantly increased level of transmissibility and disease severity have been classified as variants of concern (VOC), while variants that we have a limited knowledge of but may have a greater ability to cause more severe disease than the original strain, are classified as variants of interest (VOI) or variants under monitoring (VUM). As of the 22nd October 2021, the WHO has reported four VOC; Alpha, Beta, Gamma, and Delta, two VOI; Lambda and Mu, and fifteen VUM (5). Since the beginning of the COVID-19 pandemic, a worldwide effort to develop effective vaccines to protect against SARS-CoV-2 took shape. As of 17th October 2021, there has been 4,887,154 COVID-19-associated deaths worldwide (2), however, as of 20th October 2021 there are 23 approved vaccines in use in 194 countries, with seven vaccines having gained emergency use listing approval from the WHO (6).

In this review, we provide an overview of the genome and structure of SARS-CoV-2, describing how these elements allow the virus to infect and replicate inside of host cells, before outlining how certain mutations harboured by SARS-CoV-2 variants enhance these abilities. Next, we examine the current state of vaccine development around the world, summarising how effective these vaccines are, and giving evidence for the use of booster doses. Finally, we discuss what important lessons to take from the current pandemic and how we can better prepare for future ones.

2. Methods

We searched PubMed and Embase databases for articles related to the topic of this review. Our search terms included SARS-CoV-2, COVID-19, SARS-CoV, MERS, virology, genome, replication, viral entry, variants, vaccines, and vaccinations. We performed further manual searching for additional articles and data using relevant databases, including who.int, gov.uk, and ecdc.europa.eu/en. Due to the rapidly evolving nature of the literature involving SARS-CoV-2, we also searched preprint databases including MedRxiv and BioRxiv. Studies were selected based on their quality, with large, randomised controlled trials being of greatest interest. Following screening of articles with limited exclusion criteria, due to the novelty of the field, a total of 227 articles are included within the final review.

3. Viral transmission, clinical presentation, and genetic susceptibility of COVID-19

SARS-CoV-2 is predominantly spread via respiratory droplet transmission, spreading from person to person through close contact, coughing, or sneezing. It has been well documented that the virus can also spread through airborne transmission, fomite transmission, and via other modes, such as through biological samples including urine and faeces (7, 8). Once inside the airways, SARS-CoV-2 can directly or indirectly infect ciliated, mucus-secreting, and club cells of bronchial epithelium, type 1 pneumocytes within the lungs, and the conjunctival mucosa (9). The clinical presentation of COVID-19 is non-specific and heterogeneous, but usually mild in severity. Following an incubation period of around 5 days, ranging from 4-14 days, symptoms develop which range from mild to severe disease and, in some cases, can result in death (10). The most common COVID-19 symptoms include fever, cough, dyspnoea, and fatigue (11, 12). Asymptomatic individuals can also test positive for COVID-19 (13, 14).

Several risk factors have been identified that are associated with increased risk of hospitalisation, severe disease, and fatal outcome with COVID-19. Older age (15-17), male sex (18, 19), non-white ethnicity (19, 20), comorbidities such as diabetes, hypertension, and lung disease (16, 21-23), malignancy and immunodeficiency (24-26) have all been associated with a greater severity of COVID-19. The host genetic background is also thought to have an influence on the susceptibility of infection and severity of disease caused by SARS-CoV-2, possibly explaining the broad spectrum of clinical manifestations that can develop in seemingly similar individuals. A large international study involving more than 46,000 individuals with COVID-19 across 19 counties and six ancestry groups identified 13 loci in the human genome that may be associated with SARS-CoV-2 infection and increased severity of the disease (27). Four loci; SLC6A20, RPL24, ABO, PLEKHA4 were associated with general susceptibility to SARS-CoV-2 and nine; LZTFL1, FOXP4, TMEM65, OAS1, KANSL1, TAC4 , DPP9, RAVER1, and IFNAR2 were associated with increased risk of severe disease (27). Two genome wide association studies (GWAS) across Europe, the United States (US) and United Kingdom (UK) have identified a gene cluster on chromosome three (chr3p21.31) as being strongly associated with susceptibility and severity of COVID-19 (28, 29). Rs11385942 at locus 3p21.31, rs657152 at locus

9q34.2, and ABO rs9411378 were associated with increased susceptibility to COVID-19, while LZTFL1 rs13078854 was associated with increased susceptibility and a greater disease severity (28, 29). Additionally, research highlights the crucial role angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) polymorphisms play in SARS-CoV-2 viral entry (30). Increased ACE2 receptor levels have been associated with risk factors of COVID-19 including smoking and increasing age (31). It would therefore be entirely plausible that variants of ACE2 and increased ACE2 receptor levels are associated with increased susceptibility and disease severity. A recent comparative genetic analysis of approximately 81,000 human genomes suggested possible associations of ACE2 and TMPRSS2 genetic polymorphisms with COVID-19 susceptibility and severity (Hou et al., 2020 (32). This study identified 63 potentially deleterious variants in ACE2 and 68 deleterious variants in TMPRSS2. Specifically, they found that 39% and 54% of deleterious variants in ACE2 occur in African/African-American and Non-European populations, respectively (32). The differential polymorphisms across ethnic populations may explain why certain ethnic groups are more susceptible to severe COVID-19 infection.

4. Virology of SARS-CoV-2

SARS-CoV-2 is a positive-stranded ribonucleic acid (RNA) virus belonging to Coronaviridae family and the Nidovirales order. These viruses, which appear as crownlike structures, have genomes ranging from 25kb to 32kb, making them the largest known RNA viruses and are thought to primarily infect vertebrates (33, 34). SARS-CoV-2 belongs to the beta genus of the coronaviruses and has a genome varying from 29.8kb to 29.9kb in size (35). Human coronaviruses (HCoV) genomes consist of a variable number of open reading frames (ORFs), which is a sequence of nucleotide triplets, that are read as codons specifying amino acids, which contain no stop codons. Following the typical 5'-3' order, the beginning two-thirds of the SARS-CoV-2 genome contains two ORFs, ORF1a and ORF1b which, inside the host cell, are translated at the rough endoplasmic reticulum into polyprotein 1a (pp1a) and polyprotein 1ab (pp1ab), respectively (35). These polyproteins are cleaved into 16 non-structural proteins (nsp); nsp1-11, from pp1a and nsp12-16, from pp1ab. The proteolytic release of nsp1 occurs rapidly, which enables it to interfere with translation processes of the host cell by inducing cellular mRNA degradation (36-38). Nsp2-16 contain the replication and transcription complex (RTC) of the virus and are thought to harbour multiple enzymes with many functions including, proteases, helicase, polymerase, exo- and endo-nuclease, N7- and 2'O-methyltransferases, and de-ubiquitination enzymes (39, 40). The final third of HCoV genomes contain genes that encode structural and accessory proteins. The four major structural proteins encoded by this region of the genome are the nucleocapsid (N), membrane (M), envelope (E), and spike glycoprotein (S) proteins (41, 42). The N protein is associated with the viral RNA genome and is involved in RNA synthesis regulation and may also interact with the M protein during viral budding (34, 43). The M protein is important for viral assembly, it contains a short N-terminal domain that projects onto the external surface of the envelope and a long internal C terminus (34). The E protein function is largely unknown; however it spans the envelope and, along with the N and M proteins, is required for viral assembly and release (42) . Lastly, the S protein gives coronaviruses their characteristic spikes that compose their crownlike appearance. This protein projects through the viral envelope, is heavily glycosylated, and regulates host cell membrane receptor binding and fusion of the viral and cellular membrane (44). The functions of the eleven accessory proteins encoded within the one-third closest to the 3' end of the SARS-CoV-2 genome are not fully understood. These accessory proteins are encoded by the ORF3a, ORF3b, ORF3c, ORF3d,

ORF6, ORF7a, ORF7b, ORF8, ORF9b, ORC9c, and ORF10 genes. Some of these proteins, including ORF3b, ORF6, ORF7a and ORF8 are important interferon antagonists and hence impair the host cell immune response (45-48), while ORF3a may promote virus release (49) and is involved in apoptosis of host cells through caspase-3 activation (50). ORF9b and ORF9c are known to supress the host antiviral response by interacting host cell organelles (51-53), while a clear understanding of the functions of ORF3c, ORF7b, and ORF10 remains elusive (54). ***Figure 1*** (A and B) outlines the genome and structure of SARS-CoV-2.

The S protein, which is composed of two functionally distinct subunits (S1 and S2), is essential for viral entry into host cells. The N-terminal S1 domain of the protein contains the receptor-binding domain (RBD) that directly interacts with the host cell and therefore determines the tropism and pathogenicity of the virus (55). The C-terminal S2 domain, meanwhile, causes the host and viral membranes to fuse and allow for entry of the viral genome into the host cell (56). The RBD of SARS-CoV-2 contains the structural information required for the S protein to interact with host ACE2 receptors, the primary receptor that SARS-Cov-2 utilises for cell entry (57). Following binding between the S glycoprotein and the host cell receptor, host cell proteases cleave the S protein which results in the release of the S2 domain, allowing for fusion and cell entry (58). ***Figure 1*** (C and D) demonstrate the structure and function of the S protein.

TMPRSS2 is a host cell protease that plays an important role in activating the SARS S protein and facilitating fusion of viral and cell membranes (59), while TMPRSS2 has also been shown to play a role in the spread of the virus in the airways of SARS-CoV animal models (59). Host cell cathepsin L has also been demonstrated to play a role in SARS-CoV-2 entry into the host cell, with it thought to cleave the S protein and enhance viral entry (60). Indeed, a clinically approved protease inhibitor has been shown to block SARS-CoV-2 cell entry (61).

Moreover, the ACE2 receptor has been found to be expressed in numerous cell types throughout the human body, including in the lungs, the oral and nasal mucosa, the heart, gastrointestinal tract, kidneys, liver, spleen, brain, and endothelial cells of the blood vessels (62), highlighting the widespread infection that SARS-CoV-2 can inflict. ***Figure 2*** depicts the mechanism by which SARS-CoV-2 gains entry into and replicates inside host cells, and overviews the host cell immune response.

4.1 Other human coronaviruses

HCoVs have been characterised since the 1960s (63) and, more recently, have been the group of viruses responsible for three large outbreaks that have resulted in illness and death throughout the world. The first HCoV outbreak, caused by SARS-CoV, began in Foshan city, Guangdong Province, China in November 2002 (64) and became global in 2003, with a worldwide mortality rate of 10%, although only 8098 cases were reported (65, 66). The genome of SARS-CoV-2 is 80% similar to SARS-CoV (67), however, SARS-CoV-2 has a higher reproduction number, which highlights it's increased transmissibility (68). A furin cleavage site that is present in SARS-CoV-2 has been shown to facilitate S protein priming and to improve the efficiency of the spread and virulence of SARS-CoV-2 in comparison to other beta coronaviruses, which lack this cleavage site (69, 70). Moreover, compared with SARS-CoV, SARS-CoV-2 binds to the ACE2 receptor an estimated two-four times more strongly (71). The second HCoV outbreak was caused by Middle East Respiratory Syndrome (MERS-CoV). MERS-CoV was first reported in 2012 in Jeddah, Saudi Arabia (64) and has since been detected in 27 countries, resulting in 858 known deaths due to the infection (72). SARS-CoV-2 shares only 50% genetic similarity with MERS-CoV (70) while, unlike SARS-CoV-2, MERS-CoV binds to dipeptidyl-peptidase 4 (DPP-4) in order to gain entry to human host cells (73). It is thought that the SARS-CoV virus originated

from Chinese horseshoe bats (74, 75), while the MERS-CoV virus is thought to have been passed to humans from dromedary camels, which acted as an intermediate host from its bat origin (76, 77). The genome of SARS-CoV-2 has been reported to be more than 80% identical to previous human coronaviruses (78) with better sequence identity to SARS-CoV than MERS CoV (79). However, SARS-CoV-2 has a little homology with SARS-CoV in the regions of ORF8, ORF3B, ORF10 and S proteins (80, 81). Two other beta coronaviruses, HCoV-HKU1 and HCoV-OC43, and two alpha coronaviruses HCoV-229E and HCov-NL63 are known to infect humans, however these usually only cause mild respiratory infections in humans (70, 82).

5. Variants of SARS-CoV-2

Most viral mutations have a limited impact on the viruses' effectiveness to infect, replicate, escape host immunity, and transmit, however, certain mutations may give a viral strain a competitive advantage and, through natural selection, give it the ability to become dominant. Although RNA viruses usually have higher rates of mutation compared to DNA viruses, a mutation correcting enzyme encoded by coronaviruses reduces the number of mutations that are made during replication (83). During the emergence and spread of SARS-CoV-2, the virus will have mutated numerous times, with estimates suggesting that circulating lineages acquire nucleotide mutations at rates of around one to two mutations per month (84).

The WHO have been tracking and monitoring possible mutations and variants since the COVID-19 pandemic began in order to identify variants of concern. Certain variants that have appeared during the COVID-19 pandemic have a significantly increased level of transmissibility and disease severity; these have been termed variants of concern (VOC). Meanwhile, variants that we have a limited knowledge of but may have a greater ability to cause more severe disease than the original strain, are classified as variants of interest (VOI) or variants under monitoring (VUM). The full working definitions of VOC, VOI and VUM can be found on the WHO 'tracking SARS-CoV-2 variants' website (5). As of the 22nd October 2021, the WHO has reported four VOC; Alpha, Beta, Gamma, and Delta, two VOI; Lambda and Mu, and fifteen VUM (***Table 1***). Globally as of the 19th October 2021, the Alpha variant has been reported in 196 countries; the Beta variant has been reported in 145 countries; the Gamma variant has been reported in 99 countries; and the Delta variant has been reported in 193 countries (85).

5.1 Variants of concern

5.1.1 Alpha

The Alpha SARS-CoV-2 variant, of the B.1.1.7 Pango lineage, was first documented in the UK in September 2020 and classified as a VOC on 18th December 2020 (5, 86) and, as of 19th October 2021, has been reported in 196 countries (85). This variant contains eight mutations in the S gene, three of which may have potential biological effects. First, the S protein residue 501 is a key contact residue within the RBD, which makes the N501Y mutation that the Alpha variant harbours a notable one. The N501 residue in the RBD of the S protein forms a portion of the binding loop in the contact region of the ACE2 receptor, forms a hydrogen bond with the Y41 residue of the ACE2 receptor, and stabilises the ACE2 K353 residue (87-89). It is widely believed that the N501Y mutation increases the binding affinity of the RBD to the ACE2 receptor (90), while this mutation has also been associated with an increase in infectivity and virulence in mice (91). Next, the S protein residue 681 is located immediately adjacent to the 682-685 furin cleavage site, at the interface of the S1 and S2 domains (92). The S1/S2 furin cleavage site is not found in coronaviruses closely related to SARS-CoV-2 and this site has been

demonstrated to promote entry into respiratory epithelial cells and increase transmissibility (93-95). The P681H mutation found in the Alpha variant of SARS-CoV-2 may enhance the abilities of the furin cleavage site by making it less acidic and, therefore, allowing the site to be more effectively recognised and cleaved by furin and therefore, enhance transmissibility (96, 97). This variant also harbours a D614G mutation which has been shown to increase SARS-CoV-2 binding affinity to the ACE2 receptor and increase infectivity (98). Additionally, the Alpha variant contains a two amino acid deletion at the sites 69-70 in the S protein, which is a recurrent deletion frequently observed in the N-terminal domain of the S protein that may enhance the ability of the virus to escape antibody detection (99, 100). Other mutations have been identified in the Alpha SARS-CoV-2 variant, however, these are likely to have limited or no effect on the efficacy of the virus (101). In February 2021, genetic sequencing found viruses of the B.1.1.7 lineage with the added mutation of E484K. The E484 residue is located in the RBD and variants with the E484K mutation were found to be more resistant to neutralising vaccine-elicited and monoclonal antibodies compared to the B.1.1.7 lineage without the E484K mutation, suggesting it may threaten the efficacy of vaccines (102). Fortunately, this variant failed to become the dominant strain, with a total of only 46 confirmed and probably cases of this variant detected in the UK (103).

Several studies have explored the epidemiology of the Alpha variant. In Madrid, Spain, the probability of admission to an intensive care unit (ICU) was twice as high in patients infected with the Alpha variant compared to those infected with the original strain, , the Alpha variant quickly became the dominant strain within four months, and led to an increase in disease burden as a result (104). Meanwhile, in Cannes, France, being infected with the Alpha variant was associated with a 3.8-fold higher risk of transfer to an ICU or death in comparison to the older viral strain (105). During the third COVID-19 wave in Ontario, Canada, where 91% of infections were caused by the Alpha variant, the risk of both hospitalisation (adjusted odds ratio (OR) =1.57) and death (adjusted OR=1.52) was higher compared to infections with wild-type infections (106). A similar trend was seen in Alberta, Canada (106). Overall, the Alpha variant has proven to be approximately 50-70% more transmissible and increase the risk of hospitalisation and death by around 30-60% compared to the original strain (107-112).

The Alpha variant has been shown to have a minimal impact on the neutralising activity of current vaccines, however (113, 114), while the risk of reinfection remained similar for this variant as with previous ones (115). On 3rd September 2021, the European Centre for Disease Prevention and Control (ECDC) reclassified the Alpha variant from a VOC to a 'de-escalated variant' based on at least one of the following criteria; the variant is no longer circulating, had circulated for a long period without affecting the global epidemiological situation, and evidence demonstrates that it is not associated with any concerning properties (116). The Alpha variant B.1.1.7 with the additional E484K mutation has also been deesculated by the ECDC (116).

5.1.2 Beta

The Beta SARS-CoV-2 variant, of the B.1.351 Pango lineage, was first documented in South Africa in May 2020 (5) and has been reported in 145 countries, as of 19th October 2021 (85). The ECDC state that the Beta variant contains five S protein mutations of interest; N501Y, E484K, K417N, D614G, and A701V. Homogenously to the Alpha variant, the Beta variants contain the S protein mutations N501Y and E484K, which have been found to increase ACE2 receptor binding affinity (90), increase virulence (91), and have heightened resistance to neutralising antibodies (102). The K417 residue of the SARS-CoV-2 S protein interacts with the ACE2 receptor by forming a salt bridge with the D30

residue of ACE2, across the central contact region (87, 88), however, the K417N mutation appears to have a limited impact on ACE2 receptor binding (90). The D614 residue is not located within the RBD, rather it is located between the S1 and S2 subunits. The D614G mutation does change the receptor binding conformation, however, leading to an increased binding affinity to the ACE2 receptor and an increase in infectivity (98). This mutation has been shown to increase viral loads, increase transmissibility, and is associated with infecting younger people, however, it does not increase disease severity (117, 118). Additionally, D614G mutated SARS-CoV-2 has a greater resistance to neutralisation by antibodies than the D614 residue expressing virus, as measured using hamster sera (119). The A701V mutation is located close to the furin cleavage site but has a minimal effect on transmissibility or antibody resistance (113).

In a genomic and epidemiological study conducted in South Africa, it was concluded that the Beta SARS-CoV-2 variant had a selective advantage over previous variants from its increased transmissibility and immune escape abilities (120, 121). Another study found that the E484K/N501K mutations significantly enhanced the binding affinity of the Beta variant and, hence, increased its transmissibility (122). A retrospective cohort study in the US found that infection with the Beta variant was associated with an increased hospitalisation risk compared to an infection with a non-VOC, with a hazard ratio of 2.30 reported (112). Overall, the Beta variant is approximately 25-50% more transmissible, is associated with a possible increase in risk of hospital mortality and has a resistance to antibody neutralisation from antibodies created through contact with previous variants (120, 121, 123).

5.1.3 Gamma

The Gamma variant belongs to the P.1 Pango lineage and was first reported in November 2020 from travellers returning to Japan from Brazil, and was then later discovered in Brazil (5, 124). Cases of the Gamma variant have been reported in 99 countries, as of 19th October 2021 (85). This variant contains 11 non-synonymous mutations in the S protein compared to the B.1.1.28 lineage (124), which Gamma is thought to have evolved from, with K417T, E484K, N501Y, D614G, and H655Y being classified as S mutations of interest by the ECDC (116). Some of the mutations identified within the Gamma variant genome are shared with the Alpha and Beta variants. The aforementioned N501Y and D614G mutations are also present within the Alpha variant and have been demonstrated to increase ACE2 receptor binding affinity and increase infectivity of the SARS-CoV-2 virus (90, 98). Meanwhile, the N501Y, K417N/T, and E484K mutation triplet is similarly shared by both Gamma and Beta variants. The trinity of mutations present in these variants enhances the infectivity and lethality of them, in comparison to SARS-CoV-2 variants containing the N501Y mutation alone, possibly due to tighter binding of the viral S protein to the ACE2 receptor as a result of increased electrostatic contribution (125). Furthermore, as previously mentioned, the N501Y, K417N/T, and E484K mutations all enhance ACE2 receptor binding and infectivity of the SARS-CoV-2 virus individually. The Gamma variant also possesses the H655Y mutation, located outside of the RBD in the S protein. This mutation has been shown to provide enhanced viral escape abilities from multiple human monoclonal antibodies *in vitro* (126).

The Gamma SARS-CoV-2 variant is associated with a heightened transmissibility (122, 123, 127), with one study concluding that it holds a 1.7- to 2.4-fold increased level of transmissibility compared to previous variants (128). An epidemiological study conducted in Brazil found that the second local COVID-19 wave, caused by the Gamma variant, was associated with an increased death rate compared to the first wave. The wave associated with the Gamma variant saw a 13% increase in

death rate compared to the first wave, suggesting that the Gamma variant had a greater pathogenicity and virulence than the original strain (129). A surveillance study that collated data from seven European countries concluded that the Gamma variant was associated with a higher adjusted odds ratio for hospitalisation (OR=2.6) and admission to an ICU (OR=2.2) when compared to non-variant cases (130). In Manaus, Brazil the resurgence of COVID-19, despite high seroprevalence, suggested that the Gamma variant had a moderate resistance to neutralising antibodies (131) and, while the E484K, K417N/T, and N501Y mutation triplet present in the Gamma variant may increase ACE2 binding affinity, this variant has been shown to be significantly less resistant to antibodies, either naturally acquired or vaccine-induced, compared to other variants containing these mutations, including the Beta variant (132). This reduced resistance to neutralisation could possibly be due to mutations outside of the RBD.

5.1.4 Delta

The Delta variant, from the B.1.617.2 lineage, was first documented in India in October 2020 and was later classified as a VOC on 11th May 2021 (5). As of 19th October 2021, the Delta variant has been reported in 193 countries (85). The Delta variant has spread around the world rapidly, and is now the dominant variant in many counties, including the UK (103, 116). Of the S protein mutations of particular interest, P681H, present in the Alpha variant, and D614G, present within the Alpha, Beta, and Gamma variants, are also harboured by the Delta variant (116) and will have similar impacts on ACE2 receptor binding affinity and transmissibility. The Alpha (B.1.1.7 with E484K), Beta, and Gamma variants all harbour the same mutation in the E484 residue, within the RBD of the SARS-CoV-2 virus. The Delta variant, meanwhile, harbours the E484Q mutation, which, along with a L452R mutation also located in the RBD, demonstrates significantly higher affinity for the ACE2 receptor than the wild-type or the E484K mutation alone (133). Furthermore, the L452R mutation alone is likely to result in greater RBD-ACE2 receptor binding affinity as well as enhanced escape from neutralising antibodies (134, 135). The T478K mutation is currently unique to the delta variant (136). The position of this mutation is within the RBD, on the interface between the S protein and the ACE2 receptor when bound. The amino acid change in this mutation likely increases the electrostatic potential of the S protein to a more positive surface, while the lysine residue encoded by this mutation has a larger side chain than the wild-type threonine, therefore may further affect the binding affinity by increasing steric hindrance (137).

The Delta variant is now the dominant strain circulating in the UK (138), US (139), Europe, and around the world (140), probably due to its increased transmissibility and ability to escape the host immune response. The mutations present harboured by the Delta variant, especially those within the RBD, have enhanced the transmissibility of the SARS-CoV-2 virus as a result of increased binding affinity to the ACE2 receptor (122). It is estimated that the transmissibility of the Delta variant is 97% greater than that of previous variants, approximately three times that of the Alpha, Beta, and Gamma variants (123). This, in addition to the higher reproduction number of the Delta variant compared to others (123), highlights the competitive advantage that this variant has over previous ones and how it has rapidly become the dominant strain around the world. In addition to its increased transmissibility, the fast replication rate of the Delta variant may have contributed to its rise to become the dominant SARS-CoV-2 strain. A study that sequenced the viral samples from a number of participants discovered that the Delta variant could be detected by PCR test within the first four days from exposure, while non-Delta variant infections could only be detected after six days. Furthermore, the relative viral loads of people infected with the Delta variant were 1260 times higher than that of people infected with

SARS-CoV-2 viruses from 19A and 19B clades (141). Together, these findings suggest that the Delta variant replicates faster and more than previous variants. Another study corroborated this, finding that the relative viral load of those infected with the Delta variant was 2.5-fold higher than the viral load of those infected with the Beta variant ($P<0.05$) (142). This variant is also thought to be better equipped at escaping the host immune response. In India, the frequency of post-vaccination infections was much higher for the Delta variant than infections with the wild-type (B.1) strain (143), while blood sera samples from individuals who had received one dose of an approved COVID-19 vaccine showed a minimal amount of neutralisation of the Delta variant (144), demonstrating that this variant is associated with escape from antibodies. Overall, the combination of increased transmissibility, high reproduction rate, and enhanced escape from host immunity have contributed to the spread of the Delta variant and its rise to dominance.

In addition to having a higher infectivity, the Delta variant has been associated with an increased severity of disease. In Scotland, infection with the Delta variant was associated with an increased risk of hospitalisation (hazard ratio=1.85) compared to infection with the Alpha variant (145), while in Canada, infections with the Delta variant were associated with a 108% increased risk for hospitalisation, a 234% increased risk for admission to an ICU, and a 132% increased risk of death, compared to non-VOC infections (146). A retrospective cohort study conducted in the US concluded that risk of hospitalisation was higher for those infected with the Delta variant (hazard ratio=2.30) compared to those infected with a non-VOC variant (112). Lasty, another study demonstrated that the Delta variant infected and caused the development of symptoms and hospitalisation of significantly younger people, compared to the B.1 strain, while the risk of death was around 1.8 times higher for the Delta variant (143).

5.2 Variants of interest

5.2.1 Lambda

The Lambda variant belongs to the C.37 lineage, was first documented in Peru in December 2020, and was designated as a VOI on 14th June 2021 (5). This variant contains the S protein mutations D614G, L452Q, and F490S (116). As previously mentioned, the D614 residue of the S protein is located outside of the RBD, however, the replacement of this by the G614 residue alters the receptor binding conformation and increases binding affinity to the ACE2 receptor (98). This mutation has been demonstrated to increase viral loads, transmissibility, and resistance to neutralisation (117-119). The Lambda variant harbours two novel mutation within the RBD; L452Q and F490S. The L452 residue is also mutated in the Delta variant which, although the leucine is replaced with arginine rather than glutamine, results in greater ACE2 receptor binding affinity and enhanced escape from neutralising antibodies (134, 135). A study demonstrated that the Lambda S protein increases infectivity, an effect that is solely due to the L452Q mutation (147). This was likely due to an increased binding affinity for the ACE2 receptor (147). This study also demonstrated that the Lambda variant was resistant to vaccine-induced antibody neutralisation, an effect that was attributed by the L452Q and F490S mutations (147). Furthermore, a large-scale study that assessed 506,768 SARS-CoV-2 genome isolates from patients with COVID-19 and identified the F490S mutation as a high-risk mutation that enhances vaccine-escape from the host immune response (147).

Currently, studies examining the Lambda variant are limited, however one study found that the infectivity of this variant was higher than the Alpha, Gamma, and D614G containing lineage B variants (148), suggesting that this variant may hold the potential to spread more rapidly and effectively than previous ones. The ability of the Lambda variant to escape host immunity is currently

controversial. The aforementioned study found that, compared to the wild-type SARS-CoV-2 virus, neutralisation was decreased by 3.05-fold for the Lambda variant, while for the Gamma and Alpha variants a 2.33- and 2.03-fold reduction was found, respectively (148). This finding suggests that the Lambda variant is more resistant to neutralisation than the Gamma and Alpha variants. Contrastingly, another study concluded that the Lambda variant could be neutralised by monoclonal antibodies and that current vaccines will continue to be protective against this variant (147).

5.2.2 Mu

The Mu variant is from the B.1.621 lineage and was first documented in Columbia in January 2021, before receiving designation as a VOI on 30th August 2021 (5). This variant contains S protein mutations also harboured by previous variants, including E484K, N501Y, D614G, and P681H (116), therefore will provide this variant with similarly increased levels of transmissibility and immune escapes compared to the wild-type virus. The Mu variant also contains the R346K mutation, which is a S protein mutation of interest and is located within the RBD (116, 149). The R346K mutation has been found to induce large binding free energy changes that could potentially disrupt the binding of antibodies to the S protein and enhance the ability of the Mu variant to escape neutralisation (150). As mentioned with previous variants, the E484K, N501Y, D614G, and P681H mutations have been shown to increase transmissibility (90, 91, 96, 98, 117, 118, 122, 125) and neutralisation escape (102, 119) which suggests the Mu SARS-CoV-2 variant is likely to be more infectious than the wild-type virus, as well as other previous variants.

The development and spread of VOI will need to be closely monitored and studied in order to appreciate their pathogenicity, transmissibility and lethality.

5.3 VUM

VUM are defined by the WHO as in section 5.1. There are currently fourteen VUM listed by the WHO (5), which are described in ***table 1***.

6. Vaccinations

The COVID-19 pandemic has resulted in detrimental outcomes for health, healthcare systems, and the economy around the world and has prompted a rapid international search for a safe, effective, and timely treatment therapy for the SARS-CoV-2 infection and its associated disease. Research from previous vaccine development highlights that vaccines can induce a strong immune response against the S protein and, generally, have a significant blocking effect that effectively prevents entry into host cells (151). In line with previous vaccine development, including for both SARS-CoV and MERS-CoV, the S protein is a key target for COVID-19 vaccine development (152). Vaccines have been shown to be highly efficacious in preventing infection and severe disease from SARS-CoV-2. According to the WHO, the first mass vaccination programme started in early December 2020 (153). As of 20th October 2021, there are 23 approved vaccines in use in 194 countries, with seven vaccines having gained emergency use listing approval from the WHO (6), highlighting their tolerability and effectiveness (***table 2***). The vaccines that have gained approval from the WHO are mRNA, non-replicating viral vector, and inactivated virus vaccines. Many more vaccine therapies are currently being developed and tested, including some that belong to the same class as those already approved, and others such as saRNA, DNA, and protein subunit vaccines. According to the WHO, as of 19th October 2021 there are 194 vaccines in pre-clinical development and 124 in clinical development (154).

6.1 Pfizer/BioNtech - BNT162b2

The BNT162b2 vaccine is an mRNA vaccine developed through a collaborative effort between Pfizer (New York, New York, US) and BioNTech (Mainz, Germany) which gained WHO emergency use listing on 31st December 2020 (153). As of 20th October 2021, this vaccine has been approved for use in 103 countries (155). BNT162b2 is a lipid nanoparticle-formulated, nucleoside-modified RNA vaccine that encodes the full length of the SARS-CoV-2 S protein which has been modified by two proline mutations to ensure it is locked into the prefusion conformation (80, 156). This vaccine prompts a host immune response that allows the body to create antibodies that bind to the S-protein of invading SARS-CoV-2 viruses and neutralises them. BNT162b2 has been demonstrated to elicit a strong and BNT162b2 elicits a strong and resolute interferon gamma (IFNγ) or interleukin-2 (IL-2) $CD8^+$ and $CD4^+$ Th1 cell response (157), while the highest neutralising antibody titres are found between seven and fourteen days after the second vaccine dose (158). In a non-human primate study, BNT162b2 demonstrated a Th-1 biased response which resulted in complete viral clearance from three to ten days post-infection, while neutralising antibody response persisted for up to eight weeks (159).

The BNT162b2 vaccine has been shown to be highly effective at protecting against SARS-CoV-2 infection and severe disease (***table 2***). Two doses of this vaccine are approximately 60-95% effective in preventing SARS-CoV-2 infection, including those caused by VOC.

6.2 Oxford-AtraZeneca – AZD1222

The AZD1222 vaccine is given as an intramuscular injection of a non-replicating vector of the chimpanzee adenovirus ChAdOx1, which has been modified to encode the SARS-CoV-2 S protein (160). Developed through a collaborative project between the University of Oxford and AstraZeneca (Cambridge, UK), this vaccine was given WHO emergency use listing on 16th February 2021 (153) and has been approved for use in 124 countries, as of 20th October 2021 (155). Detection of the S protein expressed by the modified adenovirus has been shown to induce antibody production of predominantly IgG1 and IgG3 subclasses, prompt a Th-1 biased response, and induce a number of other human immune system responses including IFNγ and tumour necrosis factor-α (TNF-α) (133, 161). A study found that one dose of AZD1222 produced a neutralising antibody response in 91% of participants, while a second dose resulted in 100% of participants producing neutralising antibodies (162). The WHO has also listed two versions of this vaccine (AZD1222 and Covishield) for emergency use listing in order to utilise Covishield as part of their worldwide COVAX initiate, which are being produced by the Serum Institute of India and AstraZeneca-SKBio (Republic of Korea) (163).

The AZD1222 vaccine has also been shown to be highly effective in preventing both infection and severe disease as a result of SARS-CoV-2, including VOC (***table 2***). Two doses of this vaccine provide approximately 55-100% protection against infection from SARS-CoV-2.

6.3 Johnson & Johnson - Ad26.COV.2.S

Similarly to the University of Oxford/AtraZeneca AZD1222 vaccine, the Ad26.COV.2.S is also a non-replicating adenovirus vector that has been modified to contain the full-length SARS-CoV-2 S protein in a prefusion-stabilised conformation (164). Unlike AZD122, however, this vector was made from the recombinant human adenovirus type 26 by the Janssen pharmaceutical company of Johnson & Johnson (New Brunswick, New Jersey, US) (164). This vaccine was listed for WHO emergency use listing on 12th March 2021 (153) and, as of 20th October 2021, has been approved for use in 75 countries (155). The SARS-CoV-2 S protein contained in the Ad26.COV.2.S vaccine elicits a host

immune response that induces the production of a variety of antibody subclasses, such as IgG, IgM and IgA, and a number of non-neutralising antibody responses, including activation of CD4+ and CD8+ Th1 cells and production if IFNγ, IL-2, and TNFα (164, 165).

Johnson & Johnson's Ad26.COV.2.S COVID-19 vaccine only requires a single dose and has also shown high levels of effectiveness (***table 2***). Being vaccinated with Ad26.COV.2.S provides approximately 30-85% protection against being infected with SARS-CoV-2, with a longer duration, such as being vaccinated for longer than 28 days, being associated a greater vaccine effectiveness than with being vaccinated for a shorter period of time.

6.4 Moderna – mRNA-1273

The mRNA-1273 vaccine was developed by Moderna (Massachusetts, US), gained WHO emergency use listing on 30th April 2021 (153), and as of 20th October 2021, has been approved for use in 76 countries (155). mRNA-1273 is a lipid-nanoparticle-encapsulated mRNA vaccine expressing the SARS-CoV-2 S protein that has been prefusion-stabilised (166). The S protein contained in this vaccine elicits an immune response including antibody production and CD4+ Th1 cell activation (167). In one non-human primate study, by two days after vaccination, no viral replication in the nose and limited inflammation or viral genome in the lungs could be detected (168), while in another study, mRNA-1273 was the top ranked vaccine when assessing the efficacy of 18 COVID-19 vaccines (159). In humans, neutralising antibody titres have been shown to significantly increase up until around 28 days following the second dose of the vaccine, and afterwards remain consistently high (169).

The mRNA-1273 vaccine has been demonstrated to be highly effective in preventing infection with, and negative outcomes following SARS-CoV-2 infection (***table 2***). Two doses of the vaccine confer approximately 50-95% protection against infection from SARS-CoV-2 and its variants.

6.5 Sinopharm - BBIBP-CorV

The Sinopharm BBIBP-CorV COVID-19 vaccine was developed by the Beijing Bio-Institute of Biological Products, a subsidiary of China National Biotec Group, and was given WHO emergency use listing on 7th May 2021 (153). As of 20th October 2021, this vaccine has been approved for use in 67 countries (155). The Sinopharm BIBP vaccine is an inactivated SARS-CoV-2 antigen that is produced in Vero cells, inactivated by β-propiolactone, and then purified and absorbed with aluminium hydroxide (170). The inactivated vaccine is based on the SARS-CoV-2 19nCoV-CDC-Tan-HB02 (HB02) strain (170). A phase 1/2 clinical trial of this vaccine demonstrated that 100% of participants that received the vaccine produced a neutralising antibody response by day 42 after the second dose (171), while it has also been shown that this vaccine induces the production of IgG and IgA antibodies and a IFNγ positive T-cell response (172).

Studies have demonstrated that two doses of the BBIBP-CorV vaccine confers a strong effectiveness against infection and severe disease as a result of SARS-CoV-2 (***table 2***).

6.6 Sinovac - CoronaVac

The Sinovac CoronaVac vaccine was developed by Sinovac Biotech (Beijing, China), was listed for WHO emergency use listing on 1st June 2021 (153), and has been approved for use in 41 countries, as of 20th October 2021 (155). Like the BBIBP-CorV vaccine, this vaccine is a Vero cell-based, aluminium hydroxide-adjuvanted, β-propiolactone-inactivated vaccine, however, it is based on the SARS-CoV-2 CZ02 strain (173). CoronaVac has been shown to produce an adequate neutralising antibody response

(174), however, this response is lower for infections with VOCs compared to those with the wild type strain (175).

Alike the previous vaccines, CoronaVac provides a strong protection against SARS-CoV-2 related infection, hospitalisation, and death especially after the recommended two doses (***table 2***).

6.7 Other approved vaccines

In addition to the vaccines described above that have received emergency use listing from the WHO, companies around the world have developed, tested and approved vaccines to combat COVID-19. As of 20th October 2021, 23 vaccines, including the seven described above, have been approved (6). The remaining 16 approved vaccines consist of a range of vaccine types and are outlined in ***table 3***.

6.8 Waning immunity and boosters

Throughout the COVID-19 pandemic, the scientific community has been troubled by the effect that emerging SARS-CoV-2 variants may have on the effectiveness of the vaccine rollout. Indeed, a combination of mutations could lead SARS-CoV-2 to develop an exceptional ability to escape neutralisation by vaccine-induced antibodies, rendering the current vaccine strategy insufficient. Although circulating variants have been shown to decrease the effectiveness of certain vaccines (***table 2***), the current vaccines still confer a robust effectiveness against the current VOC. Another issue is that of waning immunity following administration of a COVID-19 vaccine that brings into question the importance of a booster dose. Indeed, immunity against SARS-CoV-2 following full vaccination has been demonstrated to decrease over time, both in terms of antibody titre and vaccine effectiveness. One study found that the SARS-CoV-2 S antibodies decreased by two-fold and five-fold between 21-41 days and 70 days following the second dose of the BNT162b2 Pfizer/BioNtech vaccine and the AZD1222 Oxford University/AstraZeneca, respectively (176). Contrastingly, a six-month longitudinal observational study demonstrated that neutralising antibody levels did not decrease as much as initially feared, in their cohort of 196 hospital workers (177). However, a systematic review of 150 studies concluded that antibody titres do gradually decrease from around eight weeks post-vaccination but suggested that further evidence is required to fully understand this decline (178). In addition to antibody production, COVID-19 vaccines induce other immune factors, which may also play a role in long-lasting, or the decline of, immunity against COVID-19. Several studies have demonstrated that vaccine effectiveness decreases over time. One such study found that the effectiveness of the BNT162b2 vaccine against SARS-CoV-2 infection decreased from 77.5% at one-month after second dose to 17.3% at six-months after second dose, with a decrease also seen in the effectiveness of the vaccine against severe or fatal infection (179). Other studies have corroborated this finding (180, 181), demonstrating that effectiveness of the BNT162b vaccine weakens over time. Similar waning in immunity against SARS-CoV-2 infection has been seen following full vaccination with the mRNA-1273 vaccine (182). Together, these findings suggest that a booster COVID-19 vaccine dose may be required to regain levels of immunity in some individuals.

As booster programme rollouts are still in their infancy, there is limited evidence on their real-world effects, however, data is beginning to infer the utility of a booster vaccine dose. On 30th July 2021, On 30th July 2021, Israel was the first country to offer a third dose of the BNT162b2 vaccine to people aged 60 years or older and who had been fully vaccinated for at least five months. Since then, a study has revealed that a third dose was effective, with those receiving the booster dose significantly less likely to be infected with SARS-CoV-2 or be severely ill with the virus, compared to those who did

not receive the booster (183). In a phase 2 randomised controlled trial, a third dose of vaccine significantly increased neutralising antibody titres, which had decreased below the seropositive cut-off after six to eight months following the prime vaccination regimen (184). Another trial showed that a third dose of mRNA-1273 or variant-targeting variations of the mRNA-1273 vaccine, administered six to eight months after the primary series, significantly improved titres of neutralising antibodies, which were waning before the booster dose was given. Moreover, all boosters were found to increase neutralisation tires against Beta, Gamma and Delta variants (185). Other studies have corroborated the findings discussed here with other vaccines (186, 187). Heterologous boosting, whereby a different vaccine is given from that given in the primary regimen, has been shown to be well tolerated and induce humoral and cellular responses similar to that of homologous boosting (187-189). There is increasing evidence that booster doses of COVID-19 vaccines are well tolerated and effective at boosting immunity and reducing the risk of SARS-CoV-2 infection, therefore, it is likely that many countries will implement vaccine booster programmes, if they have not already done so. It is still unclear, however, who will most likely benefit from receiving a booster dose and which sections of the population will receive it. Furthermore, not all countries are fortunate enough to be in the position to offer booster vaccines, which highlights the controversy of these programmes and the disparity in vaccine rollouts around the world.

7. Considerations for the future

In recent history, only the 1918 'Spanish flu' pandemic, caused by the H1N1 virus, has resulted in a greater amount of illness and death than the current COVID-19 pandemic (190). Pandemics are an unpredictable aspect of nature and it is important that we learn from the current and past pandemics in order to prepare for future ones. The responsibility of improving pandemic response lies with policy makers, the medical/scientific community, and the public, and will ultimately require a collaborative approach. Scientists argue that, globally, we did not learn from the previous SARS-CoV and MERS-CoV pandemics and were ill-prepared for the COVID-19 pandemic (191). One example of this ill preparation was the lack of availability of personal protective equipment (PPE) and medical devices that were vital for protecting healthcare workers and treating patients. Global limited availability of PPE was a result of many factors, including a sudden increased demand and price, and severe disruptions to global supply chains. Therefore, a major lesson to take from this pandemic is to strengthen the capacity to maintain and distribute PPE stockpiles, enforce regulations on PPE, and remove the motive of profit for purchasing PPE products which will allow the equipment to be distributed more effectively and supplies to be more regularly available (192).

Additionally, the COVID-19 pandemic has highlighted the increased vulnerability of the socio-economically deprived. Non-white ethnicity, social disadvantage (as measured by education, housing and income), and unemployment are risk factors for testing positive for COVID-19 (193), while non-white ethnicity is also associated with COVID-19 related death (20). Financially poorer people are also more often employed in occupations that do not allow them to work from home, therefore, are more likely to become unemployed during a global pandemic, which could have negative consequences on stress and mental health (194). Special consideration should be given for those who are likely to be most greatly affected by future pandemics.

Funding is also essential for the current and future pandemics for immediate response and secondary factors, such as remote education/working, food availability, and furlough schemes, while taking into consideration the effect on the economic impact. It is important that governments and leading scientists work together to identify areas of improvement from the COVID-19 pandemic, which

is why inquiries into the handling of it, such as the coronavirus inquiry set to take place in the UK (195), are welcomed.

Moreover, certain aspects of the response to the pandemic have been a huge triumph. The rapid identification, sequencing and ongoing epidemiological information related to the transmission and mutation of SARS-CoV-2 have helped to better understand the virus and how it spreads. Pharmacological developments, such as the gradual improvement of treatment strategies have helped to reduce the number of people that die from COVID-19, while the expeditious development, approval, rollout, and effectiveness of vaccines have been an enormous success. With SARS-CoV-2 reinfection likely (196), even after infection and vaccination, policymakers should remain vigilant and ready to implement prevention and treatment strategies in order to prevent further waves of infection. Scientific-backed strategy, informed decision-making, and public involvement are three important steps to improve the control and response to future pandemics.

8. Conclusion

COVID-19 remains a debilitating and life-threatening disease. Although the timely development and rollout of vaccines have assisted in reducing the spread of the virus, it has yet to be eradicated. With the Delta variant continuing to circulate, and with new variants likely to arise in the future, we must remain vigilant to reduce the risk of further waves of infection. In this review, we have provided an overview of SARS-CoV-2, including its genome, structure, and routes of transmission. We have also outlined the mutations harboured by SARS-CoV-2 variants and how these mutations enhance the ability of the variants to spread more easily and inflict more severe disease. Lastly, we discussed the major vaccines that have been developed and administered around the world and provided evidence supporting the rollout of booster doses.

Priority should be focused on maintaining efficacy of vaccines against emerging variants, monitoring the spread and the emergence of genetic mutations of SARS-CoV-2. Achievement of an effective vaccination rollout will not only help us get through this pandemic but will better our response and management of the next one.

Research Questions

1) How will the SARS-CoV-2 virus mutate, and which mutations will give a competitive advantage that will allow the virus to inflict severe disease?
2) How can we keep up with the rapidly changing SARS-CoV-2 environment and ensure vaccines remain effective?
3) When should booster doses be given and who should they be given to in order to achieve the most effective outcome?
4) How can we learn from the current and past pandemics so that we are better prepared for the next one?

Patient Involvement: Patients who had been infected with covid-19 were contacted and requested to review the initial drafts of this manuscript. The received feedback was mostly positive and assisted in developing and focusing our review. Final drafts were also reviewed by patients who had had covid-19 and similar positive feedback was received.

Contributorship statement and guarantor: MY and HC performed the literature search and drafted the manuscript. MY and HC revised and finalised the manuscript and are joint-first authors. JS reviewed and revised the manuscript. PE was responsible for the concept and design of the work. PE reviewed, revised and finalised the manuscript. PE is the guarantor.

Competing interests: We have read and understood the BMJ policy on declaration of interests and declare the following interests: PE was funded by the Medical Research Council and now by Higher Education Funding Council for England (HEFCE). He has also received grants from Alzheimer's Research, UK, Alzheimer's Drug Discovery Foundation, Alzheimer's Society, UK, Medical Research Council, Alzheimer's Association US, Van-Geest foundation, and European Union grants. PE is a consultant to Roche, Pfizer, and Novo Nordisk. He has received educational and research grants from GE Healthcare, Novo Nordisk, Piramal Life Science/Life Molecular Imaging, Avid Radiopharmaceuticals and Eli Lilly. He is a member of the Scientific Advisory Board at Novo Nordisk. None of these were related to COVID-19

Figure Legends:

Figure 1: Genome and structure of SARS-CoV-2. A) SARS-CoV-2 genome and S protein amino acid composition. The SARS-CoV-2 genome is approximately 30,000 base pairs (bp) long and consists of open reading frames (ORF) and elements that are essential for the virus' structure. The spike S protein is responsible for binding and entry into host cells. SARS-CoV-2 variants of concern (VOC) contain various S protein non-synonymous mutations that result in amino acid changes in the receptor binding domain (orange text) and the S1/S2 subunit interface (black text) which have been demonstrated to enhance transmissibility of the virus. VOC include Alpha (α), Beta (β), Gamma (γ), and Delta (δ). **B) SARS-CoV-2 structure.** SARS-CoV-2 is a RNA virus that has a crown-like appearance and contains four major structural proteins: nucleocapsid (N), spike (S), envelope (E), and membrane (M). **C) S and ACE2 interaction.** The SARS-CoV-2 S protein directly interacts with human angiotensin-converting enzyme 2 (ACE2) receptors in order to gain entry into host cells. The receptor binding domain (RBD) of the S protein tightly binds to ACE2. **D) Spike protein structure.** The S protein protrudes out from the main SARS-CoV-2 bulk and is comprised of two subunits: S1 and S2. S1 contains the RBD which directly interacts with the human ACE2 receptor, while the S1/S2 interface contains a furin cleavage site which is cleaved to allow S2 to fuse with the host cell membrane. Both the RBD and the S1/S2 interface contain transmissibility increasing mutations that are harboured in variants of concern.

Figure 2: Viral entry and host response. A) At the alveolar epithelial cell layer. Epithelial cells in the lungs express both angiotensin-converting enzyme 2 (ACE2) receptors and transmembrane protease serine 2 (TMPRSS2), allowing for infection by SARS-CoV-2. Replication of the virus within these cells induces an intense immune response that attracts monocytes, T-cells and macrophages and, in some cases, can result in a cytokine storm. **B) Within nearby blood vessels.** Cytokines produced by the epithelial cell layer are released into blood vessels supplying the infected tissue, which causes the

recruitment of further immune cells to the area, driving the damaging inflammatory response further. Circulating cytokines also create a systemic inflammatory environment. **C) Adaptive immune response.** Circulating lymphocytes carry viral antigens to lymph nodes and bone marrow to begin the adaptive immune system processes whereby B-cells, and later antibodies, are activated. **D) SARS-CoV-2 host replication.** The SARS-CoV-2 virus utilises the ACE2 receptor and TMPRSS2 to gain entry into human cells. Following release of the viral RNA within the host cell, the virus utilises the host endoplasmic reticulum (ER) and Golgi apparatus to produce and manufacture new viral particles, which are released out of the cell to infect other cells and new hosts.

Table 1: SARS-CoV-2 variants. *first detection worldwide. data from WHO (https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/). Zeta (P.2) and Theta (P.3) is no longer considered a variant under monitoring (VUM) and, therefore, has been removed. Epsilon: Former variant of interest (VOI) (designated 5 Mar 2021), downgraded to a VUM 6 Jul 2021. Kappa: Former VOI (designated 4 Apr 2021), downgraded to a VUM 20 Sept 2021. Iota: Former VOI (designated 24 Mar 2021), downgraded to a VUM 20 Sept 2021. Eta: Former VOI (designated 17 Mar 2021), downgraded to a VUM 20 Sept 2021.

Table 2: Vaccines that have gained WHO emergency use listing. *Adjusted for covariates where reported in study. Days/Months refers to days/months since vaccination dose.

Table 3: COVID-19 vaccines that have been approved around the world that have not gained emergency use listing from the World Health Organisation.

References:

1. Centers for Disease Control and Prevention. Human Coronavirus Types. Available from: https://www.cdc.gov/coronavirus/types.html [Accessed 15 October 2021].

2. World Health Organisation. Weekly Operational Update on COVID-19 – 18 October 2021. Available from: https://www.who.int/publications/m/item/weekly-operational-update-on-covid-19---18-october-2021 [Accessed 21 October 2021].3. Wong MC, Cregeen SJJ, Ajami NJ, Petrosino JF. Evidence of recombination in coronaviruses implicating pangolin origins of nCoV-2019. BioRxiv [preprint]. 2020.

4. Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science. 2020;367(6485):1444-8.

5. World Health Organisation. Tracking SARS-CoV-2 variants. Available from: https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/ [Accessed 23 October 2021].

6. Covid-19 Vaccine tracker. Approved Vaccines. Available from: https://covid19.trackvaccines.org/vaccines/approved/ [Accessed 21 October 2021].

7. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet. 2020;395(10223):514-23.

8. World Health Organisation. Transmission of SARS-CoV-2: implications for infection prevention precautions. Scientific Brief. Available from: https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions [Accessed 15 October 2021].

9. Hui KP, Cheung M-C, Perera RA, Ng K-C, Bui CH, Ho JC, et al. Tropism, replication competence, and innate immune responses of the coronavirus SARS-CoV-2 in human respiratory tract and conjunctiva: an analysis in ex-vivo and in-vitro cultures. The Lancet Respiratory Medicine. 2020;8(7):687-95.

10. McAloon C, Collins A, Hunt K, Barber A, Byrne AW, Butler F, et al. Incubation period of COVID-19: a rapid systematic review and meta-analysis of observational research. BMJ Open. 2020;10(8):e039652.

11. Bliddal S, Banasik K, Pedersen OB, Nissen J, Cantwell L, Schwinn M, et al. Acute and persistent symptoms in non-hospitalized PCR-confirmed COVID-19 patients. Sci Rep. 2021;11(1):13153.

12. Grant MC, Geoghegan L, Arbyn M, Mohammed Z, McGuinness L, Clarke EL, et al. The prevalence of symptoms in 24,410 adults infected by the novel coronavirus (SARS-CoV-2; COVID-19): A systematic review and meta-analysis of 148 studies from 9 countries. PLoS One. 2020;15(6):e0234765.

13. Kronbichler A, Kresse D, Yoon S, Lee KH, Effenberger M, Shin JI. Asymptomatic patients as a source of COVID-19 infections: A systematic review and meta-analysis. Int J Infect Dis. 2020;98:180-6.

14. Arons MM, Hatfield KM, Reddy SC, Kimball A, James A, Jacobs JR, et al. Presymptomatic SARS-CoV-2 Infections and Transmission in a Skilled Nursing Facility. N Engl J Med. 2020;382(22):2081-90.

15. Zhang JJ, Cao YY, Tan G, Dong X, Wang BC, Lin J, et al. Clinical, radiological, and laboratory characteristics and risk factors for severity and mortality of 289 hospitalized COVID-19 patients. Allergy. 2021;76(2):533-50.

16. Wolff D, Nee S, Hickey NS, Marschollek M. Risk factors for Covid-19 severity and fatality: a structured literature review. Infection. 2021;49(1):15-28.

17. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62.

18. Zhang J, Wang X, Jia X, Li J, Hu K, Chen G, et al. Risk factors for disease severity, unimprovement, and mortality in COVID-19 patients in Wuhan, China. Clin Microbiol Infect. 2020;26(6):767-72.

19. Ebinger JE, Achamallah N, Ji H, Claggett BL, Sun N, Botting P, et al. Pre-existing traits associated with Covid-19 illness severity. PLoS One. 2020;15(7):e0236240.

20. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;584(7821):430-6.

21. Li R, Tian J, Yang F, Lv L, Yu J, Sun G, et al. Clinical characteristics of 225 patients with COVID-19 in a tertiary Hospital near Wuhan, China. J Clin Virol. 2020;127:104363.

22. Guo L, Shi Z, Zhang Y, Wang C, Do Vale Moreira NC, Zuo H, et al. Comorbid diabetes and the risk of disease severity or death among 8807 COVID-19 patients in China: A meta-analysis. Diabetes Res Clin Pract. 2020;166:108346.

23. Feng Y, Ling Y, Bai T, Xie Y, Huang J, Li J, et al. COVID-19 with Different Severities: A Multicenter Study of Clinical Features. Am J Respir Crit Care Med. 2020;201(11):1380-8.

24. Tian J, Yuan X, Xiao J, Zhong Q, Yang C, Liu B, et al. Clinical characteristics and risk factors associated with COVID-19 disease severity in patients with cancer in Wuhan, China: a multicentre, retrospective, cohort study. Lancet Oncol. 2020;21(7):893-903.

25. Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020;21(3):335-7.

26. Vizcarra P, Perez-Elias MJ, Quereda C, Moreno A, Vivancos MJ, Dronda F, et al. Description of COVID-19 in HIV-infected individuals: a single-centre, prospective cohort. Lancet HIV. 2020;7(8):e554-e64.

27. Baillie JK, Wilson JF, Bulteel N, Hayward C, Klaric L, Porteous DJ, et al. Mapping the human genetic architecture of COVID-19. Nature. 2021.

28. Shelton JF, Shastri AJ, Ye C, Weldon CH, Filshtein-Somnez T, Coker D, et al. Trans-ethnic analysis reveals genetic and non-genetic associations with COVID-19 susceptibility and severity. MedRxiv [preprint]. 2020.

29. Ellinghaus D, Degenhardt F, Bujanda L, Buti M, Albillos A, Invernizzi P, et al. Genomewide association study of severe covid-19 with respiratory failure/[...]. New England Journal of Medicine Boston: Massachusetts Medical Society, 2020, vol 383, no 16. 2020.

30. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. cell. 2020;181(2):271-80. e8.

31. Barbry P, Muus C, Luecken M, Eraslan G, Waghray A, Heimberg G, et al. Integrated analyses of single-cell atlases reveal age, gender, and smoking status associations with cell type-specific expression of mediators of SARS-CoV-2 viral entry and highlights inflammatory programs in putative target cells. 2020.

32. Hou Y, Zhao J, Martin W, Kallianpur A, Chung MK, Jehi L, et al. New insights into genetic susceptibility of COVID-19: an ACE2 and TMPRSS2 polymorphism analysis. BMC medicine. 2020;18(1):1-8.

33. Payne S. Family Coronaviridae. Viruses2017. p. 149-58.

34. Masters PS, Kuo L, Ye R, Hurst KR, Koetzner CA, Hsue B. Genetic and molecular biological analysis of protein-protein interactions in coronavirus assembly. Adv Exp Med Biol. 2006;581:163-73.

35. Khailany RA, Safdar M, Ozaslan M. Genomic characterization of a novel SARS-CoV-2. Gene Rep. 2020;19:100682.

36. Thoms M, Buschauer R, Ameismeier M, Koepke L, Denk T, Hirschenberger M, et al. Structural basis for translational shutdown and immune evasion by the Nsp1 protein of SARS-CoV-2. Science. 2020;369(6508):1249-55.

37. Schubert K, Karousis ED, Jomaa A, Scaiola A, Echeverria B, Gurzeler LA, et al. SARS-CoV-2 Nsp1 binds the ribosomal mRNA channel to inhibit translation. Nat Struct Mol Biol. 2020;27(10):959-66.

38. Huang C, Lokugamage KG, Rozovics JM, Narayanan K, Semler BL, Makino S. SARS coronavirus nsp1 protein induces template-dependent endonucleolytic cleavage of mRNAs: viral mRNAs are resistant to nsp1-induced RNA cleavage. PLoS Pathog. 2011;7(12):e1002433.

39. Snijder EJ, Decroly E, Ziebuhr J. The Nonstructural Proteins Directing Coronavirus RNA Synthesis and Processing. Adv Virus Res. 2016;96:59-126.

40. V'Kovski P, Gerber M, Kelly J, Pfaender S, Ebert N, Braga Lagache S, et al. Determination of host proteins composing the microenvironment of coronavirus replicase complexes by proximity-labeling. Elife. 2019;8.

41. Masters PS. The molecular biology of coronaviruses. Advances in virus research. 2006;66:193-292.

42. Siu Y, Teoh K, Lo J, Chan C, Kien F, Escriou N, et al. The M, E, and N structural proteins of the severe acute respiratory syndrome coronavirus are required for efficient assembly, trafficking, and release of virus-like particles. Journal of virology. 2008;82(22):11318-30.

43. Kuo L, Masters PS. Genetic evidence for a structural interaction between the carboxy termini of the membrane and nucleocapsid proteins of mouse hepatitis virus. J Virol. 2002;76(10):4987-99.

44. Hulswit RJ, de Haan CA, Bosch BJ. Coronavirus Spike Protein and Tropism Changes. Adv Virus Res. 2016;96:29-57.

45. Konno Y, Kimura I, Uriu K, Fukushi M, Irie T, Koyanagi Y, et al. SARS-CoV-2 ORF3b Is a Potent Interferon Antagonist Whose Activity Is Increased by a Naturally Occurring Elongation Variant. Cell Rep. 2020;32(12):108185.

46. Kopecky-Bromberg SA, Martinez-Sobrido L, Frieman M, Baric RA, Palese P. Severe acute respiratory syndrome coronavirus open reading frame (ORF) 3b, ORF 6, and nucleocapsid proteins function as interferon antagonists. J Virol. 2007;81(2):548-57.

47. Xia H, Cao Z, Xie X, Zhang X, Chen JY, Wang H, et al. Evasion of Type I Interferon by SARS-CoV-2. Cell Rep. 2020;33(1):108234.

48. Wong HH, Fung TS, Fang S, Huang M, Le MT, Liu DX. Accessory proteins 8b and 8ab of severe acute respiratory syndrome coronavirus suppress the interferon signaling pathway by mediating ubiquitin-dependent rapid degradation of interferon regulatory factor 3. Virology. 2018;515:165-75.

49. Azad GK, Khan PK. Variations in Orf3a protein of SARS-CoV-2 alter its structure and function. Biochem Biophys Rep. 2021;26:100933.

50. Ren Y, Shu T, Wu D, Mu J, Wang C, Huang M, et al. The ORF3a protein of SARS-CoV-2 induces apoptosis in cells. Cell Mol Immunol. 2020;17(8):881-3.

51. Kreimendahl S, Rassow J. The Mitochondrial Outer Membrane Protein Tom70-Mediator in Protein Traffic, Membrane Contact Sites and Innate Immunity. Int J Mol Sci. 2020;21(19).

52. Gordon DE, Jang GM, Bouhaddou M, Xu J, Obernier K, White KM, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. Nature. 2020;583(7816):459-68.

53. Dominguez Andres A, Feng Y, Campos AR, Yin J, Yang CC, James B, et al. SARS-CoV-2 ORF9c Is a Membrane-Associated Protein that Suppresses Antiviral Responses in Cells. BioRxiv [preprint]. 2020.

54. Redondo N, Zaldivar-Lopez S, Garrido JJ, Montoya M. SARS-CoV-2 Accessory Proteins in Viral Pathogenesis: Knowns and Unknowns. Front Immunol. 2021;12:708264.

55. Bosch BJ, van der Zee R, de Haan CA, Rottier PJ. The coronavirus spike protein is a class I virus fusion protein: structural and functional characterization of the fusion core complex. J Virol. 2003;77(16):8801-11.

56. Li F. Structure, Function, and Evolution of Coronavirus Spike Proteins. Annu Rev Virol. 2016;3(1):237-61.

57. Letko M, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. Nat Microbiol. 2020;5(4):562-9.

58. Millet JK, Whittaker GR. Host cell proteases: Critical determinants of coronavirus tropism and pathogenesis. Virus Res. 2015;202:120-34.

59. Glowacka I, Bertram S, Muller MA, Allen P, Soilleux E, Pfefferle S, et al. Evidence that TMPRSS2 activates the severe acute respiratory syndrome coronavirus spike protein for membrane fusion and reduces viral control by the humoral immune response. J Virol. 2011;85(9):4122-34.

60. Zhao MM, Yang WL, Yang FY, Zhang L, Huang WJ, Hou W, et al. Cathepsin L plays a key role in SARS-CoV-2 infection in humans and humanized mice and is a promising target for new drug development. Signal Transduct Target Ther. 2021;6(1):134.

61. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020;181(2):271-80 e8.

62. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004;203(2):631-7.

63. Kahn JS, McIntosh K. History and recent advances in coronavirus discovery. Pediatr Infect Dis J. 2005;24(11 Suppl):S223-7, discussion S6.

64. Ge XY, Hu B, Shi ZL. Bat Coronaviruses. Bats and Viruses. 2015:127–55.

65. Lee N, Hui D, Wu A, Chan P, Cameron P, Joynt GM, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. N Engl J Med. 2003;348(20):1986-94.

66. Centers for Disease Control and Prevention. Severe Acute Respiratory Syndrome (SARS). Available from: https://www.cdc.gov/sars/about/faq.html [Accessed 05 Oct 2021].

67. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-3.

68. Liu Y, Gayle AA, Wilder-Smith A, Rocklov J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. J Travel Med. 2020;27(2).

69. Coutard B, Valle C, de Lamballerie X, Canard B, Seidah NG, Decroly E. The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. Antiviral Res. 2020;176:104742.

70. Rabaan AA, Al-Ahmed SH, Haque S, Sah R, Tiwari R, Malik YS, et al. SARS-CoV-2, SARS-CoV, and MERS-COV: A comparative overview. Infez Med. 2020;28(2):174-84.

71. Nguyen HL, Lan PD, Thai NQ, Nissley DA, O'Brien EP, Li MS. Does SARS-CoV-2 Bind to Human ACE2 More Strongly Than Does SARS-CoV? J Phys Chem B. 2020;124(34):7336-47.

72. World Health Organisation. Middle East respiratory syndrome coronavirus (MERS-CoV). Available from: https://www.who.int/health-topics/middle-east-respiratory-syndrome-coronavirus-mers#tab=tab_1 [Accessed 05 Oct 2021].

73. Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. Methods Mol Biol. 2015;1282:1-23.

74. Lau SK, Woo PC, Li KS, Huang Y, Tsoi HW, Wong BH, et al. Severe acute respiratory syndrome coronavirus-like virus in Chinese horseshoe bats. Proc Natl Acad Sci U S A. 2005;102(39):14040-5.

75. Li W, Shi Z, Yu M, Ren W, Smith C, Epstein JH, et al. Bats are natural reservoirs of SARS-like coronaviruses. Science. 2005;310(5748):676-9.

76. van Boheemen S, de Graaf M, Lauber C, Bestebroer TM, Raj VS, Zaki AM, et al. Genomic characterization of a newly discovered coronavirus associated with acute respiratory distress syndrome in humans. mBio. 2012;3(6).

77. Meyer B, Muller MA, Corman VM, Reusken CB, Ritz D, Godeke GJ, et al. Antibodies against MERS coronavirus in dromedary camels, United Arab Emirates, 2003 and 2013. Emerg Infect Dis. 2014;20(4):552-9.

78. Wu A, Peng Y, Huang B, Ding X, Wang X, Niu P, et al. Genome composition and divergence of the novel coronavirus (2019-nCoV) originating in China. Cell host & microbe. 2020;27(3):325-8.

79. Wu F, Zhao S, Yu B, Chen Y-M, Wang W, Hu Y, et al. Complete genome characterisation of a novel coronavirus associated with severe human respiratory disease in Wuhan, China. BioRxiv [preprint]. 2020.

80. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh C-L, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020;367(6483):1260-3.

81. Chan JF-W, Kok K-H, Zhu Z, Chu H, To KK-W, Yuan S, et al. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. Emerging microbes & infections. 2020;9(1):221-36.

82. Chen B, Tian EK, He B, Tian L, Han R, Wang S, et al. Overview of lethal human coronaviruses. Signal Transduct Target Ther. 2020;5(1):89.

83. Lauring AS, Hodcroft EB. Genetic Variants of SARS-CoV-2-What Do They Mean? JAMA. 2021;325(6):529-31.

84. Duchene S, Featherstone L, Haritopoulou-Sinanidou M, Rambaut A, Lemey P, Baele G. Temporal signal and the phylodynamic threshold of SARS-CoV-2. Virus Evol. 2020;6(2):veaa061.

85. World Health Organisation. Weekly epidemiological update on COVID-19 - 19 October 2021. Available from: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---19-october-2021 [Accessed 21 October 2021].

86. gov.uk. Investigation of novel SARS-CoV-2 variant - Variant of Concern 202012/01 - Technical briefing 5. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/959426/Variant_of_Concern_VOC_202012_01_Technical_Briefing_5.pdf [Accessed 06 Oct 2021].

87. Lan J, Ge J, Yu J, Shan S, Zhou H, Fan S, et al. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. Nature. 2020;581(7807):215-20.

88. Wang Y, Liu M, Gao J. Enhanced receptor binding of SARS-CoV-2 through networks of hydrogen-bonding and hydrophobic interactions. Proc Natl Acad Sci U S A. 2020;117(25):13967-74.

89. Yi C, Sun X, Ye J, Ding L, Liu M, Yang Z, et al. Key residues of the receptor binding motif in the spike protein of SARS-CoV-2 that interact with ACE2 and neutralizing antibodies. Cell Mol Immunol. 2020;17(6):621-30.

90. Starr TN, Greaney AJ, Hilton SK, Ellis D, Crawford KHD, Dingens AS, et al. Deep Mutational Scanning of SARS-CoV-2 Receptor Binding Domain Reveals Constraints on Folding and ACE2 Binding. Cell. 2020;182(5):1295-310 e20.

91. Gu H, Chen Q, Yang G, He L, Fan H, Deng YQ, et al. Adaptation of SARS-CoV-2 in BALB/c mice for testing vaccine efficacy. Science. 2020;369(6511):1603-7.

92. Huang Y, Yang C, Xu XF, Xu W, Liu SW. Structural and functional properties of SARS-CoV-2 spike protein: potential antivirus drug development for COVID-19. Acta Pharmacol Sin. 2020;41(9):1141-9.

93. Hoffmann M, Kleine-Weber H, Pohlmann S. A Multibasic Cleavage Site in the Spike Protein of SARS-CoV-2 Is Essential for Infection of Human Lung Cells. Mol Cell. 2020;78(4):779-84 e5.

94. Peacock TP, Goldhill DH, Zhou J, Baillon L, Frise R, Swann OC, et al. The furin cleavage site of SARS-CoV-2 spike protein is a key determinant for transmission due to enhanced replication in airway cells. BioRxiv [preprint]. 2020.

95. Zhu Y, Feng F, Hu G, Wang Y, Yu Y, Zhu Y, et al. The S1/S2 boundary of SARS-CoV-2 spike protein modulates cell entry pathways and transmission. BioRxiv [preprint]. 2020.

96. Scudellari M. How the coronavirus infects cells - and why Delta is so dangerous. Nature. 2021;595(7869):640-4.

97. Wang Q, Qiu Y, Li JY, Zhou ZJ, Liao CH, Ge XY. A Unique Protease Cleavage Site Predicted in the Spike Protein of the Novel Pneumonia Coronavirus (2019-nCoV) Potentially Related to Viral Transmissibility. Virol Sin. 2020;35(3):337-9.

98. Yurkovetskiy L, Wang X, Pascal KE, Tomkins-Tinch C, Nyalile TP, Wang Y, et al. Structural and Functional Analysis of the D614G SARS-CoV-2 Spike Protein Variant. Cell. 2020;183(3):739-51 e8.

99. McCarthy KR, Rennick LJ, Nambulli S, Robinson-McCarthy LR, Bain WG, Haidar G, et al. Natural deletions in the SARS-CoV-2 spike glycoprotein drive antibody escape. BioRxiv [preprint]. 2021.

100. Kemp SA, Collier DA, Datir R, Ferreira I, Gayed S, Jahun A, et al. Neutralising antibodies in Spike mediated SARS-CoV-2 adaptation. MedRxiv [preprint]. 2020.

101. Gamage AM, Tan KS, Chan WOY, Liu J, Tan CW, Ong YK, et al. Infection of human Nasal Epithelial Cells with SARS-CoV-2 and a 382-nt deletion isolate lacking ORF8 reveals similar viral kinetics and host transcriptional profiles. PLoS Pathog. 2020;16(12):e1009130.

102. Collier DA, De Marco A, Ferreira I, Meng B, Datir RP, Walls AC, et al. Sensitivity of SARS-CoV-2 B.1.1.7 to mRNA vaccine-elicited antibodies. Nature. 2021;593(7857):136-41.

103. gov.uk. Variants: distribution of case data, 15 October 2021. Available from: https://www.gov.uk/government/publications/covid-19-variants-genomically-confirmed-case-numbers/variants-distribution-of-case-data-15-october-2021 [Accessed 23 October 2021].

104. Martínez-García L, Espinel MA, Abreu M, González-Alba JM, Gijón D, McGee A, et al. Emergence and Spread of B. 1.1. 7 Lineage in Primary Care and Clinical Impact in the Morbi-Mortality among Hospitalized Patients in Madrid, Spain. Microorganisms. 2021;9(7):1517.

105. Vassallo M, Manni S, Klotz C, Fabre R, Pini P, Blanchouin E, et al. Patients Admitted for Variant Alpha COVID-19 Have Poorer Outcomes than Those Infected with the Old Strain. J Clin Med. 2021;10(16).

106. McAlister FA, Nabipoor M, Chu A, Lee DS, Saxinger L, Bakal JA. Lessons from the COVID-19 third wave in Canada: the impact of variants of concern and shifting demographics. . MedRxiv [preprint]. 2021.

107. Davies NG, Abbott S, Barnard RC, Jarvis CI, Kucharski AJ, Munday JD, et al. Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. Science. 2021;372(6538).

108. Leung K, Shum MH, Leung GM, Lam TT, Wu JT. Early transmissibility assessment of the N501Y mutant strains of SARS-CoV-2 in the United Kingdom, October to November 2020. Euro Surveill. 2021;26(1).

109. Zhao S, Lou J, Cao L, Zheng H, Chong MKC, Chen Z, et al. Quantifying the transmission advantage associated with N501Y substitution of SARS-CoV-2 in the UK: an early data-driven analysis. J Travel Med. 2021;28(2).

110. gov.uk. NERVTAG paper on COVID-19 variant of concern B.1.1.7. NERVTAG - COVID-19 Public statements. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/961037/NERVTAG_note_on_B.1.1.7_severity_for_SAGE_77__1_.pdf [Accessed 07 Oct 2021].

111. Challen R, Brooks-Pollock E, Read JM, Dyson L, Tsaneva-Atanasova K, Danon L. Risk of mortality in patients infected with SARS-CoV-2 variant of concern 202012/1: matched cohort study. BMJ. 2021;372:n579.

112. Paredes MI, Lunn SM, Famulare M, Frisbie LA, Painter I, Burstein R, et al. Associations between SARS-CoV-2 variants and risk of COVID-19 hospitalization among confirmed cases in Washington State: a retrospective cohort study. MedRxiv [preprint]. 2021.

113. Wang P, Nair MS, Liu L, Iketani S, Luo Y, Guo Y, et al. Antibody Resistance of SARS-CoV-2 Variants B.1.351 and B.1.1.7. BioRxiv [preprint]. 2021:2021.01.25.428137.

114. Wu K, Werner AP, Moliva JI, Koch M, Choi A, Stewart-Jones GBE, et al. mRNA-1273 vaccine induces neutralizing antibodies against spike mutants from global SARS-CoV-2 variants. BioRxiv [preprint]. 2021.

115. Gallais F, Gantner P, Bruel T, Velay A, Planas D, Wendling M-J, et al. Anti-SARS-CoV-2 Antibodies Persist for up to 13 Months and Reduce Risk of Reinfection. MedRxiv [preprint]. 2021.

116. European Centre for Disease Prevention and Control. SARS-CoV-2 variants of concern as of 7 October 2021. Available from: https://www.ecdc.europa.eu/en/covid-19/variants-concern [Accessed 8 Oct 2021].

117. Korber B, Fischer WM, Gnanakaran S, Yoon H, Theiler J, Abfalterer W, et al. Tracking Changes in SARS-CoV-2 Spike: Evidence that D614G Increases Infectivity of the COVID-19 Virus. Cell. 2020;182(4):812-27 e19.

118. Volz E, Hill V, McCrone JT, Price A, Jorgensen D, O'Toole A, et al. Evaluating the Effects of SARS-CoV-2 Spike Mutation D614G on Transmissibility and Pathogenicity. Cell. 2021;184(1):64-75 e11.

119. Plante JA, Liu Y, Liu J, Xia H, Johnson BA, Lokugamage KG, et al. Spike mutation D614G alters SARS-CoV-2 fitness. Nature. 2021;592(7852):116-21.

120. Pearson CA, Russell TW, Davies NG, Kucharski AJ, group CC-w, Edmunds WJ, et al. Estimates of severity and transmissibility of novel South Africa SARS-CoV-2 variant 501Y.V2. Centre for Mathematical Modelling of Infectious Diseases. 2021;Pre-print.

121. Wibmer CK, Ayres F, Hermanus T, Madzivhandila M, Kgagudi P, Oosthuysen B, et al. SARS-CoV-2 501Y.V2 escapes neutralization by South African COVID-19 donor plasma. Nat Med. 2021;27(4):622-5.

122. Sinha S, Tam B, Wang SM. Altered interaction between RBD and ACE2 receptor contributes towards the increased transmissibility of SARS CoV-2 delta, kappa, beta, and gamma strains with RBD double mutations. BioRxiv [preprint]. 2021.

123. Campbell F, Archer B, Laurenson-Schafer H, Jinnai Y, Konings F, Batra N, et al. Increased transmissibility and global spread of SARS-CoV-2 variants of concern as at June 2021. Euro Surveill. 2021;26(24).

124. European Centre for Disease Prevention and Control. SARS-CoV-2 increased circulation of variants of concern and vaccine rollout in the EU/EEA,14th update. Available from:

https://www.ecdc.europa.eu/sites/default/files/documents/RRA-covid-19-14th-update-15-feb-2021.pdf [Accessed 8 October 2021].

125. Khan A, Zia T, Suleman M, Khan T, Ali SS, Abbasi AA, et al. Higher infectivity of the SARS-CoV-2 new variants is associated with K417N/T, E484K, and N501Y mutants: An insight from structural data. J Cell Physiol. 2021;236(10):7045-57.

126. Baum A, Fulton BO, Wloga E, Copin R, Pascal KE, Russo V, et al. Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies. Science. 2020;369(6506):1014-8.

127. Curran J, Dol J, Boulos L, Somerville M, McCulloch H, MacDonald M, et al. Transmission characteristics of SARS-CoV-2 variants of concern. MedRxiv [preprint]. 2021.

128. Faria NR, Mellan TA, Whittaker C, Claro IM, Candido DDS, Mishra S, et al. Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil. Science. 2021;372(6544):815-21.

129. Freitas ARR, Beckedorff OA, Cavalcanti LPG, Siqueira AM, Castro DB, Costa CFD, et al. The emergence of novel SARS-CoV-2 variant P.1 in Amazonas (Brazil) was temporally associated with a change in the age and sex profile of COVID-19 mortality: A population based ecological study. Lancet Reg Health Am. 2021;1:100021.

130. Funk T, Pharris A, Spiteri G, Bundle N, Melidou A, Carr M, et al. Characteristics of SARS-CoV-2 variants of concern B.1.1.7, B.1.351 or P.1: data from seven EU/EEA countries, weeks 38/2020 to 10/2021. Euro Surveill. 2021;26(16).

131. Sabino EC, Buss LF, Carvalho MPS, Prete CA, Jr., Crispim MAE, Fraiji NA, et al. Resurgence of COVID-19 in Manaus, Brazil, despite high seroprevalence. Lancet. 2021;397(10273):452-5.

132. Dejnirattisai W, Zhou D, Supasa P, Liu C, Mentzer AJ, Ginn HM, et al. Antibody evasion by the P.1 strain of SARS-CoV-2. Cell. 2021;184(11):2939-54 e9.

133. Augusto G, Mohsen MO, Zinkhan S, Liu X, Vogel M, Bachmann MF. In vitro data suggest that Indian delta variant B.1.617 of SARS-CoV-2 escapes neutralization by both receptor affinity and immune evasion. Allergy. 2021.

134. Tchesnokova V, Kulakesara H, Larson L, Bowers V, Rechkina E, Kisiela D, et al. Acquisition of the L452R mutation in the ACE2-binding interface of Spike protein triggers recent massive expansion of SARS-Cov-2 variants. BioRxiv [preprint]. 2021.

135. Li Q, Wu J, Nie J, Zhang L, Hao H, Liu S, et al. The Impact of Mutations in SARS-CoV-2 Spike on Viral Infectivity and Antigenicity. Cell. 2020;182(5):1284-94 e9.

136. Kumar V, Singh J, Hasnain SE, Sundar D. Possible Link between Higher Transmissibility of Alpha, Kappa and Delta Variants of SARS-CoV-2 and Increased Structural Stability of Its Spike Protein and hACE2 Affinity. Int J Mol Sci. 2021;22(17).

137. Di Giacomo S, Mercatelli D, Rakhimov A, Giorgi FM. Preliminary report on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Spike mutation T478K. J Med Virol. 2021;93(9):5638-43.

138. Torjesen I. Covid-19: Delta variant is now UK's most dominant strain and spreading through schools. BMJ. 2021;373:n1445.

139. Centers for Disease Prevention and Control. COVID data tracker. Available from: https://covid.cdc.gov/covid-data-tracker/#variant-proportions [Accessed 11 October 2021].

140. World Health Organisation. SARS-CoV-2 Delta variant now dominant in much of European region; efforts must be reinforced to prevent transmission, warns WHO Regional Office for Europe and ECDC. Available from: https://www.euro.who.int/en/media-centre/sections/press-releases/2021/sars-cov-2-delta-variant-now-dominant-in-much-of-european-region-efforts-must-be-reinforced-to-prevent-transmission,-warns-who-regional-office-for-europe-and-ecdc [Accessed 11 October 2021].

141. Li B, Deng A, Li K, Hu Y, Li Z, Xiong Q, et al. Viral infection and transmission in a large, well-traced outbreak caused by the SARS-CoV-2 Delta variant MedRxiv [preprint]. 2021.

142. Teyssou E, Delagreverie H, Visseaux B, Lambert-Niclot S, Brichler S, Ferre V, et al. The Delta SARS-CoV-2 variant has a higher viral load than the Beta and the historical variants in nasopharyngeal samples from newly diagnosed COVID-19 patients. J Infect. 2021;83(4):e1-e3.

143. Kumar A, Asghar A, Raza K, Narayan RK, Jha RK, Satyam A, et al. Demographic characteristics of SARS-CoV-2 B.1.617.2 (Delta) variant infections in Indian population. MedRxiv [preprint]. 2021.

144. Planas D, Veyer D, Baidaliuk A, Staropoli I, Guivel-Benhassine F, Rajah MM, et al. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. Nature. 2021;596(7871):276-80.

145. Sheikh A, McMenamin J, Taylor B, Robertson C, Public Health S, the EIIC. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. Lancet. 2021;397(10293):2461-2.

146. Fisman DN, Tuite AR. Progressive Increase in Virulence of Novel SARS-CoV-2 Variants in Ontario, Canada. MedRxiv [preprint]. 2021.

147. Tada T, Zhou H, Dcosta BM, Samanovic MI, Mulligan MJ, Landau NR. SARS-CoV-2 Lambda Variant Remains Susceptible to Neutralization by mRNA Vaccine-elicited Antibodies and Convalescent Serum. BioRxiv [preprint]. 2021.

148. Acevedo ML, Alonso-Palomares L, Bustamante A, Gaggero A, Paredes F, Cortés CP, et al. Infectivity and immune escape of the new SARS-CoV-2 variant of interest Lambda. MedRxiv [preprint]. 2021.

149. Laiton-Donato K, Franco-Munoz C, Alvarez-Diaz DA, Ruiz-Moreno HA, Usme-Ciro JA, Prada DA, et al. Characterization of the emerging B.1.621 variant of interest of SARS-CoV-2. Infect Genet Evol. 2021;95:105038.

150. Chen J, Gao K, Wang R, Wei GW. Revealing the Threat of Emerging SARS-CoV-2 Mutations to Antibody Therapies. J Mol Biol. 2021;433(18):167155.

151. Padron-Regalado E. Vaccines for SARS-CoV-2: lessons from other coronavirus strains. Infectious diseases and therapy. 2020;9(2):255-74.

152. Amanat F, Krammer F. SARS-CoV-2 vaccines: status report. Immunity. 2020;52(4):583-9.

153. World Health Organisation. Coronavirus disease (COVID-19): Vaccines. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines [Accessed 11 October 2021].

154. World Health Organisation. COVID-19 vaccine tracker and landscape. Available from: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines [Accessed 20 October 2021].

155. COVID-19 Vaccine tracker. COVID-19 Vaccine Tracker - 7 Vaccines Approved for Use by WHO. Available from: https://covid19.trackvaccines.org/agency/who/ [Accessed 21 October 2021].

156. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020;383(27):2603-15.

157. Sahin U, Muik A, Vogler I, Derhovanessian E, Kranz LM, Vormehr M, et al. BNT162b2 vaccine induces neutralizing antibodies and poly-specific T cells in humans. Nature. 2021;595(7868):572-7.

158. Walsh EE, Frenck RW, Jr., Falsey AR, Kitchin N, Absalon J, Gurtman A, et al. Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates. N Engl J Med. 2020;383(25):2439-50.

159. Mukhopadhyay L, Yadav PD, Gupta N, Mohandas S, Patil DY, Shete-Aich A, et al. Comparison of the immunogenicity & protective efficacy of various SARS-CoV-2 vaccine candidates in non-human primates. Indian J Med Res. 2021;153(1 & 2):93-114.

160. Sharma O, Sultan AA, Ding H, Triggle CR. A Review of the Progress and Challenges of Developing a Vaccine for COVID-19. Front Immunol. 2020;11:585354.

161. Ewer KJ, Barrett JR, Belij-Rammerstorfer S, Sharpe H, Makinson R, Morter R, et al. T cell and antibody responses induced by a single dose of ChAdOx1 nCoV-19 (AZD1222) vaccine in a phase 1/2 clinical trial. Nat Med. 2021;27(2):270-8.

162. Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij-Rammerstorfer S, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. Lancet. 2020;396(10249):467-78.

163. World Health Organisation. WHO lists two additional COVID-19 vaccines for emergency use and COVAX roll-out. Available from: https://www.who.int/news/item/15-02-2021-who-lists-two-additional-covid-19-vaccines-for-emergency-use-and-covax-roll-out [Accessed 13 October 2021].

164. Sadoff J, Gray G, Vandebosch A, Cardenas V, Shukarev G, Grinsztejn B, et al. Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19. N Engl J Med. 2021;384(23):2187-201.

165. Alter G, Yu J, Liu J, Chandrashekar A, Borducchi EN, Tostanoski LH, et al. Immunogenicity of Ad26.COV2.S vaccine against SARS-CoV-2 variants in humans. Nature. 2021;596(7871):268-72.

166. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2021;384(5):403-16.

167. Jackson LA, Anderson EJ, Rouphael NG, Roberts PC, Makhene M, Coler RN, et al. An mRNA Vaccine against SARS-CoV-2 - Preliminary Report. N Engl J Med. 2020;383(20):1920-31.

168. Corbett KS, Flynn B, Foulds KE, Francica JR, Boyoglu-Barnum S, Werner AP, et al. Evaluation of the mRNA-1273 Vaccine against SARS-CoV-2 in Nonhuman Primates. N Engl J Med. 2020;383(16):1544-55.

169. Chu L, McPhee R, Huang W, Bennett H, Pajon R, Nestorova B, et al. A preliminary report of a randomized controlled phase 2 trial of the safety and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine. Vaccine. 2021;39(20):2791-9.

170. World Health Organisation. Recommendation for an emergency use listing of COVID-19 vaccine BIBP submitted by Beijing Institute of Biological Products Co., Ltd. 4 June 2021. Available from: who.int [Accessed 13 October 2021].

171. Xia S, Zhang Y, Wang Y, Wang H, Yang Y, Gao GF, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial. Lancet Infect Dis. 2021;21(1):39-51.

172. Valyi-Nagy I, Matula Z, Gonczi M, Tasnady S, Beko G, Reti M, et al. Comparison of antibody and T cell responses elicited by BBIBP-CorV (Sinopharm) and BNT162b2 (Pfizer-BioNTech) vaccines against SARS-CoV-2 in healthy adult humans. Geroscience. 2021.

173. World Health Organisation. Background document on the inactivated vaccine Sinovac-CoronaVac against COVID-19. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-Sinovac-CoronaVac-background-2021.1 [Accessed 13 October 2021].

174. Zhang Y, Zeng G, Pan H, Li C, Hu Y, Chu K, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18-59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infect Dis. 2021;21(2):181-92.

175. Vacharathit V, Aiewsakun P, Manopwisedjaroen S, Srisaowakarn C, Laopanupong T, Ludowyke N, et al. CoronaVac induces lower neutralising activity against variants of concern than natural infection. Lancet Infect Dis. 2021;21(10):1352-4.

176. Shrotri M, Navaratnam AMD, Nguyen V, Byrne T, Geismar C, Fragaszy E, et al. Spike-antibody waning after second dose of BNT162b2 or ChAdOx1. Lancet. 2021;398(10298):385-7.

177. L'Huillier AG, Meyer B, Andrey DO, Arm-Vernez I, Baggio S, Didierlaurent A, et al. Antibody persistence in the first 6 months following SARS-CoV-2 infection among hospital workers: a prospective longitudinal study. Clin Microbiol Infect. 2021.

178. Post N, Eddy D, Huntley C, van Schalkwyk MCI, Shrotri M, Leeman D, et al. Antibody response to SARS-CoV-2 infection in humans: A systematic review. PLoS One. 2020;15(12):e0244126.

179. Chemaitelly H, Tang P, Hasan MR, AlMukdad S, Yassine HM, Benslimane FM, et al. Waning of BNT162b2 Vaccine Protection against SARS-CoV-2 Infection in Qatar. N Engl J Med. 2021.

180. Mizrahi B, Lotan R, Kalkstein N, Peretz A, Perez G, Ben-Tov A, et al. Correlation of SARS-CoV-2 Breakthrough Infections to Time-from-vaccine; Preliminary Study. MedRxiv [preprint]. 2021.

181. Thomas SJ, Moreira ED, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Six Month Safety and Efficacy of the BNT162b2 mRNA COVID-19 Vaccine. MedRxiv [preprint]. 2021.

182. Tre-Hardy M, Cupaiolo R, Wilmet A, Antoine-Moussiaux T, Della Vecchia A, Horeanga A, et al. Six-month interim analysis of ongoing immunogenicity surveillance of the mRNA-1273 vaccine in healthcare workers: A third dose is expected. J Infect. 2021.

183. Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Kalkstein N, et al. Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel. N Engl J Med. 2021;385(15):1393-400.

184. Pan H, Wu Q, Zeng G, Yang J, Jiang D, Deng X, et al. Immunogenicity and safety of a third dose, and immune persistence of CoronaVac vaccine in healthy adults aged 18-59 years: interim results from a double-blind, randomized, placebo-controlled phase 2 clinical trial MedRxiv [preprint]. 2021.

185. Choi A, Koch M, Wu K, Chu L, Ma L, Hill A, et al. Safety and immunogenicity of SARS-CoV-2 variant mRNA vaccine boosters in healthy adults: an interim analysis. Nat Med. 2021.

186. Flaxman A, Marchevsky N, Jenkin D, Aboagye J, Aley PK, Angus BJ, et al. Tolerability and immunogenicity after a late second dose or a third dose of ChAdOx1 nCoV-19 (AZD1222). Preprints with the Lancet [Preprint]. 28 Jun 2021.

187. Iketani S, Liu L, Nair MS, Mohri H, Wang M, Huang Y, et al. A third COVID-19 vaccine shot markedly boosts neutralizing antibody potency and breadth MedRxiv [preprint]. 2021.

188. Schmidt T, Klemis V, Schub D, Mihm J, Hielscher F, Marx S, et al. Immunogenicity and reactogenicity of a heterologous COVID-19 prime-boost vaccination compared with homologous vaccine regimens MedRxiv [preprint]. 2021.

189. Borobia AM, Carcas AJ, Perez-Olmeda M, Castano L, Bertran MJ, Garcia-Perez J, et al. Immunogenicity and reactogenicity of BNT162b2 booster in ChAdOx1-S-primed participants (CombiVacS): a multicentre, open-label, randomised, controlled, phase 2 trial. Lancet. 2021;398(10295):121-30.

190. Centres for Disease Control and Prevention. Pandemic Influenza. Available from: https://www.cdc.gov/flu/pandemic-resources/1918-pandemic-h1n1.html [Accessed 21 October 2021].191. Peeri NC, Shrestha N, Rahman MS, Zaki R, Tan Z, Bibi S, et al. The SARS, MERS and novel coronavirus (COVID-19) epidemics, the newest and biggest global health threats: what lessons have we learned? Int J Epidemiol. 2020;49(3):717-26.

192. Cohen J, Rodgers YVM. Contributing factors to personal protective equipment shortages during the COVID-19 pandemic. Prev Med. 2020;141:106263.

193. Chadeau-Hyam M, Bodinier B, Elliott J, Whitaker MD, Tzoulaki I, Vermeulen R, et al. Risk factors for positive and negative COVID-19 tests: a cautious and in-depth analysis of UK biobank data. Int J Epidemiol. 2020;49(5):1454-67.

194. Patel JA, Nielsen FBH, Badiani AA, Assi S, Unadkat VA, Patel B, et al. Poverty, inequality and COVID-19: the forgotten vulnerable. Public Health. 2020;183:110-1.

195. Marcus Shepheard, Emma Norris, gov.uk Institue for Government. The coronavirus inquiry - The case for an investigation of government actions during the Covid pandemic. https://www.instituteforgovernment.org.uk/publications/coronavirus-inquiry [Accessed 21 October 2021].

196. Townsend JP, Hassler HB, Wang Z, Miura S, Singh J, Kumar S, et al. The durability of immunity against reinfection by SARS-CoV-2: a comparative evolutionary study. Lancet Microbe. 2021.

197. Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. N Engl J Med. 2021;384(15):1412-23.

98. Lopez Bernal J, Andrews N, Gower C, Gallagher E, Simmons R, Thelwall S, et al. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. N Engl J Med. 2021;385(7):585-94.

199. Abu-Raddad LJ, Chemaitelly H, Butt AA, National Study Group for C-V. Effectiveness of the BNT162b2 Covid-19 Vaccine against the B.1.1.7 and B.1.351 Variants. N Engl J Med. 2021;385(2):187-9.

200. Chung H, He S, Nasreen S, Sundaram ME, Buchan SA, Wilson SE, et al. Effectiveness of BNT162b2 and mRNA-1273 covid-19 vaccines against symptomatic SARS-CoV-2 infection and severe covid-19 outcomes in Ontario, Canada: test negative design study. BMJ. 2021;374:n1943.

201. Nasreen S, Chung H, He S, Brown KA, Gubbay JB, Buchan SA, et al. Effectiveness of mRNA and ChAdOx1 COVID-19 vaccines against symptomatic SARS CoV-2 infection and severe outcomes with variants of concern in Ontario. MedRxiv [preprint]. 2021.

202. Puranik A, Lenehan PJ, Silvert E, Niesen MJM, Corchado-Garcia J, O'Horo JC, et al. Comparison of two highly-effective mRNA vaccines for COVID-19 during periods of Alpha and Delta variant prevalence. MedRxiv [preprint]. 2021.

203. Julia Stowe, Nick Andrews, Charlotte Gower, Eileen Gallagher, Lara Utsi, Ruth Simmons, et al. Effectiveness of COVID-19 vaccines against hospital admission with the Delta (B.1.617.2) variant. Public Health England [preprint]. 2021.

204. Lopez Bernal J, Andrews N, Gower C, Robertson C, Stowe J, Tessier E, et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. BMJ. 2021;373:n1088.

205. Skowronski DM, Setayeshgar S, Zou M, Prystajecky N, Tyson JR, Galanis E, et al. Single-dose mRNA vaccine effectiveness against SARS-CoV-2, including Alpha and Gamma variants: a test-negative design in adults 70 years and older in British Columbia, Canada. Clin Infect Dis. 2021.

206. Carazo S, Talbot D, Boulianne N, Brisson M, Gilca R, Deceuninck G, et al. Single-dose mRNA vaccine effectiveness against SARS-CoV-2 in healthcare workers extending 16 weeks post-vaccination: a test-negative design from Quebec, Canada. Clin Infect Dis. 2021.

207. Charmet T, Schaeffer L, Grant R, Galmiche S, Cheny O, Von Platen C, et al. Impact of original, B.1.1.7, and B.1.351/P.1 SARS-CoV-2 lineages on vaccine effectiveness of two doses of COVID-19 mRNA vaccines: Results from a nationwide case-control study in France. Lancet Reg Health Eur. 2021;8:100171.

208. Tang P, Hasan MR, Chemaitelly H, Yassine HM, Benslimane FM, Khatib HAA, et al. BNT162b2 and mRNA-1273 COVID-19 vaccine effectiveness against the Delta (B.1.617.2) variant in Qatar. MedRxiv [preprint]. 2021.

209. Hall VJ, Foulkes S, Saei A, Andrews N, Oguti B, Charlett A, et al. COVID-19 vaccine coverage in health-care workers in England and effectiveness of BNT162b2 mRNA vaccine against infection (SIREN): a prospective, multicentre, cohort study. Lancet. 2021;397(10286):1725-35.

210. Haas EJ, Angulo FJ, McLaughlin JM, Anis E, Singer SR, Khan F, et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. Lancet. 2021;397(10287):1819-29.

211. Nanduri S, Pilishvili T, Derado G, Soe MM, Dollard P, Wu H, et al. Effectiveness of Pfizer-BioNTech and Moderna Vaccines in Preventing SARS-CoV-2 Infection Among Nursing Home Residents Before and During Widespread Circulation of the SARS-CoV-2 B.1.617.2 (Delta) Variant - National Healthcare Safety Network, March 1-August 1, 2021. MMWR Morb Mortal Wkly Rep. 2021;70(34):1163-6.

212. Fowlkes A, Gaglani M, Groover K, Thiese MS, Tyner H, Ellingson K, et al. Effectiveness of COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Frontline Workers Before and During B.1.617.2 (Delta) Variant Predominance - Eight U.S. Locations, December 2020-August 2021. MMWR Morb Mortal Wkly Rep. 2021;70(34):1167-9.

213. Lefevre B, Tondeur L, Madec Y, Grant R, Lina B, van der Werf S, et al. Beta SARS-CoV-2 variant and BNT162b2 vaccine effectiveness in long-term care facilities in France. Lancet Healthy Longev. 2021.

214. Pouwels KB, Pritchard E, Matthews PC, Stoesser N, Eyre DW, Vihta K-D, et al. Effect of Delta variant on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK. Nature Medicine. 2021.

215. Williams C, Al-Bargash D, Macalintal C, Stuart R, Seth A, Latham J, et al. COVID-19 Outbreak Associated with a SARS-CoV-2 P.1 Lineage in a Long-Term Care Home after Implementation of a Vaccination Program - Ontario, April-May 2021. Clin Infect Dis. 2021.

216. Emary KRW, Golubchik T, Aley PK, Ariani CV, Angus B, Bibi S, et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B.1.1.7): an exploratory analysis of a randomised controlled trial. Lancet. 2021;397(10282):1351-62.

217. AstraZeneca. AZD1222 US Phase III trial met primary efficacy endpoint in preventing COVID-19 at interim analysis. Available from: https://www.astrazeneca.com/media-centre/press-releases/2021/astrazeneca-us-vaccine-trial-met-primary-endpoint.html [Accessed 15 October 2021].

218. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet. 2021;397(10269):99-111.

219. Madhi SA, Baillie V, Cutland CL, Voysey M, Koen AL, Fairlie L, et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant. N Engl J Med. 2021;384(20):1885-98.

220. Pramod S, Govindan D, Ramasubramani P, Kar SS, Aggarwal R, Manoharan N, et al. Effectiveness of Covishield vaccine in preventing Covid-19 – A test-negative case control study. MedRxiv [preprint]. 2021.

221. Ranzani OT, dos Santos Leite R, Castilho LD, Gonçalves CCM, Resende G, de Melo RL, et al. Vaccine effectiveness of Ad26.COV2.S against symptomatic COVID-19 and clinical outcomes in Brazil: a test-negative study design. MedRxiv [preprint]. 18 October 2021.

222. Corchado-Garcia J, Puyraimond-Zemmour D, Hughes T, Cristea-Platon T, Lenehan P, Pawlowski C, et al. Real-world effectiveness of Ad26.COV2.S adenoviral vector vaccine for COVID-19. MedRxiv [preprint]. 2021.

223. Barlow RS, Jian K, Larson L. Effectiveness of COVID-19 Vaccines Against SARS-CoV-2 Infection During a Delta Variant Epidemic Surge in Multnomah County, Oregon, July 2021. MedRxiv [preprint]. 2021.

224. Polinski JM, Weckstein AR, Batech M, Kabelac C, Kamath T, Harvey R, et al. Effectiveness of the Single-Dose Ad26.COV2.S COVID Vaccine. MedRxiv [preprint]. 2021.

225. Li XN, Huang Y, Wang W, Jing QL, Zhang CH, Qin PZ, et al. Effectiveness of inactivated SARS-CoV-2 vaccines against the Delta variant infection in Guangzhou: a test-negative case-control real-world study. Emerg Microbes Infect. 2021;10(1):1751-9.

226. Jara A, Undurraga EA, Gonzalez C, Paredes F, Fontecilla T, Jara G, et al. Effectiveness of an Inactivated SARS-CoV-2 Vaccine in Chile. N Engl J Med. 2021;385(10):875-84.

227. Ranzani OT, Hitchings MDT, Dorion M, D'Agostini TL, de Paula RC, de Paula OFP, et al. Effectiveness of the CoronaVac vaccine in older adults during a gamma variant associated epidemic of covid-19 in Brazil: test negative case-control study. BMJ. 2021;374:n2015.

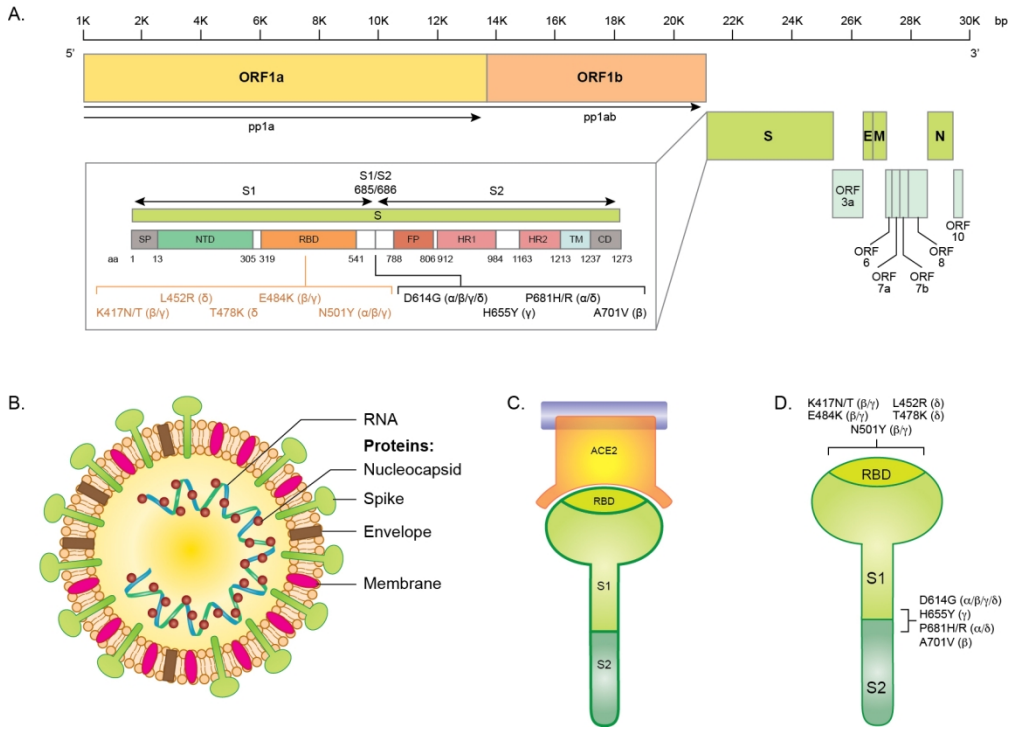

Figure 1: Genome and structure of SARS-CoV-2.

150x109mm (300 x 300 DPI)

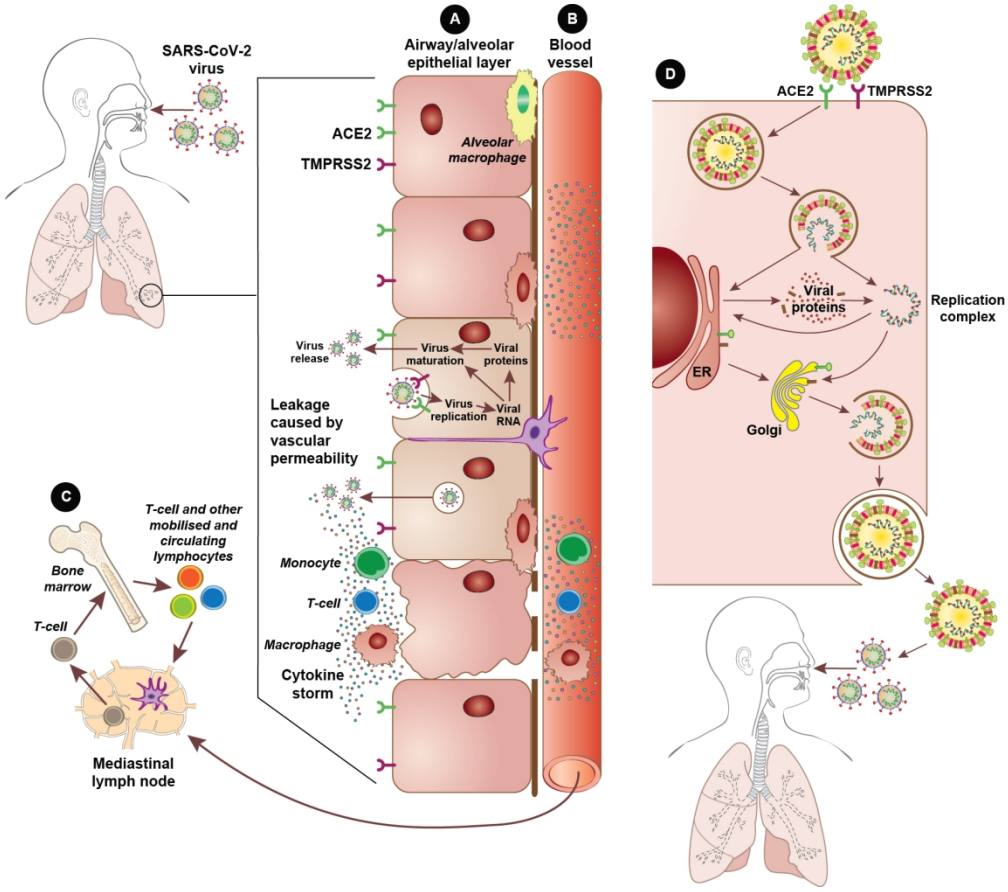

Figure 2: Viral entry and host response.

153x135mm (300 x 300 DPI)

Variants of concern			
WHO nomenclature or designation	**Pango Lineage**	**S protein mutations of interest**	**First detected samples ***
Alpha	B.1.1.7	N501Y D614G P681H	UK, Sept 2020
Beta	B.1.351	K417N E484K N501Y D614G A701V	South Africa, May 2020
Gamma	P.1	K417T E484K N501Y D614G H655Y	Brazil, Nov 2020
Delta	B.1.617.2	L452R T478K D614G P681R	India, Oct 2020
Variants of Interest			
WHO nomenclature or designation	**Pango Lineage**	**S protein mutations of interest**	**First detected samples ***
Lambda	C.37	L452Q F490S D614G	Peru, Dec 2020
Mu	B.1.621	R346K E484K N501Y D614G P681H	Columbia, Jan 2021
Variants under monitoring			
Pango Lineage (WHO nomenclature)		**S protein mutations of interest**	**First detected samples ***
R.1		E484K D614G W152L G769V	Multiple countries, Jan 2021
B.1.466.2		N439K D614G P681R	Indonesia, Nov 2020
B.1.1.318		E484K D614G P681H	Multiple countries, Jan 2021
B.1.1.519		T478K D614G	Multiple countries, Nov 2020
C.36.3		R346S L452R D614G Q677H A899S	Multiple countries, Jan 2021
B.1.214.2		Q414K N450K D614G ins214TDR	Multiple countries, Nov 2020
B.1.427, B.1.429 (Epsilon)		L452R D614G	USA, Mar 2020
B.1.1.523		E484K S494P D614G E780A	Multiple countries, May 2020
B.1.620		S477N E484K D614G P681H	Multiple countries, Nov 2020
C.1.2		D614G E484K H655Y N501Y N679K Y449H	South Africa, May 2021
B.1.617.1 (Kappa)		L452R E484Q D614G P681R	India, Oct 2020
B.1.526 (Iota)		E484K D614G A701V	USA, Nov 2020
B.1.525 (Eta)		E484K D614G Q677H	Multiple countries, Dec 2020
B.1.630		E484K L452R S477N P681H	Dominican Republic, Mar 2021

Vaccine and vaccine type	Recommended dose and administration	Study	Study type	N	Vaccine effectiveness % (95% confidence interval) *		
					Against	One dose	Two doses
Pfizer/BioNtech (BNT162b2) – mRNA.	Two doses (30µg, 0.3ml each) intramuscularly (deltoid) with a recommended interval of 21-28 days between doses.	(156)	Placebo-controlled clinical trial	37,706	Symptomatic infection		95% (90.3–97.6%)
		(197)	Observational	1,193,236	Documented infection	46% (40-51%)	92% (88-95%)
					Symptomatic infection	57% (50-63%)	94% (87-98%)
					Hospitalisation	74% (56-86%)	87% (55-100%)
					Severe disease	62% (39-80%)	92% (75-100%)
		(198)	Test-negative case-control	19,109	Infection with Alpha	47.5% (41.6–52.8%)	93.7% (91.6–95.3%)
					Infection with Delta	35.6% (22.7–46.4%)	88.0% (85.3–90.1%)
		(199)	Test-negative case-control	213,758	Infection with Beta		75.0% (70.5-78.9%)
					Infection with Alpha or Beta		97.4% (92.2-99.5%)
		(200)	Test-negative case-control	324,033	Symptomatic infection	14-20 days: 48% (41-54%)	≥7 days: 91% (89-93%)
						≥14 days: 60% (57-64%)	
						35-41 days: 71% (63-78%)	
					Hospital admission or death	14-20 days: 62% (44-75%)	≥7 days: 98% (88-100%)
						≥14 days: 70% (60-77%)	
						≥35 days: 91% (73-97%)	
				[NOTE: Participants in this study received an mRNA vaccine (either BNT162b2 or mRNA-1273)]			
		(201)	Test-negative case-control	682,071	Symptomatic infection - ≥14 days - Alpha	66% (95% CI: 64-68%)	
					Symptomatic infection - ≥14 days – Beta or Gamma variants	60% (52-67%)	
					Symptomatic infection - ≥14 days – Delta	56% (45-64%)	
					Symptomatic infection - ≥7 days – Alpha		89% (86–91%)
					Symptomatic infection - ≥7 days – Beta or Gamma		84% (69–92%)
					Symptomatic infection - ≥7 days – Delta		87% (64–95%)
					Against hospitalisation or death - ≥14 days – Alpha	80% (78-82%)	
					Against hospitalisation or death - ≥14 days – Beta or Gamma	77% (69-83%)	
					Against hospitalisation or death - ≥14 days – Delta	78% (65-86%)	
					Against hospitalisation or death - ≥7 days – Alpha		95% (92-97%)
					Against hospitalisation or death - ≥7 days – Beta or Gamma		95% (81-99%)
		(202)	Retrospective case-control	119,463	Infection		≥14 days: 86% (81-90.6%)
					Hospitalisation		≥14 days: 85% (73-93%)
					Admission to an ICU		≥14 days: 87% (46-98.6%)

		(145)	Test-negative observational	400,827	Infection with Alpha variant		92% (90–93%)
					Infection with Delta variant		79% (75-82%)
		(203)	Test-negative case-control	14,019	Hospitalisation with Alpha variant	83% (62-93%)	95% (78-99%)
					Hospitalisation with Delta variant	94% (46-99%)	96% (86-99%)
		(181)	Placebo-controlled pivotal efficacy trial	44,047	Infection		91.1% (88.8-93.0%)
		(11)	Test-negative case-control	156,930	Infection		10-13 days: 70% (59-78%)
							≥14 days: 89% (85-93%)
							28-34 days: 61% (51-69%)
		(205)	Test-negative case-control	16,993	Infection	0-13 days: 14% (0-26%)	
						14-20 days: 43% (30-53%)	
						35-41 days: 75% (63-83%)	
					Infection - ≥21 days postvaccination		65% (58-71%)
					Infection - non-VOC		72% (58-81%)
					Infection - Alpha		67% (57-75%)
					Infection - Gamma		61% (45-72%)
		(206)	Test-negative case-control	5,8476	Infection	≥14 days: 70.3% (68.1-72.4%)	≥7 days: 85.5% (80.4-89.3%)
		(207)	Case-control	67,760	Infection - ≥7 days		88% (81-92%)
					Infection - ≥7 days - Alpha		86% (81-90%)
					Infection - ≥7 days - Beta/Gamma		77% (63-86%)
		(208)	Test-negative case-control	1 dose: 906,078 2 doses: 877,354	Infection - ≥14 days – Delta	65.5% (40.9-79.9%)	59.6% (50.7-66.9%)
					Severe disease or death - Delta		97.3% (84.4-99.5%)
		(179)	Test-negative case-control	1 dose: 947,035 2 doses: 907,763	Symptomatic infection	0-13 days: -5.5% (-12.9-1.4%)	
						≥14 days: 47.9% (43.6-51.9%)	
						1 month: 81.5% (79.9-83.0%)	
						2 months: 72.5% (69.6-75.1%)	
						3 months: 70.6% (66.4-74.3%)	
						4 months: 57.0% (48.6-64.0%)	
						5 months: 12.0% (-6.1-27.1%)	
						6 months: 12.8% (-9.1-30.3%)	
						≥7 months: 27.8% (-1.4-48.7%)	
					Hospitalisation and death	0-13 days: 7.5% (−11.9-23.6%)	
						≥14 days: 65.0% (55.0-72.8%)	
						1 month: 95.9% (93.6-97.3%)	
						2 months: 96.3% (92.9-98.0%)	
						3 months: 93.4% (87.5-96.5%)	

						4 months: 80.8% (56.9-91.4%)	
						6 months: 81.8% (18.5-95.9%)	
						≥7 months: 44.1% (-86.5-83.3%)	
		(209)	Prospective cohort	23,324	Infection	≥21 days: 70% (55-85%)	≥7 days: 85% (74-96%)
		(210)	Observational	186,109	Infection		≥7 days: 95.3% (94.9-95.7%)
					Asymptomatic infection		≥7 days: 91.5% (90.7-92.2%)
					Symptomatic infection		≥7 days: 97.0% (96.7-97.2%)
					Hospitalisation		≥7 days: 97.2% (96.8-97.5%)
					Severe or critical infection		≥7 days: 97.5% (97.1-97.8%)
					Death		≥7 days: 96.7% (96.0-97.3%)
		(211)	Observational	10,428,783	Infection – Pre-Delta period		≥14 days: 74.2% (68.9-78.7%)
					Infection – Intermediate period		≥14 days: 66.5% (58.3-73.1%)
					Infection – Delta		≥14 days: 52.4% (48.0-56.4%)
		(212)	Observational	Delta: 2,840 Pre-Delta: 7,012	Infection – Delta		14–119 days: 85% (68-93%)
							120–149 days: 81% (34-95%)
							≥150 days: 73% (49-86%)
					Infection – Pre-Delta		91% (81-96%)
				[NOTE only 65% of participants in this study received BNT162b2 (33% received mRNA-1273, and 2% received Ad26.COV2.S]			
		(213)	Observational	378	Infection – Beta		≥7 days: 49% (14-69%)
					Severe disease		≥7 days: 86% (67-94%)
		(214)	Observational	384,543	Infection – Alpha	≥21 days: 59% (52-65%)	
					Infection – Delta	≥21 days: 57% (50-63%)	
					Infection – Alpha		0-13 days: 77% (66-84%)
							≥14 days: 78% (68-84%)
					Infection – Delta		0-13 days: 82% (75-87%)
							≥14 days: 80% (77-83%)
		(215)	Observational	224	Infection		66.2% (2.3-88.3%)
					Symptomatic infection		25.6% (-157.8-78.5%)
Oxford University/ AstraZeneca (AZD1222) - Non-replicating adenovirus viral vector.	Two doses (0.5ml each) intramuscularly (deltoid) with a recommended interval window of 8 to 12 weeks.	(198)	Test-negative case-control	19,109	Infection - Alpha	48.7% (45.2–51.9%)	74.5% (68.4–79.4%)
					Infection - Delta	30.0% (24.3–35.3%)	67.0% (61.3–71.8%)
		(201)	Test-negative case-control	682,071	Symptomatic infection - Alpha	64% (60-68%)	
					Symptomatic infection – Beta or Gamma	48% (28-63%)	
					Symptomatic infection - Delta	67% (44-80%)	
					Hospitalisation or death - Alpha	85% (81-88%)	
					Hospitalisation or death – Bet or Gamma	83% (66-92%)	
					Hospitalisation or death - Delta	88% (60-96%)	
		(145)	Test-negative observational	462,755	Infection with Alpha variant		73% (66-78%)
					Infection with Delta variant		60% (53-66%)

		(216)	Randomised controlled trial	8,534	Symptomatic infection – Alpha		70.4% (43.6-84%%)
					Symptomatic infection – non-Alpha		81.5% (67.9-89.4%)
		(217)	Randomised controlled trial	32,449	Symptomatic infection		79%
					Severe disease or hospitalisation		100%
		(203)	Test-negative case-control	14,019	Hospitalisation – Alpha	76% (61-85%)	86% (53-96%)
					Hospitalisation – Delta	71% (51-83%)	92% (75-97%)
		(218)	Randomised controlled trial	11,636	Infection		62.1% (41.0-75.7%)
		(219)	Randomised controlled trial	2,026	Symptomatic infection		21.9% (-49.9-59.8%)
					Symptomatic infection - Beta		10.4% (-76.8-54.8%)
		(204)	Test-negative case-control	156,930	Symptomatic infection		28-34 days: 60% (41-73%)
							≥35 days: 73% (27-90%)
		(214)	Observational	384,543	Infection - Alpha	≥21 days: 63% (55–69%)	0-13 days: 72% (50-84%)
							≥14 days: 79% (56–90%)
					Infection Delta	≥21 days: 46% (35–55%)	0-13 days: 71% (64–77%)
							≥14 days: 67% (62–71%)
		(220)	Test-negative case-control	720	Infection	49% (17-68%)	54% (27-71%)
					Symptomatic infection	58% (28-75%)	64% (38-78%)
					Moderately severe disease	Any dosage >3 weeks ago: 95% (44-100%)	
Johnson & Johnson (Ad26.COV2.S) - Recombinant, replication-incompetent adenovirus serotype 26 (Ad26) vector.	One dose (0.5ml) intramuscularly (deltoid).	(164)	Randomised controlled trial	39,321	Moderate to severe-critical infection	≥14 days: 66.9% (59.0-73.4%)	
						≥28 days: 66.1% (55.0-74.8%)	
					Severe-critical infection	≥14 days: 76.7% (54.6-89.1%)	
						≥28 days: 85.4% (54.2-96.9%)	
		(221)	Test-negative case-control	11,817	Symptomatic infection	14-27 days: 27.4% (8.7-42.7%)	
						≥28 days: 50.9% (35.5-63.0%)	
					Hospitalisation	14-27 days: 33.5% (-29.1-69.8%)	
						≥28 days: 72.9% (35.1-91.1%)	
					Admission to an ICU	14-27 days: 56.0% (-52.8-93.1%)	
						≥28 days: 92.5% (54.9-99.6%)	
					Mechanical ventilation	14-27 days: 65.2% (-74.7-98.1%)	
						≥28 days: 88.7% (17.9-99.5%)	
					Death	14-27 days: 48.9% (-92.3-92.5%)	
						≥28 days: 90.5% (31.5-99.6%)	
		(222)	Retrospective case-control	126,572	Symptomatic infection	≥1 day: 50.6% (14.0-74.0%)	
						≥8 days: 65.5% (23.3-87.5%)	
						≥15 days: 76.7% (30.3-95.3%)	

		(223)	Test-negative case-control	1,000	Symptomatic infection	51% (95% CI: -2-76%)	
		(212)	Observational	Delta: 2,840 Pre-Delta: 7,012	Infection – Delta	14–119 days: 85% (68-93%)	
						120–149 days: 81% (34-95%)	
						≥150 days: 73% (49-86%)	
					Infection – Pre-Delta	91% (81-96%)	
				[NOTE: 2% of study participants received Ad26.COV2.S (65% received BNT162b2, and 33% received mRNA-1273)]			
		(224)	Cohort	1,914,670	Infection	79% (77-80%)	
					Hospitalisation	81% (79-84%)	
Moderna (mRNA-1273) - mRNA	Two doses (100µg, 0.5ml each) intramuscularly (deltoid) with a recommended interval of 28 days between doses.	(201)			Symptomatic infection – Alpha	≥14 days: 83% (80-86%)	≥7 days: 92% (86-96%)
					Symptomatic infection – Beta or Gamma	≥14 days: 77% (63-86%)	
					Symptomatic infection – Delta	≥14 days: 72% (57-82%)	
					Hospitalisation - Alpha	≥14 days: 79% (74-83%)	≥7 days: 94% (89-97%)
					Hospitalisation – Beta or Gamma	≥14 days: 89% (73-95%)	
					Hospitalisation - Delta	≥14 days: 96% (72-99%)	
		(202)	Retrospective case-control	60,083	Infection		≥14 days: 86% (81-90.6%)
					Hospitalisation		≥14 days: 91.6% (81-97%)
					Admission to an ICU		≥14 days: 93.3% (57-99.8%)
		(206)	Test-negative case-control	5,8476	Infection	≥14 days: 68.7% (59.5-75.9%)	≥7 days: 84.1% (34.9-96.1%)
		(208)	Test-negative case-control	1 dose: 490,828 2 doses: 409,041	Infection - Delta	≥14 days: 79.7% (60.8-89.5%)	≥14 days: 86.1% (78.0-91.3%)
		(211)	Observational	10,428,783	Infection – Pre-Delta period		≥14 days: 74.7% (66.2-81.1%)
					Infection – Intermediate period		≥14 days: 70.4% (60.1-78.0%)
					Infection – Delta		≥14 days: 50.6% (45.0-55.7%)
		(212)	Observational	Delta: 2,840 Pre-Delta: 7,012	Infection – Delta		14–119 days: 85% (68-93%)
							120–149 days: 81% (34-95%)
							≥150 days: 73% (49-86%)
					Infection – Pre-Delta		91% (81-96%)
				[NOTE: 33% of study participants received mRNA-1273 (2% received Ad26.COV2.S, and 65% received BNT162b2)]			
		(214)	Observational	384,543	Infection - Delta	75% (64-83%)	
		(215)	Observational	124	Infection		52.5% (26.9-69.1%)
					Symptomatic infection		65.6% (33.8-82.1%)
					Severe infection		78.6% (47.9-91.2%)
Sinopharm BBIBP-CorV - Aluminium-	Two doses (0.5ml) intramuscularly (deltoid) with a	(225)	Test-negative case-control	366	Infection	13.8% (-60.2-54.8%)	59.0% (16.0-81.6%)
					Moderately severe infection		70.2% (29.6-89.3%)
				[NOTE: 27.5% of study participants were vaccinated with Sinopharm BIBP (61.3% received CoronaVac)]			

hydroxide-adjuvanted, inactivated whole virus vaccine	recommended interval of 3 weeks between doses.						
Sinovac-CoronaVac - Aluminium-hydroxide-adjuvanted, inactivated whole virus vaccine	Two doses (0.5ml) intramuscularly (deltoid) with a recommended interval window of 2 to 4 weeks.	(225)	Test-negative case-control	366	Infection	13.8% (-60.2-54.8%)	59.0% (16.0-81.6%)
					Moderately severe infection		70.2% (29.6-89.3%)
					[NOTE: 61.3% of study participants were vaccinated with CoronaVac (27.5% recieved Sinopharm BIBP)]		
		(226)	Observational	10,187,720	Infection	17.2% (15.8–18.6%)	63.7% (62.8–64.6%)
					Hospitalisation	40.3% (37.6–42.8%)	86.5% (85.6–87.4%)
					Admission to an ICU	45.3% (41.2–49.2%)	90.2% (88.9–91.4%)
					Death	46.0% (40.7–50.8%)	86.7% (84.9–88.3%)
		(227)	Test-negative case-control	43,774	Symptomatic infection - Gamma	0-13 days: −0.8% (−9.4 to 7.2%)	0-13 days: 24.7% (14.7 to 33.4%)
						≥14 days: 12.5% (3.7 to 20.6%)	≥14 days: 46.8% (38.7 to 53.8%)
					Hospitalisation - Gamma	0-13 days: 6.6% (−4.3 to 16.3%)	0-13 days: 39.1% (28.0 to 48.5%)
						≥14 days: 16.9% (5.7 to 26.8%)	≥14 days: 55.5% (46.5 to 62.9%)
					Death - Gamma	0-13 days: 13.1% (−1.5 to 25.6%)	0-13 days: 48.9% (34.4 to 60.1%)
						≥14 days: 31.2% (17.6 to 42.5%)	≥14 days: 61.2% (48.9 to 70.5%)

Vaccine type	Vaccine	Company	Countries approved for use in	Clinical trials
Inactivated virus	**Covaxin**	Bharat Biotech (Hyderabad, India)	***9 countries:*** Guyana, India, Iran, Mauritius, Mexico, Nepal, Paraguay, Philippines, Zimbabwe	Phase 1: NCT04471519 (India). CTRI/2020/09/027674 (India). Phase 2: CTRI/2020/07/026300, NCT04471519 (India). CTRI/2020/09/027674 (India). NCT04918797 (India). Phase 3: CTRI/2020/11/028976, NCT04641481 (India). NCT04918797 (India).
	KoviVac	Chumakov Center (Moscow, Russia)	***1 county:*** Russian Federation	Phase 1: 502 (Russian Federation) Phase 2: 502 (Russian Federation)
	QazVac	Kazakhstan Research Institute for Biological Safety Problems (RIBSP) (Kazakhstan)	***2 countries:*** Kazakhstan, Kyrgyzstan	Phase 1: NCT04530357 (Kazakhstan) Phase 2: NCT04530357 (Kazakhstan) Phase 3: NCT04691908 (Kazakhstan)
	SARS-CoV-2 Vaccine (Vero Cells)	Minhai Biotechnology Co. (Beijing, China)	***1 country:*** China	Phase 1: NCT05003479 (China). ChiCTR2000038804, NCT04758273 (China). Phase 2: ChiCTR2000039462, NCT04756323 (China). NCT05003466 (China). Phase 3: NCT04852705
	COVID-19 Inactivated Vaccine	Shifa Pharmed Industrial Co. (Tehran, Iran)	***1 country:*** Iran	Phase 1: IRCT20201202049567N1 (Iran). IRCT20201202049567N2 (Iran). Phase 2: IRCT20201202049567N3 (Iran). Phase 3: IRCT20201202049567N3 (Iran).
	Inactivated (Vero Cells)	Sinopharm (Wuhan, China)	***2 countries:*** China, Philippines	Phase 1: ChiCTR2000031809 (China) Phase 2: NCT04885764 (Egypt). ChiCTR2000031809 (China). Phase 3: NCT04885764 (Egypt). ChiCTR2000034780 (United Arab Emirates). NCT04612972 (Peru). NCT04510207 (Bahrain, Egypt, Jordan, United Arab Emirates). ChiCTR2000039000 (Morocco).
Non-replicating viral vector	**Ad5-nCoV**	CanSino (Tianjin, China)	***9 countries:*** Argentina, Chile, China, Ecuador, Hungary, Indonesia, Malaysia, Mexico, Pakistan	Phase 1: NCT05043259 (China). ChiCTR2000030906, NCT04313127 (China). NCT04568811 (China). NCT04840992 (China). Phase 2: NCT05043259 (China). NCT04840992 (China).

				ChiCTR2000031781, NCT04341389 (China). NCT04566770 (China). NCT05005156 (Argentina). Phase 3: NCT04526990 (Argentina, Chile, Mexico, Pakistan, Russian Federation). NCT04540419 (Russian Federation).
	Sputnik Light	Gamaleya Research Institute of Epidemiology and Microbiology (Moscow, Russia)	***18 countries:*** Angola, Armenia, Bahrain, Belarus, Egypt, Iran, Kazakhstan, Kyrgyzstan, Mauritius, Mongolia, Nicaragua, Philippines, Republic of the Congo, Russian Federation, United Arab Emirates, United Republic of Tanzania, Venezuela, West Bank	Phase 1: NCT04713488 (Russian Federation). Phase 2: NCT04713488 (Russian Federation). NCT05027672 (Argentina). Phase 3: NCT04741061 (Russian Federation).
	Sputnik V	Gamaleya Research Institute of Epidemiology and Microbiology (Moscow, Russia)	***72 countries:*** Albania, Algeria, Angola, Antigua and Barbuda, Argentina, Armenia, Azerbaijan, Bahrain, Bangladesh, Belarus, Bolivia, Bosnia and Herzegovina, Brazil, Cameroon, Chile, Djibouti, Ecuador, Egypt, Gabon, Ghana, Guatemala, Guinea, Guyana, Honduras, Hungary, India, Indonesia, Iran, Iraq, Jordan, Kazakhstan, Kenya, Kyrgyzstan, Lao People's Democratic Republic, Lebanon, Libya, Maldives, Mali, Mauritius, Mexico, Mongolia, Montenegro, Morocco, Myanmar, Namibia, Nepal, Nicaragua, Nigeria, North Macedonia, Oman, Pakistan, Panama, Paraguay, Philippines, Republic of Moldova, Republic of the Congo, Russian Federation, Saint Vincent and the Grenadines, San Marino, Serbia, Seychelles, Sri Lanka, Syrian Arab Republic, Tunisia, Turkey, Turkmenistan, United Arab Emirates, Uzbekistan, Venezuela, Vietnam, West Bank, Zimbabwe	Phase 1: NCT04760730 (United Arab Emirates). NCT04684446 (Belarus, Russian Federation). NCT04436471, 241 (Russian Federation). NCT04437875 (Russian Federation). Phase 2: NCT05027672 (Argentina). NCT04988048 (Argentina). NCT04954092 (Russian Federation). NCT04962906 (Argentina). NCT04983537 (Argentina). NCT04760730 (United Arab Emirates). NCT04684446 (Belarus, Russian Federation). NCT04686773 (Azerbaijan). NCT04436471, 241 (Russian Federation). NCT04437875 (Russian Federation). NCT04587219 (Russian Federation). NCT04640233 (India). Phase 3: NCT04564716 (Belarus). NCT04530396 (Russian Federation). NCT04642339 (Venezuela). NCT04656613 (United Arab Emirates). NCT04954092 (Russian Federation). NCT04640233 (India).
RNA	**TAK-919 (Moderna formulation)**	Takeda (Tokyo, Japan)	***1 country:*** Japan	Phase 1: NCT04677660 (Japan) Phase 2: NCT04677660 (Japan)
DNA	**ZyCoV-D**	Zydus Cadila (Ahmedabad, India)	***1 country:*** India	Phase 1: CTRI/2020/07/026352 (India) CTRI/2021/03/032051 (India) Phase 2: CTRI/2020/07/026352 (India) CTRI/2021/03/032051 (India) Phase 3: CTRI/2021/01/030416 (India)

Protein subunit	**ZF2001**	Anhui Zhifei Longcom (Hefei, China)	***3 countries:*** China, Indonesia, Uzbekistan	Phase 1: NCT04445194 (China). NCT04636333 (China). NCT04550351, ChiCTR2000035691 (China). NCT04961359 (China). Phase 2: NCT04466085 (China). NCT04813562 (China). Phase 3: ChiCTR2000040153, NCT04646590 (China, Ecuador, Indonesia, Pakistan, Uzbekistan). ChiCTR2100050849 (China).
	CIGB-66	Center for Genetic Engineering and Biotechnology (CIGB) (Havana, Cuba)	***4 countries:*** Cuba, Nicaragua, Venezuela, Vietnam	Phase 1: RPCEC00000345 (Cuba). RPCEC00000346 (Cuba). Phase 2: RPCEC00000345 (Cuba) RPCEC00000346 (Cuba). Phase 3: RPCEC00000359 (Cuba).
	EpiVacCorona	FBRI (Koltsovo, Russia)	***2 countries:*** Russian Federation, Turkmenistan	Phase 1: NCT04527575 (Russian Federation). Phase 2: NCT04527575 (Russian Federation). Phase 3: NCT04780035 (Russian Federation).
	MVC-COV1901	Medigen Biotechnology Corp. (Taipei City, Taiwan)	***1 country:*** Taiwan	Phase 1: NCT04487210 (Taiwan). Phase 2: NCT04695652 (Taiwan, Vietnam). NCT04822025 (Taiwan). NCT04951388 (Taiwan). NCT05038618 (Taiwan). NCT05048849 (Taiwan). NCT05054621 (Taiwan).
	COVAX-19	Vaxine/CinnaGen Co. (Iran)	***1 country:*** Iran	Phase 1: NCT04453852 (Australia). Phase 2: IRCT20150303021315N23 (Iran). NCT04944368, IRCT20150303021315N23 (Iran). Phase 3: NCT05005559, IRCT20150303021315N24 (Iran).

bmjmedicine

COVID-19: Virology, variants, and vaccines

Journal:	*BMJ Medicine*
Manuscript ID	bmjmed-2021-000040.R1
Article Type:	Specialist review
Date Submitted by the Author:	08-Feb-2022
Complete List of Authors:	Young, Megan; Imperial College London, Faculty of Medicine Crook, Harry; Imperial College London, Faculty of Medicine Scott, Janet; University of Glasgow, Centre for Virus Research Edison, Paul; Imperial College London, Faculty of Medicine; Cardiff University, School of Medicine
Keywords:	Covid-19, COVID-19, Virology

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COVID-19: Virology, variants, and vaccinations

Keywords: Covid-19, Coronavirus, Virology, SARS-CoV-2 variants, Vaccines.

Megan Young[1†], Harry Crook[1†], Janet Scott[2], Paul Edison[1,3,*]

[1] Faculty of Medicine, Imperial College London, London, UK.
[2] Medical Research Council-University of Glasgow Centre for Virus Research, University of Glasgow, UK
[3] School of Medicine, Cardiff University, Cardiff, UK.

† Both authors contributed equally to the manuscript

*Corresponding author:
Dr Paul Edison, MD, MRCP, PhD, FRCP, FRCPI,
Clinical Senior Lecturer and Professor,
Clinical Senior Lecturer, Imperial College London and Honorary Professor, Cardiff University, UK
Division of Neurology, Faculty of Medicine, Imperial College London
Level 2, Commonwealth Building,
Hammersmith Campus, Imperial College London,
Du Cane Road, London, W12 0NN, UK

Tel: +442075941081
E-mail: paul.edison@imperial.ac.uk

No authors have any competing interests.

Abstract

As of 25th January 2022, there have been over 349 million confirmed cases of COVID-19, with over 5.59 million confirmed deaths associated with the SARS-CoV-2 virus. The COVID-19 pandemic has prompted an extensive, global effort to study the molecular evolution of the virus and develop vaccines to combat its spread. Although rigorous determination of SARS-CoV-2 infectivity remains elusive, due to the continuous evolution of the virus, steps have been made to understand its genome, structure, and emerging genetic mutations. The SARS-CoV-2 genome is composed of a number of open reading frames (ORFs) and structural proteins, including the spike protein, which is essential for entry into host cells. As of 25th January 2022, the WHO reports five variants of concern (VOC) two variants of interest (VOI) and three variants under monitoring (VUM). The mutations harboured in these variants confer an increased transmissibility, severity of disease, and escape from neutralising antibodies compared to the primary strain. The current vaccine strategy, including booster doses, provides protection from severe disease. As of 24th January 2022, there are 33 approved vaccines in use in 197 countries. In this review, we discuss the genetics, structure and transmission methods of SARS-CoV-2 and its variants, highlighting how mutations provide enhanced abilities to spread and inflict disease. We also outline the vaccines currently in use around the world, providing evidence for the immunogenicity and effectiveness of each.

1. Introduction

There are seven coronaviruses that infect humans, all belonging to either alpha- or beta-coronavirus subgroups, including 229E (alpha), NL63 (alpha), OC43 (beta), and HKU1 (beta)(1). Over the last two decades, three notable beta-coronaviruses, severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002, Middle East respiratory syndrome coronavirus (MERS-CoV) in 2011, and most recently, severe acute respiratory syndrome 2 (SARS-CoV-2) in 2019, have emerged and caused severe illness resulting in debilitating disease and worldwide fatalities. SARS-CoV-2 is the pathogen responsible for the current Coronavirus 2019 (COVID-19) pandemic and has caused more than 5.59 million deaths in approximately two years and resulted in multisystem illness in several million people(2).

All viruses change and mutate over time, with most changes having little to no impact. However, some mutations may alter its pathogenic or transmission potential and could, therefore, increase disease severity or hinder the effectiveness of vaccines and therapeutic strategies. The World Health Organisation (WHO) classify SARS-CoV-2 variants that increase transmissibility, disease severity or virulence, or decrease the effectiveness of public health measures, diagnostics, therapeutics, or vaccines as variants of concern (VOC). Variants with genetic changes that are predicted to enhance the virulence and transmissibility of the virus which have been identified to cause community transmission in multiple countries posing a possible risk to global public health are defined as variants of interest (VOI). Lastly, the WHO defines variants with genetic changes that are suspected to affect virus characteristics and have currently unclear phenotypic or epidemiological effects as variants under monitoring (VUM). VUM are not typically assigned a name until they are upgraded to VOI or VOC. The full working definitions of VOC, VOI and VUM can be found on the WHO ‘tracking SARS-CoV-2 variants’ website: www.who.int/en/activities/tracking-SARS-CoV-2-variants/(3). As of 25th January 2022, the WHO reports five VOC; Alpha, Beta, Gamma, Delta and Omicron, two VOI; Lambda and Mu, and three VUM(3). Former VOC/VOI/VUM have been reclassified as ‘formerly monitored variants’ due to them either no longer circulating, having little impact on the epidemiological situation, or having no concerning properties(3). Since the beginning of the COVID-19 pandemic, the rapid

development of effective COVID-19 vaccines has taken place around the world. As of 24th January 2022, there are 33 approved vaccines in use in 197 countries, with ten vaccines having gained emergency use listing approval from the WHO(4).

In this review, we provide an overview of the genome and structure of SARS-CoV-2, describing how these elements allow the virus to infect and replicate inside of host cells, before outlining how certain mutations harboured by SARS-CoV-2 variants enhance these abilities. Next, we examine the current state of vaccine development around the world and provide evidence of the effectiveness of booster doses.

2. Methods

We searched PubMed and Embase databases for COVID-19-related articles published between 1st January 2020 and 25th January 2022 and for general coronavirus-related articles published from 1st January 2000 onwards. Our search terms included SARS-CoV-2, COVID-19, and specific terms including virology, genome, variants, and vaccine. Additional, specific search terms are outlined in supplementary file 1. We performed further manual searching for additional articles and data using relevant databases, including who.int, gov.uk, and ecdc.europa.eu/en. Due to the rapidly evolving nature of the literature involving SARS-CoV-2, we also searched preprint databases including MedRxiv and BioRxiv. Due to the various topics addressed here, studies were selected through different criteria, details of which can be found in supplementary file 1. Overall, studies were selected based on quality and journal reputation, with real-world studies with large sample sizes of greatest interest.

3. Viral transmission, clinical presentation, and genetic susceptibility of COVID-19

SARS-CoV-2 is predominantly spread via respiratory droplet transmission, spreading between people through close contact, coughing, or sneezing. It has been documented that the virus can also spread through airborne transmission, fomite transmission, and via other modes, such as through biological material including urine and faeces, and through (5, 6). The SARS-CoV-2 virus may survive on surfaces or suspended in air droplets for some time. Indeed, on plastic, stainless steel, and glass surfaces, the half-life of the virus is around 5.3, 4.4, and 4.2 hours, respectively(7), with no difference seen between SARS-CoV-2 variants(8). Although SARS-CoV-2 can be detected on inanimate surfaces for hours and days, due to the evaporation of water droplets, the viruses' living environment, the concentration of the virus plummets rapidly(9). Protective measures, including using personal protective equipment (PPE), maintaining indoor ventilation, and disinfecting hands and surfaces, can effectively limit the spread of SARS-CoV-2(10).

Once inside the airways, SARS-CoV-2 can directly or indirectly infect ciliated, mucus-secreting, and club cells of bronchial epithelium, type 1 pneumocytes within the lungs, and the conjunctival mucosa(11). The clinical presentation of COVID-19 is non-specific, heterogeneous, and infection can result in a wide spectrum of symptoms. Following an incubation period of 4-14 days, symptoms develop ranging from mild to severe disease and, in some cases, can result in death(12). The most common COVID-19 symptoms include fever, cough, dyspnoea, and fatigue(13, 14), while myalgia, gastrointestinal issues, cognitive deficits, and other symptoms are reported. Asymptomatic individuals can also test positive for COVID-19(15, 16). Although the entire population is susceptible to COVID-19 infection, some subgroups within the general population exist that are more susceptible to developing poorer clinical outcomes.

Risk factors associated with increased risk of hospitalisation, severe disease, and fatal outcome with COVID-19 have been identified. Older age(17-19), male sex(20, 21), non-white

ethnicity(21, 22), comorbidities including diabetes, hypertension, and lung disease(18, 23-25), malignancy and immunodeficiency(26-28) have all been associated with more severe COVID-19. The duration of symptoms endured by COVID-19 patients, as well as the treatment they receive will also have profound influences on the severity of disease they experience and both the acute and long-term outcomes following recovery. The host genetic background is thought to have an influence on the susceptibility and severity of COVID-19, possibly explaining the broad spectrum of clinical manifestations that can develop in seemingly similar individuals. A study examining individuals with COVID-19 across numerous ancestry groups identified four gene loci associated with susceptibility to COVID-19; SLC6A20, RPL24, ABO, PLEKHA4, and nine associated with increased risk of severe COVID-19; LZTFL1, FOXP4, TMEM65, OAS1, KANSL1, TAC4 , DPP9, RAVER1, and IFNAR2(29). Meanwhile, genome-wide association studies spanning across Europe, the United States (US), and the United Kingdom (UK) identified a gene cluster on chromosome three (chr3p21.31) as being strongly linked with susceptibility and severity of COVID-19(30, 31). Polymorphisms in the angiotensin-converting enzyme 2 (ACE2) receptor and transmembrane protease serine 2 (TMPRSS2) have also been shown to enhance SARS-CoV-2 viral entry(32, 33), with differential polymorphisms seen across ethnic populations, which may partly explain why certain ethnic groups are more susceptible to severe COVID-19. Increased ACE2 receptor levels have also been associated with other risk factors of COVID-19 including smoking and increasing age(34). The utilisation of polygenetic risk scores (PRS) may be useful in determining an individual's risk for developing severe disease caused by COVID-19(35). A PRS infers a person's risk of susceptibility to, or development of a certain disease based on the total number of genomic variations they possess. Determining PRS with the inclusion of comorbidities, such as chronic obstructive pulmonary disease(36), or other aspects, such as coagulation factors(37), may improve the usefulness of PRS in determining a person's risk of severe COVID-19.

4. Virology of SARS-CoV-2

SARS-CoV-2 is a positive-stranded ribonucleic acid (RNA) virus belonging to Coronaviridae family. Coronaviruses, which have crownlike appearances, are the largest known RNA viruses and are thought to primarily infect vertebrates(38, 39). SARS-CoV-2 belongs to the beta genus of the coronaviruses and has a genome varying from 29.8kb to 29.9kb in size(40). Human coronaviruses (HCoV) genomes consist of a variable number of open reading frames (ORFs). Following the typical 5'-3' order, the beginning two-thirds of the SARS-CoV-2 genome contains two ORFs, ORF1a and ORF1b which, inside the host cell, are translated at the rough endoplasmic reticulum into polyprotein 1a (pp1a) and polyprotein 1ab (pp1ab), respectively(40). These polyproteins are cleaved into 16 non-structural proteins (nsp); nsp1-11, from pp1a and nsp12-16, from pp1ab. The proteolytic release of nsp1 occurs rapidly, which enables it to interfere with translation processes of the host cell by inducing cellular mRNA degradation(41-43). Nsp2-16 contain the viruses' replication and transcription complex (RTC) and encode multiple enzymes with many functions including, proteases, helicase, polymerase, exo- and endo-nuclease, N7- and 2'O-methyltransferases, and de-ubiquitination enzymes(44, 45). The final third of HCoV genomes contain genes that encode structural and accessory proteins. The four major structural proteins encoded here are the nucleocapsid (N), membrane (M), envelope (E), and spike glycoprotein (S) proteins(46, 47). The N protein is associated with the viral RNA genome and is involved in RNA synthesis regulation and interacts with the M protein during viral budding(39, 48). The M protein is important for viral assembly, it contains a short N-terminal domain that projects onto the external surface of the envelope and a long internal C terminus(39). The E protein function is largely unknown; however, along with the N and M proteins, it is required for viral assembly and

release(47) . Lastly, the S protein gives coronaviruses their characteristic spikes that compose their crownlike appearance. This protein projects through the viral envelope, is heavily glycosylated, and regulates host cell membrane receptor binding and fusion of the viral and cellular membrane(49). The functions of the eleven accessory proteins encoded within the one-third closest to the 3' end of the SARS-CoV-2 genome are not fully understood. These accessory proteins are encoded by the ORF3a, ORF3b, ORF3c, ORF3d, ORF6, ORF7a, ORF7b, ORF8, ORF9b, ORC9c, and ORF10 genes. Some of these proteins, including ORF3b, ORF6, ORF7a and ORF8 are interferon antagonists which impair the host cell immune response(50-53), while ORF3a may promote virus release(54) and is involved in apoptosis of host cells through caspase-3 activation(55). ORF9b and ORF9c are known to supress the host antiviral response by interacting with host cell organelles(56-58), while a clear understanding of the functions of ORF3c, ORF7b, and ORF10 remains elusive(59). ***Figure 1*** (A and B) depicts the genome and structure of SARS-CoV-2.

The S glycoprotein is composed of two functionally distinct subunits (S1 and S2) and is essential for viral entry into host cells. The N-terminal S1 domain of the protein contains the receptor-binding domain (RBD) that directly interacts with the ACE2 receptor on the host cell, the primary receptor that SARS-Cov-2 utilises for cell entry(60). The C-terminal S2 domain fuses the host and viral membranes to allow for entry of the viral genome into the host cell(61). The subunits of the trimeric S complex are either in a closed (pre-fusion stage) or open (post-fusion stage) conformation(62), with one subunit always in an open conformation to allow for ACE2 recognition and binding(63). The RBD itself consists of five anti-parallel β-strands surrounded by several α-helices(64). From closed to open conformation, the RBD undergoes structural rearrangement whereby the globular head region rotates clockwise, which alters is elecropotential surface(64). Once positioned, numerous residues within the RBD form either hydrogen bonds or salt bridges with residues of the ACE2 receptor, allowing for tight binding(65), while the concave structure of the RBD allows for three distinct binding regions(64). Following binding between the S protein and the host cell receptor, host cell proteases cleave the S protein, causing the release of the S2 domain which allows for fusion and cell entry(66). ***Figure 1*** (C and D) demonstrate the structure and function of the S protein.

The ACE2 receptor is expressed in numerous cell types throughout the human body, including in the lungs, oral and nasal mucosa, heart, gastrointestinal tract, kidneys, liver, spleen, and brain(67), highlighting the widespread infection that SARS-CoV-2 can inflict. Meanwhile, TMPRSS2, a host cell protease, facilitates fusion of the viral and host cell membranes(68), and may play a role in the spread of the virus in the airways(68). Host cell cathepsin L may also aid in SARS-CoV-2 cell entry by cleaving the S protein(69). Indeed, a clinically approved protease inhibitor has been shown to block SARS-CoV-2 cell entry(70). ***Figure 2*** depicts the mechanism by which SARS-CoV-2 gains entry into and replicates inside host cells, and overviews the host cell immune response.

5. Variants of SARS-CoV-2

Most viral mutations have a limited impact on the viruses' ability to infect, replicate, escape host immunity, and transmit, however, certain mutations may give a viral strain a competitive advantage and, through natural selection, give it the ability to become dominant. Many of the mutations observed in SARS-CoV-2 variants are found within the RBD or the N-terminal domain of the S protein, which alters the three-dimensional structure of the S protein. Not only can these changes affect the transmission abilities of the virus but can also allow it to better escape the immune response, including from neutralising antibodies either elicited through vaccine administration or natural infection. The SARS-CoV-2 virus has mutated numerous times, with estimates suggesting that

circulating lineages acquire nucleotide mutations at rates of around one to two mutations per month(71). The current method of identifying variants relies on the use of genomic testing such as whole genome sequencing, partial S-gene sequencing, or nucleic acid amplification technique (NAAT)-based assays(72). The aspects of different variants that most people experience, however, is the clinical symptoms they inflict. Certain variants induce a greater risk of severe disease and death, such as Alpha and Delta(73), while others are more likely to induce milder symptoms, such as Omicron(74, 75). Moreover, individual symptoms can differ between variants. For example, the Gamma variant is associated inflicting anosmia and dysgeusia(76), which is less commonly seen in Omicron infections. Moving forward, the clinical themes and symptoms associated with emerging variants should be elucidated rapidly in order for the public and healthcare professionals to rapidly identify possible cases of COVID-19.

The WHO have tracked and monitored SARS-CoV-2 variants since the COVID-19 pandemic began to identify VOCs. As of 25th January 2022, the WHO reports five VOC, two VOI, and three VUM(3) (***Table 1***). Herein, we report studies that compare SARS-CoV-2 variants to the 'primary' virus strain. 'Primary strain' refers to the strain of the virus that first emerged in Wuhan, China at the end of 2019 and spread around the world in the first wave of infections, which is often also referred to as the Wuhan-Hu-1, B.1, or wild-type strain.

5.1 Variants of concern

5.1.1 Alpha

The Alpha SARS-CoV-2 variant, of the B.1.1.7 lineage, was first documented in the UK in September 2020 and classified as a VOC on 18th December 2020(3, 77). This variant contains S protein mutations which have potential biological effects. Firstly, the S protein residue 501, a key contact residue within the RBD, forms a portion of the binding loop in the contact region of the ACE2 receptor, forms a hydrogen bond with the Y41 residue of the ACE2 receptor, and stabilises the ACE2 K353 residue(65, 78, 79). Alpha harbours an N501Y mutation which increases the binding affinity of the RBD to the ACE2 receptor(80). Next, the P681H mutation contained within the Alpha variant is located immediately adjacent to the 682-685 furin cleavage site, at the interface of the S1 and S2 domains(81). The S1/S2 furin cleavage site prompts entry into respiratory epithelial cells and partly determines the transmissibility of the virus(82-84), while the P681H mutation makes the furin cleavage site less acidic, meaning it is more effectively recognised and cleaved(85, 86). Alpha also contains a D614G mutation, located within the S1/S2 furin cleavage site, which increases SARS-CoV-2 binding affinity to the ACE2 receptor and increases infectivity(87). Other mutations harboured within the Alpha variant enhance the ability of the virus to escape antibody detection, such as the two amino acid deletion at the sites 69-70 in the N-terminal domain of the S protein(88, 89), while other mutations demonstrate limited or no effects(90). In February 2021, viruses of the B.1.1.7 lineage with the added S protein mutation E484K were identified, which may have threatened vaccine effectiveness due to the mutation conferring an increased resistance to neutralising vaccine-elicited and monoclonal antibodies(91). This mutation had limited effects, however, and variants containing it failed to dominate.

Epidemiological studies explored the Alpha variant, with a study in Madrid, Spain finding that the probability of admission to an intensive care unit (ICU) was twice as high in patients infected with the Alpha variant compared to those infected with the primary strain, while this variant became the dominant strain within four months, and led to an increase in disease burden as a result(92). Meanwhile in Cannes, France, infection with the Alpha variant was associated with a 3.8-fold higher

risk of transfer to an ICU or death compared to the primary strain(93). During the third COVID-19 wave in Ontario, Canada, where 91% of infections were caused by the Alpha variant, the risk of both hospitalisation (adjusted odds ratio (aOR)=1.57) and death (aOR=1.52) was higher compared to primary strain infections(94). Overall, the Alpha variant was approximately 50-70% more transmissible and was associated with a 30-60% increased risk of hospitalisation and death compared to the primary strain(95-100).

The Alpha variant was found to have a minimal impact on the effectiveness of current vaccines(101, 102), while the risk of reinfection remained similar for this variant as with previous ones(103). On 3rd September 2021, the European Centre for Disease Prevention and Control (ECDC) reclassified the Alpha, and the Alpha+E484K mutation variants from a VOC to a 'de-escalated variant' (104).

5.1.2 Beta

The Beta SARS-CoV-2 variant, of the B.1.351 lineage, was first documented in South Africa in May 2020(3). This variant contains five S protein mutations of interest: N501Y, E484K, D614G, K417N, and A701V. Like the Alpha variant, Beta contains the mutations N501Y, E484K, and D614G, which increase ACE2 receptor binding affinity(80, 87), increase virulence(105), and enhance resistance to neutralising antibodies(91, 106). The K417 residue of the SARS-CoV-2 S protein interacts with the D30 residue of the ACE2 receptor, forming a salt bridge across the central contact region(65, 78), however, the K417N mutation appears to have a limited impact on ACE2 receptor binding(80). The A701V mutation is located close to the furin cleavage site but has a minimal impact on transmissibility or antibody resistance(101).

In a genomic and epidemiological study, it was concluded that the Beta SARS-CoV-2 variant had a selective advantage over previous variants from its increased transmissibility and immune escape abilities(107, 108), while the E484K/N501K mutations significantly enhanced the binding affinity of Beta and, hence, increased its transmissibility(109). A retrospective cohort study found that infection with the Beta variant was associated with an increased hospitalisation risk compared to an infection with a non-VOC (hazard ratio (HR)=2.30)(100). Overall, Beta is approximately 25-50% more transmissible, is associated with a possible increase in risk of hospital mortality, and has enhanced resistance to antibody neutralisation compared to previous variants(107, 108, 110).

5.1.3 Gamma

The Gamma variant is of the P.1 lineage and was first reported in November 2020 from travellers returning to Japan from Brazil, and was later discovered in Brazil(3, 111). This variant contains the S protein mutations of interest; K417T, E484K, N501Y, D614G, and H655Y(104). As mentioned, the N501Y and D614G mutations increase ACE2 receptor binding affinity and increase infectivity of the virus(80, 87). The N501Y, K417N/T, and E484K mutation trinity, meanwhile, is shared by both Gamma and Beta variants, and is associated with enhanced infectivity and lethality compared to the N501Y mutation alone, possibly due to tighter binding of the S protein to the ACE2 receptor due to increased electrostatic contribution(112). Gamma also possesses the H655Y mutation which was found to provide enhanced viral escape abilities from multiple human monoclonal antibodies *in vitro*(113).

The Gamma variant is associated with heightened transmissibility(109, 110, 114), with one study concluding that it possesses a 1.7- to 2.4-fold increased transmissibility compared to previous variants(115). Additionally, the wave of infections caused by the Gamma variant in Brazil was

associated with a 13% increase in death rate compared to the previous wave, suggesting the greater virulence held by Gamma compared to previous viral strains(116). A surveillance study from seven European countries concluded that the Gamma variant was associated with a higher risk of hospitalisation (aOR=2.6) and admission to an ICU (aOR=2.2) when compared to non-VOC cases(117). In Manaus, Brazil the resurgence of COVID-19, despite high seroprevalence, suggested that the Gamma variant had a moderate resistance to neutralising antibodies(118), however, Gamma has been shown to be significantly less resistant to neutralising antibodies, compared to other variants, including Beta(119).

5.1.4 Delta

The Delta variant, from the B.1.617.2 lineage, was first documented in India in October 2020 and was classified as a VOC on 11th May 2021(3). Of the S protein mutations of interest, the aforementioned P681H and D614G are also harboured by the Delta variant(104) and similarly impacts its ACE2 receptor binding affinity and transmissibility(106, 120, 121). Unlike the E484K mutation seen in previous variants, Delta contains the E484Q mutation which, along with a L452R mutation also located within the RBD, causes significantly higher affinity for the ACE2 receptor than the primary strain or the E484K mutation alone(122). The L452R mutation alone results in greater RBD-ACE2 receptor binding affinity and enhanced escape from neutralising antibodies(123, 124). Lastly, the Delta variant contains the T478K mutation, located on the interface between the S protein and the ACE2 receptor when bound, which increases the electrostatic potential of the S protein and enhances binding affinity(125).

The Delta variant quickly became the dominant variant in the UK(126), US(127), Europe, and around the world(128). The mutations present in the Delta variant, enhanced the transmissibility of the virus as a result of increased binding affinity to the ACE2 receptor(109). It was estimated that the reproduction number of the Delta variant is 97% greater than non-VOC/VOI and approximately three times that of the Alpha, Beta, and Gamma variants(110), which highlights the competitive advantage that this variant had over earlier ones and how it rapidly became the dominant strain globally. The fast replication rate of Delta likely contributes to its increased transmissibility compared to Alpha, Beta, and Gamma. From infected individuals, the Delta variant has been able to be detected by polymerase chain reaction (PCR) within the first four days from exposure, while non-Delta infections could only be detected after six days(129). Furthermore, viral loads of people infected with the Delta variant were found to be significantly higher than people infected with other strains(129), including Beta(130). Delta is also thought to better escape neutralisation, with the frequency of post-vaccination infections much higher for the Delta variant than infections with the primary strain in India(131) and blood sera samples from individuals who had received one dose of a COVID-19 vaccine showing minimal neutralisation of the Delta variant(132).

The Delta variant is also associated with an increased disease severity. In Scotland, infection with the Delta variant was associated with an increased risk of hospitalisation (HR=1.85) compared to infection with the Alpha variant(133). Compared to non-VOC infections, North American studies demonstrated that infection with Delta was associated with a 108%(134) or HR=2.3(100) increased risk of hospitalisation, a 234% increased risk for admission to an ICU, and a 132% increased risk of death(134). Lastly, a study in India found that the risk of death was around 1.8 times higher for Delta infections, while Delta also infected and induced symptoms in a greater proportion of younger people (0-19 years old), compared to the primary strain(131).

5.1.5 Omicron

The Omicron variant is of the B.1.1.529 lineage and was first discovered in November 2021 in South Africa and Botswana before being detected in multiple countries and classified as a VOC on 26th November 2021(3). This variant contains over 30 S protein mutations(104), 23 of which have been previously identified, including K417N, T478K, E484A, D614G, H655Y, P681H, and N501Y(135). 15 Omicron mutations are contained within the RBD(17) providing the variant with a significantly enhanced binding affinity to the ACE2 receptor(135, 136). In addition, various single mutations harboured with the RBD of the Omicron variant impair the effectiveness of neutralising antibodies, including K417N, N440K, G446S, E484A, Q493K, G496S, G339D, S371L, and S375F(17).

The emergence of Omicron has been followed by a tidal wave of infections worldwide. Early data from South Africa demonstrated that the proportion of COVID-19 cases caused by the Omicron variant rose from 3% in early October, to 98% by early December(137). In late December 2021, meanwhile, the doubling time for number of positive Omicron cases was between two and three in the UK, US, and much of Europe(138, 139), highlighting the transmissibility of this variant. The mutations harboured by Omicron that enhance its binding affinity(135, 136) and ability to escape neutralising antibodies(17) likely drove its rapid spread, as did its fast replication rate, which is around 70 times faster than the Delta and primary strains(140). The reinfection rate of Omicron has also been found to be significantly higher than that of previous variants in studies from Scotland(141) and South Africa(142).

The Omicron variant has extensive but incomplete escape from naturally acquired and vaccine-induced immunity(143, 144). Compared to the Delta variant, Omicron requires around a ten-fold increased antibody titre to be neutralised, following vaccination with either Oxford-AstraZeneca or Pfizer/BioNtech vaccines(145). Indeed, blood sera from individuals who had received two doses of the Pfizer/BioNtech vaccine exhibited more than a 25-fold reduction in neutralising antibody titres against the Omicron variant compared to the primary strain(146). T-cell responses to Omicron may remain intact, however. One preprint study demonstrated that 70-80% of the T-cell response targeting the S protein was maintained in those vaccinated or with prior infection, while the magnitude of Omicron cross-reactive T-cells was like that of both Delta and Beta variants(147). Furthermore, data from Pfizer/BioNtech revealed that 80% of the epitopes in the Omicron variant S protein that are recognised by CD8+ T-cells were not affected by this variant's mutations, following two-doses of the vaccine(146). T-cell responses induced from vaccine administration or prior infection may, therefore, provide some protection from severe disease.

Recent real-world evidence has implied that Omicron infection is milder in severity than previous variants. In an early South African analysis, the risk of hospitalisation (aOR=0.2) was lower for Omicron infections compared to non-Omicron SARS-CoV-2 infections(137) while, compared to earlier infections associated with the Delta variant, Omicron-infected individuals had a lower risk of severe disease (aOR=0.3)(137). In December 2021 in England, Omicron cases were found to induce a significantly reduced risk of hospitalisation or presentation for emergency care in comparison to Delta cases(74, 75). The decreased disease severity inflicted by Omicron may be due to its reduced capacity for replication in lung tissue, which was found to be more than ten times less in lung tissue compared to Delta(140). Concordantly, the S protein of the Omicron variant is less efficient at cleaving the ACE2 receptor and entering cells of lung organoids(145), while is also less able to cause fusion between lung cells compared to Delta(145), which is often observed in cases of severe COVID-19. The reduction in replication within the lungs, and the preservation of T-cell responses likely contribute to the milder disease exerted by the Omicron variant.

Although the Omicron variant appears to manifest in mild disease, high case numbers may still result in many hospitalisations and deaths in those vulnerable to the virus. Omicron case numbers may be beginning to peak, however. In South Africa, a 29.7% decrease in weekly COVID-19 cases were reported in the week ending 25th December 2021, compared to the previous week, and the Omicron wave is said to have passed(148). Concerningly, global case numbers continue to rise rapidly(149) and many countries will continue to feel the pressure exerted by the wave of Omicron infections.

5.2 Variants of interest

5.2.1 Lambda

The Lambda variant, of the C.37 lineage, was first documented in Peru in December 2020 and was designated as a VOI on 14th June 2021(3). This variant contains the S protein mutations; D614G, L452Q, and F490S(104). The L452Q mutation, located within the RBD, enhances binding affinity to the ACE2 receptor and increases the infectivity of Lambda(150), while, together L452Q and F490S increase the resistance of this variant to vaccine-elicited antibody neutralisation(150). Furthermore, F490S was identified as being a high-risk mutation for enhancing abilities to escape neutralisation(150).

Infectivity of the Lambda variant may be higher than that of Alpha, Gamma, and other D614G containing variants(151), suggesting that Lambda could potentially spread more rapidly and effectively. Additionally, compared to the primary SARS-CoV-2 virus, antibody neutralisation was found to be decreased by 3.05-fold for the Lambda variant, higher than that for Gamma (2.33-fold) and Alpha (2.03-fold) variants(151). However, findings suggest that the Lambda variant can be neutralised by monoclonal antibodies and current vaccines are protective against this variant(150).

5.2.2 Mu

The Mu variant, from the B.1.621 lineage, was first documented in Columbia in January 2021 before receiving designation as a VOI on 30th August 2021(3). This variant contains the aforementioned S protein mutations E484K, N501Y, D614G, and P681H(104). Mu also contains the S protein mutation R346K, located within the RBD(104, 152), which may induce large binding free energy changes that disrupt the binding of antibodies to the S protein and enhance the ability of the variant to escape neutralisation(153). As discussed, the E484K, N501Y, D614G, and P681H mutations have been shown to increase transmissibility(80, 85, 87, 105, 109, 112, 120, 121) and neutralisation escape(91, 106) suggesting that the Mu SARS-CoV-2 variant is likely to be more infectious than the primary strain.

Although the Lambda and Mu variants have been outcompeted by Delta and now Omicron, the development and spread of VOIs will need to be closely monitored and studied to appreciate their pathogenicity, transmissibility, and virulence.

5.3 VUM

As of 25th January 2022, there are three VUM listed by the WHO(3) ***(table 1)***.

6. Vaccinations

The COVID-19 pandemic prompted a rapid international search for safe and effective vaccines against the SARS-CoV-2 virus. In line with previous vaccine development, including for both SARS-CoV

and MERS-CoV, the S protein was a key target for COVID-19 vaccine development(154). As of 24th January 2022, 33 approved vaccines are in use in 197 countries, with ten vaccines having gained emergency use listing approval from the WHO(4), (***table 2***). As of 25th January 2022 there are 194 vaccines in pre-clinical development and 140 in clinical development(155). Numerous studies have explored the effectiveness of approved vaccines, however, large variations in vaccine effectiveness are reported. This variability is likely due to several factors in the studies including, the country, date, and population size of the study, as well as the SARS-CoV-2 variants circulating during the study period. These factors, along with how the effectiveness is reported, mean that it is difficult to compare vaccines and fully understand how effective each vaccine is. Here, we review the COVID-19 vaccines in use around the world.

6.1 Pfizer/BioNtech - BNT162b2

The BNT162b2 vaccine (Comirnaty) is a lipid nanoparticle-formulated, nucleoside-modified mRNA vaccine encoding a modified SARS-CoV-2 S protein which was developed through a collaborative effort between Pfizer (New York, US) and BioNTech (Mainz, Germany)(156, 157). BNT162b2 gained WHO emergency use listing on 31st December 2020(158) and, as of 24th January 2022, has been approved for use in 136 countries(4).

Following administration of BNT162b2, a Th1-biased response is observed, with tumour necrosis factor alpha (TNFα), interferon gamma (IFNγ), and interleukin-2 (IL-2) all elevated following vaccination, compared to placebo(159, 160). Highest neutralisation titres are found between seven and fourteen days following the second dose(161), while those previously infected with COVID-19 showed a four-fold increase in antibody binding and a 18-fold increase in neutralisation titres compared to previously uninfected individuals following two-doses(162). The BNT162b vaccine is well tolerated, with limited reactogenicity. Redness and swelling at injection site have been reported, however mild or moderate pain at the injection site is the most commonly reported reaction to vaccination(161). Fatigue, muscle pain, headache and chills are other commonly reported symptoms following BNT162b2 administration(163). The rate of systemic reactions after a second dose of BNT162b has been found to be 1.7 to 2 times higher than after a first dose, possibly suggesting an immunity-boosting effect(164). Many safety reports of this vaccine describe no serious adverse events(161, 164, 165), however, a large study found that BNT162b2 was associated with an increased risk of myocarditis, lymphadenopathy, appendicitis, and herpes zoster infection(166). Although rare, allergic reaction or anaphylaxis has also been reported following administration of the BNT162b2 vaccine(163). ***Table 2*** outlines clinical trial and real-world data for vaccine effectiveness.

6.2 Oxford-AstraZeneca – AZD1222

The AZD1222 vaccine (Vaxzevria) is a non-replicating vector of the chimpanzee adenovirus ChAdOx1, modified to encode the SARS-CoV-2 S protein(167). Developed through collaboration between the University of Oxford and AstraZeneca (Cambridge, UK), this vaccine was given WHO emergency use listing on 16th February 2021(158) and has been approved for use in 137 countries, as of 24th January 2022(4). The WHO has granted emergency use listing to two versions of this vaccine (AZD1222 and Covishield) in order to utilise Covishield as part of their worldwide COVAX initiate, which is being produced by the Serum Institute of India and AstraZeneca-SKBio (Republic of Korea)(168).

Following administration of AZD1222, significant antibody production, predominantly of IgG1 and IgG3 subclasses, and a Th-1 cell response, with increased expression of IFNγ and TNFα, is seen(122, 169). One dose of AZD1222 has been shown to produce a neutralising antibody response in

91% of participants, while a second dose resulted in 100% of participants producing neutralising antibodies(170). Mild and moderate itch, pain, redness, swelling, tenderness, and warmth are common local reactions, while chills, fatigue, fever, headache, muscle ache, and nausea are commonly reported systemic reactions following AZD1222 administration(170). Rare symptoms, including severe chest pain, nasal bleeding, and allergic reaction have been reported following AZD1222 administration(171). ***Table 2*** outlines clinical trial and real-world data for vaccine effectiveness.

6.3 Johnson & Johnson - Ad26.COV.2.S

The Ad26.COV.2.S vaccine is a non-replicating adenovirus vector, modified to contain the SARS-CoV-2 S protein in a prefusion-stabilised conformation and requires a single dose(172). This vector was developed from the recombinant human adenovirus type 26 by the Janssen pharmaceutical company of Johnson & Johnson (New Brunswick, New Jersey, US)(172) and was listed for WHO emergency use listing on 12th March 2021(158). As of 24th January 2022, Ad26.COV.2.S has been approved for use in 106 countries(4).

The Ad26.COV.2.S vaccine induces the production of a variety of antibody subclasses, such as IgG, IgM, and IgA, and promotes several non-neutralising antibody responses, including activation of CD4+ and CD8+ Th1-cells and production if IFNγ, IL-2, and TNFα(173, 174). Although neutralising antibody responses induced by Ad26.COV2.S are reduced against SARS-CoV-2 variants, non-neutralising antibody and T-cell responses have been found to be preserved against VOC(173), while a prior COVID-19 infection significantly increases levels of S protein-binding antibodies, antibody-dependent cellular cytotoxicity, and neutralising antibodies against VOCs including Beta and Delta(175). Ad26.COV.2.S is safe and well tolerated, with a large clinical trial demonstrating that headache, fatigue, and myalgia, are the most common systemic reactions, while injection-site pain is the most common local reaction following administration(172). Like other vaccines, Ad26.COV.2.S has been associated with serious adverse events, such as allergic reactions and cerebral venous sinus thrombosis, however, these are rare(163, 176). ***Table 2*** outlines clinical trial and real-world data for vaccine effectiveness.

6.4 Moderna – mRNA-1273

The mRNA-1273 vaccine (Spikevax) developed by Moderna (Massachusetts, US) is a lipid-nanoparticle-encapsulated mRNA vaccine expressing the SARS-CoV-2 S protein that has been prefusion-stabilised(177). This vaccine gained WHO emergency use listing on 30th April 2021(158), and as of 24th January 2022, has been approved for use in 85 countries(4).

The mRNA-1273 vaccine elicits a strong CD4+ Th-1 cell response, with TNFα, IFNγ, and IL-2 expression increased following administration(178-180), while neutralising antibody titres have been shown to significantly increase up until around 28 days following the second dose of the vaccine, and afterwards remain consistently high(181). Fatigue, muscle pain, headache, chills, joint pain, and injection-site pain/reaction are common adverse effects caused by the mRNA-1273 vaccine(163, 177), while serious adverse effects are often avoided(177, 181). Serious adverse events, including allergic reaction and anaphylaxis are rare, but not inconceivable following mRNA-1273 administration(163). ***Table 2*** outlines clinical trial and real-world data for vaccine effectiveness.

6.5 Other WHO emergency use listed COVID-19 vaccines

In addition to the five COVID-19 vaccines described previously, five other vaccines have gained emergency use listing by the WHO. First, the Sinopharm BBIBP-CorV COVID-19 vaccine (Covilo) was

developed by the Beijing Bio-Institute of Biological Products, a subsidiary of China National Biotec Group, and was given WHO emergency use listing on 7th May 2021(158). This vaccine is a 19nCoV-CDC-Tan-HB02 strain SARS-CoV-2 antigen that is produced in Vero cells, inactivated by β-propiolactone, and then purified and absorbed with aluminium hydroxide(182). Next, the CoronaVac vaccine, developed by Sinovac Biotech (Beijing, China), was listed for WHO emergency use on 1st June 2021(158). Like the BBIBP-CorV vaccine, this vaccine is a Vero cell-based, aluminium hydroxide-adjuvanted, β-propiolactone-inactivated vaccine, however, it is based on the SARS-CoV-2 CZ02 strain(183). Covaxin (BBV152) is a whole virion inactivated SARS-CoV-2 vaccine formula developed by Bharat Biotech International ltd (India)(184) which gained emergency use listing from the WHO On 3rd November 2021(185). Lastly, Covovax and its originator, Nuvaxovid (NVX-CoV2372), were both developed by Novavax (Maryland, United States) and the Coalition for Epidemic Preparedness Innovations (Oslo, Norway), and gained emergency use listing on 17st and 21th December 2021, respectively(186, 187). Both vaccines are manufactured using the same technology, and consist of a recombinant SARS-CoV-2 S protein nanoparticle administered with the adjuvant Matrix-M as a co-formulation(188). These vaccines produce similar immune responses to those already discussed. Studies assessing the efficacy of these vaccines are outlined in ***table 2***.

6.10 Other approved vaccines

In addition to the vaccines that have received emergency use listing from the WHO, around the world, vaccines have been developed, tested, and approved to combat COVID-19. As of 24th January 2022, 33 vaccines, including the ten described above, have been approved in at least one country(4). The remaining 23 approved vaccines are outlined in ***table 3***.

6.11 Waning immunity and boosters

Throughout the COVID-19 pandemic, emerging variants have threatened the effectiveness of vaccines (***table 2***). Simultaneously, waning immunity following vaccination questions how long vaccines remain effective and highlights the importance of booster doses. Indeed, protection against SARS-CoV-2 following vaccination decreases over time, both in terms of antibody titres(189-191) and vaccine effectiveness(192-195). Cellular responses, such as T-cell immunity, may persist for longer periods, however(196, 197). With a gradual loss of protection from SARS-CoV-2 following COVID-19 vaccination, many countries are now rolling out booster programmes with the aim of raising levels of immunity.

Since booster programmes began, evidence that a booster vaccine dose enhances antibody and cellular responses has accumulated. Following a third dose of vaccine, neutralising antibody titres increase significantly(198-201) and, in some cases, to higher levels than after the primary two doses(198). Additionally, boosters have also been found to increase neutralising antibody titres against Beta, Gamma, Delta, and Omicron variants(199, 202, 203). T-cell response is also enhanced following a third dose(200, 204, 205). Together, enhancing neutralising antibody and cellular responses with a booster vaccine dose is likely to provide a greater level of protection than relying on immunity built through a primary regimen.

The antibody and cellular responses observed following booster vaccinations have been found to correlate with increased levels of protection against SAR-CoV-2 infection and severe illness. On 30th July 2021, Israel was the first country to offer a third dose of BNT162b2 to certain groups. Subsequently, several studies have revealed that those who received a third vaccine dose were significantly less likely to be infected or have severe disease with SARS-CoV-2 compared to those who

received two-doses(206-209). In those aged 60 or older, an observational study demonstrated that the rate of severe COVID-19 and death was lower in the boosted group by a factor of 17.9 and 14.7, respectively, compared to the non-boosted group(210). Booster doses of COVID-19 vaccine have been shown to be effective against infection with Delta(211, 212) and, to a lesser degree, Omicron variants(75, 145, 146, 212-214) despite the numerous mutations harboured by these variants. Overall, increasing evidence is pointing towards the benefits of booster doses of COVID-19 vaccines, therefore it is expected that booster programmes will continue to roll out across the globe. Based on current evidence, the CDC recommend that the time interval for receiving a booster following the primary regiment is five months for Pfizer/BioNTech BNT162b2 primary regimen, six months for Moderna mRNA-1273 primary regimen, and two months for Johnson & Johnson Ad26.COV2.S primary regimen(215). As the pandemic progresses and new variants emerge, variant-specific vaccines may require development, with pre-clinical studies demonstrating their efficacy(216) and pharmaceutical companies, such as Pfizer, advancing in variant-specific vaccine development(146). Policy makers should also consider when vaccine boosters will be given in the future and who will receive booster doses in the long-term.

7. Emerging Treatments

As more is learnt about the virus, the therapeutic strategy against COVID-19 develops. There are currently over two thousand ongoing trials assessing certain treatment strategies for COVID-19(217). Recently, antivirals including molnupiravir (Lagevrio) and nirmatrelvir/ritonavir (Paxlovid) have been approved in the UK(218, 219), US(220, 221), and Europe(222, 223) for treating COVID-19 in certain risk groups. Similarly, sotrovimab (Xevudy), a monoclonal antibody treatment, has recently been approved for use in treating certain COVID-19 patients in the UK(224), US(225), and Europe(226). These drugs have been shown to be effective at preventing poor clinical outcomes, including death, in those vulnerable to severe COVID-19 infection. Other drug treatments, such as janus kinase inhibitors, corticosteroids, and anti-inflammatories have contrasting evidence to support their use, and therefore, the use of specific drugs is either recommended for or against by certain treatment and management guidelines, which are discussed below.

8. Guidelines

The treatment and management of COVID-19 is a continually evolving topic, however, health authorities have published and continue to update guidelines and recommendations for treating COVID-19. The WHO living guideline on COVID-19 and therapeutics is regularly updated, with the latest version, published on 14th January 2022 containing 14 recommendations on COVID-19 treatment(227). In the UK, the National Institute for Health and Care Excellence (NICE)(228) and Medicines and Healthcare products Regulatory Agency (MHRA)(229) provide updated guidelines on COVID-19 treatment, while in Europe, the ECDC regularly publishes several guidelines providing recommendations on a range of COVID-19 related topics(230). In the US, the National Institutes of Health (NIH)(231) and the CDC(232) provide guidance on COVID-19 treatment and management, with the CDC supplying guidelines for specific groups including, employers, schools, health departments, and governments.

9. Considerations for the future

Novel infectious diseases and pandemics are an unpredictable but inevitable aspect of nature and it is, therefore, important that we learn from past pandemics to prepare for future ones. Firstly,

the COVID-19 pandemic has highlighted and amplified the existing inequalities within society(233), with non-white ethnicity, social disadvantage, and unemployment all risk factors for testing positive for COVID-19(234) and those most economically deprived found to be particularly vulnerable(235). These inequalities require addressing to be better prepared for similar situations in the future. Next, to progress through a pandemic we should be racing the pathogen, not each other. This statement becomes apparent when you consider the problems countries faced when seeking out PPE(236), and the vaccine inequity seen around the world(237), with developed countries often better placed to be able to purchase these items. Initiatives such as the WHO's COVAX programme are vital to protect those most vulnerable and reduce the global spread of disease. In October 2021, the UK government released a publication outlining where the policies implemented to reduce the impact of the COVID-19 pandemic failed, and the lessons learned from these failures (238). Here, it is clear that there is room for improvement, with the publication presenting conclusions and recommendations on how to enhance pandemic preparedness, lockdown and social distancing measures, testing and contact tracing, social care, and vaccines. In countries such as the UK, US, and much of Europe, where the COVID-19 death rate has been high, steps need to be taken and lessons need to be learnt in order to be better prepared for the next pandemic. The responsibility of improving pandemic response lies with policy makers, the medical/scientific community, and the public, and will ultimately require a collaborative approach.

Certain aspects of the response to the COVID-19 pandemic have been a triumph, however. One of the major victories was the rapid development and rollout of vaccines(239), which continue to be effective. The rollout of rapid testing and quarantine for positive cases was also important to at least disrupt the spread of the virus, especially given that asymptomatic individuals can contribute to the spread. Furthermore, the swift identification and sharing of knowledge of SARS-CoV-2 variants between countries should be applauded. Lessons can be learned from countries where COVID-19 was controlled. In Taiwan, managing the pandemic as directed by pre-COVID-19 pandemic plans prompted an immediate response; screening of all airline passengers arriving from Wuhan and high risk areas, restricting entry for non-Taiwanese citizens, 14-day quarantine period for contacts of confirmed cases or returning travellers, a ban on large gatherings, and widespread mask wearing were some of the quickly implemented management strategies(240). New Zealand implemented similarly effective restrictions, with the addition of a national lockdown(240). Many of the pandemic control components that kept case and death numbers low in Taiwan and New Zealand could be adopted by other countries in the future and may lead to greater outcomes in terms of protecting both health of individuals and the health and wellbeing of the country. Overall, there is much to be learnt from the COVID-19 pandemic and, as we emerge from it, inspection of which policies failed, and which succeeded are imperative.

10. Conclusion

COVID-19 remains prevalent and life-threatening. Although rollout of vaccines has been successful, we must aim to address unmet goals, such as attaining a high global vaccination coverage and ensuring that all healthcare systems have the capacity to cope with seasonal waves. With Omicron highly prevalent, we must continue to learn, develop therapeutics, and remain vigilant to new VOCs. Here, we have provided an overview of the virology of SARS-CoV-2, including the mutations harboured by variants of the virus and how these mutations effect its transmissibility and virulence. Lastly, we discussed the vaccines that have been developed and administered around the world and provided

evidence supporting the rollout of booster doses. Future priorities should focus on continuing vaccination programmes and developing variant-specific vaccines as new mutations emerge. This, along with the expansion of our knowledge of SARS-CoV-2 and which therapies are most successful to treat infections with it will ultimately lead to favourable outcomes moving forward.

Research Questions

1) How will the SARS-CoV-2 virus mutate in the future, and which mutations will give a competitive advantage that will allow the virus to inflict disease to many people?
2) How do we keep up with the rapidly changing SARS-CoV-2 environment and ensure that vaccines remain effective?
3) How do we manage the booster programme and when will future booster vaccinations be required in order to maintain high levels of immunity?
4) How can we learn from the current and past pandemics so that we are better prepared for the next one?

Patient Involvement: Patients who had been infected with covid-19 were contacted and requested to review the initial drafts of this manuscript. The received feedback was mostly positive and assisted in developing and focusing our review. Final drafts were also reviewed by patients who had had covid-19 and similar positive feedback was received.

Contributorship statement and guarantor: MY and HC performed the literature search and drafted the manuscript. HC revised and finalised the manuscript. JS reviewed and revised the manuscript. PE was responsible for the concept and design of the work. PE reviewed, revised, and finalised the manuscript. PE is the guarantor.

Competing interests: We have read and understood the BMJ policy on declaration of interests and declare the following interests: PE was funded by the Medical Research Council and now by Higher Education Funding Council for England (HEFCE). He has also received grants from Alzheimer's Research, UK, Alzheimer's Drug Discovery Foundation, Alzheimer's Society, UK, Medical Research Council, Alzheimer's Association US, Van-Geest foundation, and European Union grants. PE is a consultant to Roche, Pfizer, and Novo Nordisk. He has received educational and research grants from GE Healthcare, Novo Nordisk, Piramal Life Science/Life Molecular Imaging, Avid Radiopharmaceuticals and Eli Lilly. He is a member of the Scientific Advisory Board at Novo Nordisk. None of these were related to COVID-19

Figure Legends:

Figure 1: Genome and structure of SARS-CoV-2. A) SARS-CoV-2 genome and S protein amino acid composition. The SARS-CoV-2 genome is approximately 30,000 base pairs (bp) long and consists of open reading frames (ORF) and elements that are essential for the virus' structure. The spike S

protein is responsible for binding and entry into host cells. SARS-CoV-2 variants of concern (VOC) contain various S protein non-synonymous mutations that result in amino acid changes in the receptor binding domain (orange text) and the S1/S2 subunit interface (black text) which have been demonstrated to enhance transmissibility of the virus. VOC include Alpha (α), Beta (β), Gamma (γ), and Delta (δ). **B) SARS-CoV-2 structure.** SARS-CoV-2 is a RNA virus that has a crown-like appearance and contains four major structural proteins: nucleocapsid (N), spike (S), envelope (E), and membrane (M). **C) S and ACE2 interaction.** The SARS-CoV-2 S protein directly interacts with human angiotensin-converting enzyme 2 (ACE2) receptors in order to gain entry into host cells. The receptor binding domain (RBD) of the S protein tightly binds to ACE2. **D) Spike protein structure.** The S protein protrudes out from the main SARS-CoV-2 bulk and is comprised of two subunits: S1 and S2. S1 contains the RBD which directly interacts with the human ACE2 receptor, while the S1/S2 interface contains a furin cleavage site which is cleaved to allow S2 to fuse with the host cell membrane. Both the RBD and the S1/S2 interface contain transmissibility increasing mutations that are harboured in variants of concern.

Figure 2: Viral entry and host response. A) At the alveolar epithelial cell layer. Epithelial cells in the lungs express both angiotensin-converting enzyme 2 (ACE2) receptors and transmembrane protease serine 2 (TMPRSS2), allowing for infection by SARS-CoV-2. Replication of the virus within these cells induces an intense immune response that attracts monocytes, T-cells and macrophages and, in some cases, can result in a cytokine storm. **B) Within nearby blood vessels.** Cytokines produced by the epithelial cell layer are released into blood vessels supplying the infected tissue, which causes the recruitment of further immune cells to the area, driving the damaging inflammatory response further. Circulating cytokines also create a systemic inflammatory environment. **C) Adaptive immune response.** Circulating lymphocytes carry viral antigens to lymph nodes and bone marrow to begin the adaptive immune system processes whereby B-cells, and later antibodies, are activated. **D) SARS-CoV2 host replication.** The SARS-CoV-2 virus utilises the ACE2 receptor and TMPRSS2 to gain entry into human cells. Following release of the viral RNA within the host cell, the virus utilises the host endoplasmic reticulum (ER) and Golgi apparatus to produce and manufacture new viral particles, which are released out of the cell to infect other cells and new hosts.

Table 1: SARS-CoV-2 variants and their S protein mutations. *first detection worldwide. Information correct as of 24th January 2022.

Table 2: Vaccine effectiveness of vaccines that have gained WHO emergency use listing. *Adjusted for covariates when reported by study, dates are reported in dd/mm/yyyy format. Vaccine effectiveness days/months refers to days/months since vaccination dose. Information correct as of reported conclusion date of each study.

Table 3: COVID-19 vaccines approved in at least one country. Information correct as of 24th January 2022.

References

1. CDC.org [Internet]. Human Coronavirus Types. Centres for Disease Control and Prevention. [15 February 2020; cited 12 October 2021]. Available from: https://www.cdc.gov/coronavirus/types.html
2. Who.int [Internet]. Weekly operational update on COVID-19 - 25 January 2022. World Health Organisation. [25 January 2022; cited 26 January 2022]. Available from: https://www.who.int/publications/m/item/weekly-operational-update-on-covid-19---25-january-2022

3. Who.int [Internet]. Tracking SARS-CoV-2 variants. World Health Organisation. [25 January 2022; cited 26 January 2022]. Available from: https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/
4. covid19.trackvaccines.org [Internet]. COVID-19 Vaccine Tracker. [24 January 2022; cited 26 January 2022]. Available from: https://covid19.trackvaccines.org/
5. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet. 2020;395(10223):514-23.
6. Who.int [Internet]. Transmission of SARS-CoV-2: implications for infection prevention precautions - Scientific Brief. World Health Organisation. [9 July 2020; cited 28 October 2021]. Available from: https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions
7. Gidari A, Sabbatini S, Bastianelli S, Pierucci S, Busti C, Bartolini D, et al. SARS-CoV-2 Survival on Surfaces and the Effect of UV-C Light. Viruses. 2021;13(3).
8. Pottage T, Garratt I, Onianwa O, Spencer A, Paton S, Verlander NQ, et al. A comparison of persistence of SARS-CoV-2 variants on stainless steel. J Hosp Infect. 2021;114:163-6.
9. Guo L, Wang M, Zhang L, Mao N, An C, Xu L, et al. Transmission risk of viruses in large mucosalivary droplets on the surface of objects: A time-based analysis. Infect Dis Now. 2021;51(3):219-27.
10. Carraturo F, Del Giudice C, Morelli M, Cerullo V, Libralato G, Galdiero E, et al. Persistence of SARS-CoV-2 in the environment and COVID-19 transmission risk from environmental matrices and surfaces. Environ Pollut. 2020;265(Pt B):115010.
11. Hui KP, Cheung M-C, Perera RA, Ng K-C, Bui CH, Ho JC, et al. Tropism, replication competence, and innate immune responses of the coronavirus SARS-CoV-2 in human respiratory tract and conjunctiva: an analysis in ex-vivo and in-vitro cultures. The Lancet Respiratory Medicine. 2020;8(7):687-95.
12. McAloon C, Collins A, Hunt K, Barber A, Byrne AW, Butler F, et al. Incubation period of COVID-19: a rapid systematic review and meta-analysis of observational research. BMJ Open. 2020;10(8):e039652.
13. Bliddal S, Banasik K, Pedersen OB, Nissen J, Cantwell L, Schwinn M, et al. Acute and persistent symptoms in non-hospitalized PCR-confirmed COVID-19 patients. Sci Rep. 2021;11(1):13153.
14. Grant MC, Geoghegan L, Arbyn M, Mohammed Z, McGuinness L, Clarke EL, et al. The prevalence of symptoms in 24,410 adults infected by the novel coronavirus (SARS-CoV-2; COVID-19): A systematic review and meta-analysis of 148 studies from 9 countries. PLoS One. 2020;15(6):e0234765.
15. Kronbichler A, Kresse D, Yoon S, Lee KH, Effenberger M, Shin JI. Asymptomatic patients as a source of COVID-19 infections: A systematic review and meta-analysis. Int J Infect Dis. 2020;98:180-6.
16. Arons MM, Hatfield KM, Reddy SC, Kimball A, James A, Jacobs JR, et al. Presymptomatic SARS-CoV-2 Infections and Transmission in a Skilled Nursing Facility. N Engl J Med. 2020;382(22):2081-90.
17. Cao Y, Wang J, Jian F, Xiao T, Song W, Yisimayi A, et al. B.1.1.529 escapes the majority of SARS-CoV-2 neutralizing antibodies of diverse epitopes. BioRxiv [Preprint]. 2021.
18. Wolff D, Nee S, Hickey NS, Marschollek M. Risk factors for Covid-19 severity and fatality: a structured literature review. Infection. 2021;49(1):15-28.
19. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62.

20. Zhang J, Wang X, Jia X, Li J, Hu K, Chen G, et al. Risk factors for disease severity, unimprovement, and mortality in COVID-19 patients in Wuhan, China. Clin Microbiol Infect. 2020;26(6):767-72.
21. Ebinger JE, Achamallah N, Ji H, Claggett BL, Sun N, Botting P, et al. Pre-existing traits associated with Covid-19 illness severity. PLoS One. 2020;15(7):e0236240.
22. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;584(7821):430-6.
23. Li R, Tian J, Yang F, Lv L, Yu J, Sun G, et al. Clinical characteristics of 225 patients with COVID-19 in a tertiary Hospital near Wuhan, China. J Clin Virol. 2020;127:104363.
24. Guo L, Shi Z, Zhang Y, Wang C, Do Vale Moreira NC, Zuo H, et al. Comorbid diabetes and the risk of disease severity or death among 8807 COVID-19 patients in China: A meta-analysis. Diabetes Res Clin Pract. 2020;166:108346.
25. Feng Y, Ling Y, Bai T, Xie Y, Huang J, Li J, et al. COVID-19 with Different Severities: A Multicenter Study of Clinical Features. Am J Respir Crit Care Med. 2020;201(11):1380-8.
26. Tian J, Yuan X, Xiao J, Zhong Q, Yang C, Liu B, et al. Clinical characteristics and risk factors associated with COVID-19 disease severity in patients with cancer in Wuhan, China: a multicentre, retrospective, cohort study. Lancet Oncol. 2020;21(7):893-903.
27. Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020;21(3):335-7.
28. Vizcarra P, Perez-Elias MJ, Quereda C, Moreno A, Vivancos MJ, Dronda F, et al. Description of COVID-19 in HIV-infected individuals: a single-centre, prospective cohort. Lancet HIV. 2020;7(8):e554-e64.
29. Baillie JK, Wilson JF, Bulteel N, Hayward C, Klaric L, Porteous DJ, et al. Mapping the human genetic architecture of COVID-19. Nature. 2021.
30. Shelton JF, Shastri AJ, Ye C, Weldon CH, Filshtein-Somnez T, Coker D, et al. Trans-ethnic analysis reveals genetic and non-genetic associations with COVID-19 susceptibility and severity. MedRxiv [Preprint]. 2020.
31. Ellinghaus D, Degenhardt F, Bujanda L, Buti M, Albillos A, Invernizzi P, et al. Genomewide association study of severe covid-19 with respiratory failure/[...]. New England Journal of Medicine Boston: Massachusetts Medical Society, 2020, vol 383, no 16. 2020.
32. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. cell. 2020;181(2):271-80. e8.
33. Hou Y, Zhao J, Martin W, Kallianpur A, Chung MK, Jehi L, et al. New insights into genetic susceptibility of COVID-19: an ACE2 and TMPRSS2 polymorphism analysis. BMC medicine. 2020;18(1):1-8.
34. Barbry P, Muus C, Luecken M, Eraslan G, Waghray A, Heimberg G, et al. Integrated analyses of single-cell atlases reveal age, gender, and smoking status associations with cell type-specific expression of mediators of SARS-CoV-2 viral entry and highlights inflammatory programs in putative target cells. BioRxiv [Preprint]. 2020.
35. Prakrithi P, Lakra P, Sundar D, Kapoor M, Mukerji M, Gupta I, et al. Genetic Risk Prediction of COVID-19 Susceptibility and Severity in the Indian Population. Front Genet. 2021;12:714185.
36. Huang QM, Zhang PD, Li ZH, Zhou JM, Liu D, Zhang XR, et al. Genetic Risk and Chronic Obstructive Pulmonary Disease Independently Predict the Risk of Incident Severe COVID-19. Ann Am Thorac Soc. 2022;19(1):58-65.
37. Zhou Y, Qian X, Liu Z, Yang H, Liu T, Chen K, et al. Coagulation factors and the incidence of COVID-19 severity: Mendelian randomization analyses and supporting evidence. Signal Transduct Target Ther. 2021;6(1):222.

38. Payne S. Family Coronaviridae. Viruses 2017. p. 149-58.
39. Masters PS, Kuo L, Ye R, Hurst KR, Koetzner CA, Hsue B. Genetic and molecular biological analysis of protein-protein interactions in coronavirus assembly. Adv Exp Med Biol. 2006;581:163-73.
40. Khailany RA, Safdar M, Ozaslan M. Genomic characterization of a novel SARS-CoV-2. Gene Rep. 2020;19:100682.
41. Thoms M, Buschauer R, Ameismeier M, Koepke L, Denk T, Hirschenberger M, et al. Structural basis for translational shutdown and immune evasion by the Nsp1 protein of SARS-CoV-2. Science. 2020;369(6508):1249-55.
42. Schubert K, Karousis ED, Jomaa A, Scaiola A, Echeverria B, Gurzeler LA, et al. SARS-CoV-2 Nsp1 binds the ribosomal mRNA channel to inhibit translation. Nat Struct Mol Biol. 2020;27(10):959-66.
43. Huang C, Lokugamage KG, Rozovics JM, Narayanan K, Semler BL, Makino S. SARS coronavirus nsp1 protein induces template-dependent endonucleolytic cleavage of mRNAs: viral mRNAs are resistant to nsp1-induced RNA cleavage. PLoS Pathog. 2011;7(12):e1002433.
44. Snijder EJ, Decroly E, Ziebuhr J. The Nonstructural Proteins Directing Coronavirus RNA Synthesis and Processing. Adv Virus Res. 2016;96:59-126.
45. V'Kovski P, Gerber M, Kelly J, Pfaender S, Ebert N, Braga Lagache S, et al. Determination of host proteins composing the microenvironment of coronavirus replicase complexes by proximity-labeling. Elife. 2019;8.
46. Masters PS. The molecular biology of coronaviruses. Advances in virus research. 2006;66:193-292.
47. Siu Y, Teoh K, Lo J, Chan C, Kien F, Escriou N, et al. The M, E, and N structural proteins of the severe acute respiratory syndrome coronavirus are required for efficient assembly, trafficking, and release of virus-like particles. Journal of virology. 2008;82(22):11318-30.
48. Kuo L, Masters PS. Genetic evidence for a structural interaction between the carboxy termini of the membrane and nucleocapsid proteins of mouse hepatitis virus. J Virol. 2002;76(10):4987-99.
49. Hulswit RJ, de Haan CA, Bosch BJ. Coronavirus Spike Protein and Tropism Changes. Adv Virus Res. 2016;96:29-57.
50. Konno Y, Kimura I, Uriu K, Fukushi M, Irie T, Koyanagi Y, et al. SARS-CoV-2 ORF3b Is a Potent Interferon Antagonist Whose Activity Is Increased by a Naturally Occurring Elongation Variant. Cell Rep. 2020;32(12):108185.
51. Kopecky-Bromberg SA, Martinez-Sobrido L, Frieman M, Baric RA, Palese P. Severe acute respiratory syndrome coronavirus open reading frame (ORF) 3b, ORF 6, and nucleocapsid proteins function as interferon antagonists. J Virol. 2007;81(2):548-57.
52. Xia H, Cao Z, Xie X, Zhang X, Chen JY, Wang H, et al. Evasion of Type I Interferon by SARS-CoV-2. Cell Rep. 2020;33(1):108234.
53. Wong HH, Fung TS, Fang S, Huang M, Le MT, Liu DX. Accessory proteins 8b and 8ab of severe acute respiratory syndrome coronavirus suppress the interferon signaling pathway by mediating ubiquitin-dependent rapid degradation of interferon regulatory factor 3. Virology. 2018;515:165-75.
54. Azad GK, Khan PK. Variations in Orf3a protein of SARS-CoV-2 alter its structure and function. Biochem Biophys Rep. 2021;26:100933.
55. Ren Y, Shu T, Wu D, Mu J, Wang C, Huang M, et al. The ORF3a protein of SARS-CoV-2 induces apoptosis in cells. Cell Mol Immunol. 2020;17(8):881-3.
56. Kreimendahl S, Rassow J. The Mitochondrial Outer Membrane Protein Tom70-Mediator in Protein Traffic, Membrane Contact Sites and Innate Immunity. Int J Mol Sci. 2020;21(19).

57. Gordon DE, Jang GM, Bouhaddou M, Xu J, Obernier K, White KM, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. Nature. 2020;583(7816):459-68.
58. Dominguez Andres A, Feng Y, Campos AR, Yin J, Yang CC, James B, et al. SARS-CoV-2 ORF9c Is a Membrane-Associated Protein that Suppresses Antiviral Responses in Cells. BioRxiv [Preprint]. 2020.
59. Redondo N, Zaldivar-Lopez S, Garrido JJ, Montoya M. SARS-CoV-2 Accessory Proteins in Viral Pathogenesis: Knowns and Unknowns. Front Immunol. 2021;12:708264.
60. Bosch BJ, van der Zee R, de Haan CA, Rottier PJ. The coronavirus spike protein is a class I virus fusion protein: structural and functional characterization of the fusion core complex. J Virol. 2003;77(16):8801-11.
61. Li F. Structure, Function, and Evolution of Coronavirus Spike Proteins. Annu Rev Virol. 2016;3(1):237-61.
62. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020;367(6483):1260-3.
63. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. Cell. 2020;181(2):281-92 e6.
64. Khare S, Azevedo M, Parajuli P, Gokulan K. Conformational Changes of the Receptor Binding Domain of SARS-CoV-2 Spike Protein and Prediction of a B-Cell Antigenic Epitope Using Structural Data. Front Artif Intell. 2021;4:630955.
65. Lan J, Ge J, Yu J, Shan S, Zhou H, Fan S, et al. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. Nature. 2020;581(7807):215-20.
66. Millet JK, Whittaker GR. Host cell proteases: Critical determinants of coronavirus tropism and pathogenesis. Virus Res. 2015;202:120-34.
67. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004;203(2):631-7.
68. Glowacka I, Bertram S, Muller MA, Allen P, Soilleux E, Pfefferle S, et al. Evidence that TMPRSS2 activates the severe acute respiratory syndrome coronavirus spike protein for membrane fusion and reduces viral control by the humoral immune response. J Virol. 2011;85(9):4122-34.
69. Zhao MM, Yang WL, Yang FY, Zhang L, Huang WJ, Hou W, et al. Cathepsin L plays a key role in SARS-CoV-2 infection in humans and humanized mice and is a promising target for new drug development. Signal Transduct Target Ther. 2021;6(1):134.
70. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020;181(2):271-80 e8.
71. Duchene S, Featherstone L, Haritopoulou-Sinanidou M, Rambaut A, Lemey P, Baele G. Temporal signal and the phylodynamic threshold of SARS-CoV-2. Virus Evol. 2020;6(2):veaa061.
72. Ecdc.europa.eu [Internet]. Methods for the detection and characterisation of SARS-CoV-2 variants - first update. European Centre for Disease Prevention and Control. [20 December 2021; cited 7 January 2022]. Available from: https://www.ecdc.europa.eu/en/publications-data/methods-detection-and-characterisation-sars-cov-2-variants-first-update
73. Cdc.gov [Internet]. COVID-19: About Variants. Centers for Disease Control and Prevention. [13 December 2021; cited 7 January 2022]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/variants/about-variants.html
74. Imperial.ac.uk [Internet]. Report 50 - Hospitalisation risk for Omicron cases in England. Imperial College London, MRC Centre for Global Infectious Disease Analysis. [22 December

2021; cited 10 January 2022]. Available from: https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/covid-19/report-50-severity-omicron/

75. Gov.uk [Internet]. SARS-CoV-2 variants of concern and variants under investigation in England - Technical briefing 33. UK Health Security Agency. [23 December 2021; cited 10 January 2022]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1043807/technical-briefing-33.pdf
76. Luna-Muschi A, Borges IC, de Faria E, Barboza AS, Maia FL, Leme MD, et al. Clinical features of COVID-19 by SARS-CoV-2 Gamma variant: A prospective cohort study of vaccinated and unvaccinated healthcare workers. J Infect. 2021.
77. Gov.uk [Internet]. Investigation of novel SARS-CoV-2 variant - Variant of Concern 202012/01 - Technical briefing 5. UK Health Security Agency (formerly Public Health England). [14 January 2021; cited 10 January 2022]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/959426/Variant_of_Concern_VOC_202012_01_Technical_Briefing_5.pdf
78. Wang Y, Liu M, Gao J. Enhanced receptor binding of SARS-CoV-2 through networks of hydrogen-bonding and hydrophobic interactions. Proc Natl Acad Sci U S A. 2020;117(25):13967-74.
79. Yi C, Sun X, Ye J, Ding L, Liu M, Yang Z, et al. Key residues of the receptor binding motif in the spike protein of SARS-CoV-2 that interact with ACE2 and neutralizing antibodies. Cell Mol Immunol. 2020;17(6):621-30.
80. Starr TN, Greaney AJ, Hilton SK, Ellis D, Crawford KHD, Dingens AS, et al. Deep Mutational Scanning of SARS-CoV-2 Receptor Binding Domain Reveals Constraints on Folding and ACE2 Binding. Cell. 2020;182(5):1295-310 e20.
81. Huang Y, Yang C, Xu XF, Xu W, Liu SW. Structural and functional properties of SARS-CoV-2 spike protein: potential antivirus drug development for COVID-19. Acta Pharmacol Sin. 2020;41(9):1141-9.
82. Hoffmann M, Kleine-Weber H, Pohlmann S. A Multibasic Cleavage Site in the Spike Protein of SARS-CoV-2 Is Essential for Infection of Human Lung Cells. Mol Cell. 2020;78(4):779-84 e5.
83. Peacock TP, Goldhill DH, Zhou J, Baillon L, Frise R, Swann OC, et al. The furin cleavage site of SARS-CoV-2 spike protein is a key determinant for transmission due to enhanced replication in airway cells. BioRxiv [Preprint]. 2020.
84. Zhu Y, Feng F, Hu G, Wang Y, Yu Y, Zhu Y, et al. The S1/S2 boundary of SARS-CoV-2 spike protein modulates cell entry pathways and transmission. BioRxiv [Preprint]. 2020.
85. Scudellari M. How the coronavirus infects cells - and why Delta is so dangerous. Nature. 2021;595(7869):640-4.
86. Wang Q, Qiu Y, Li JY, Zhou ZJ, Liao CH, Ge XY. A Unique Protease Cleavage Site Predicted in the Spike Protein of the Novel Pneumonia Coronavirus (2019-nCoV) Potentially Related to Viral Transmissibility. Virol Sin. 2020;35(3):337-9.
87. Yurkovetskiy L, Wang X, Pascal KE, Tomkins-Tinch C, Nyalile TP, Wang Y, et al. Structural and Functional Analysis of the D614G SARS-CoV-2 Spike Protein Variant. Cell. 2020;183(3):739-51 e8.
88. McCarthy KR, Rennick LJ, Nambulli S, Robinson-McCarthy LR, Bain WG, Haidar G, et al. Natural deletions in the SARS-CoV-2 spike glycoprotein drive antibody escape. BioRxiv [Preprint]. 2021.
89. Kemp SA, Collier DA, Datir R, Ferreira I, Gayed S, Jahun A, et al. Neutralising antibodies in Spike mediated SARS-CoV-2 adaptation. MedRxiv [Preprint]. 2020.

90. Gamage AM, Tan KS, Chan WOY, Liu J, Tan CW, Ong YK, et al. Infection of human Nasal Epithelial Cells with SARS-CoV-2 and a 382-nt deletion isolate lacking ORF8 reveals similar viral kinetics and host transcriptional profiles. PLoS Pathog. 2020;16(12):e1009130.
91. Collier DA, De Marco A, Ferreira I, Meng B, Datir RP, Walls AC, et al. Sensitivity of SARS-CoV-2 B.1.1.7 to mRNA vaccine-elicited antibodies. Nature. 2021;593(7857):136-41.
92. Martínez-García L, Espinel MA, Abreu M, González-Alba JM, Gijón D, McGee A, et al. Emergence and Spread of B. 1.1. 7 Lineage in Primary Care and Clinical Impact in the Morbi-Mortality among Hospitalized Patients in Madrid, Spain. Microorganisms. 2021;9(7):1517.
93. Vassallo M, Manni S, Klotz C, Fabre R, Pini P, Blanchouin E, et al. Patients Admitted for Variant Alpha COVID-19 Have Poorer Outcomes than Those Infected with the Old Strain. J Clin Med. 2021;10(16).
94. McAlister FA, Nabipoor M, Chu A, Lee DS, Saxinger L, Bakal JA. Lessons from the COVID-19 third wave in Canada: the impact of variants of concern and shifting demographics. MedRxiv [Preprint]. 2021.
95. Davies NG, Abbott S, Barnard RC, Jarvis CI, Kucharski AJ, Munday JD, et al. Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. Science. 2021;372(6538).
96. Leung K, Shum MH, Leung GM, Lam TT, Wu JT. Early transmissibility assessment of the N501Y mutant strains of SARS-CoV-2 in the United Kingdom, October to November 2020. Euro Surveill. 2021;26(1).
97. Zhao S, Lou J, Cao L, Zheng H, Chong MKC, Chen Z, et al. Quantifying the transmission advantage associated with N501Y substitution of SARS-CoV-2 in the UK: an early data-driven analysis. J Travel Med. 2021;28(2).
98. Gov.uk [Internet]. NERVTAG paper on COVID-19 variant of concern B.1.1.7. NERVTAG - COVID-19 Public statements. [22 January 2021; cited 7 October 2021] Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/961037/NERVTAG_note_on_B.1.1.7_severity_for_SAGE_77__1_.pdf
99. Challen R, Brooks-Pollock E, Read JM, Dyson L, Tsaneva-Atanasova K, Danon L. Risk of mortality in patients infected with SARS-CoV-2 variant of concern 202012/1: matched cohort study. BMJ. 2021;372:n579.
100. Paredes MI, Lunn SM, Famulare M, Frisbie LA, Painter I, Burstein R, et al. Associations between SARS-CoV-2 variants and risk of COVID-19 hospitalization among confirmed cases in Washington State: a retrospective cohort study. MedRxiv [Preprint]. 2021.
101. Wang P, Nair MS, Liu L, Iketani S, Luo Y, Guo Y, et al. Antibody Resistance of SARS-CoV-2 Variants B.1.351 and B.1.1.7. BioRxiv [Preprint]. 2021:2021.01.25.428137.
102. Wu K, Werner AP, Moliva JI, Koch M, Choi A, Stewart-Jones GBE, et al. mRNA-1273 vaccine induces neutralizing antibodies against spike mutants from global SARS-CoV-2 variants. BioRxiv [Preprint]. 2021.
103. Gallais F, Gantner P, Bruel T, Velay A, Planas D, Wendling M-J, et al. Anti-SARS-CoV-2 Antibodies Persist for up to 13 Months and Reduce Risk of Reinfection. MedRxiv [Preprint]. 2021.
104. Ecdc.europa.eu [Internet]. SARS-CoV-2 variants of concern as of 20 January 2022. European Centre for Disease Prevention and Control. [20 January 2022; cited 24 January 2022] Available from: https://www.ecdc.europa.eu/en/covid-19/variants-concern
105. Gu H, Chen Q, Yang G, He L, Fan H, Deng YQ, et al. Adaptation of SARS-CoV-2 in BALB/c mice for testing vaccine efficacy. Science. 2020;369(6511):1603-7.
106. Plante JA, Liu Y, Liu J, Xia H, Johnson BA, Lokugamage KG, et al. Spike mutation D614G alters SARS-CoV-2 fitness. Nature. 2021;592(7852):116-21.

107. Pearson CA, Russell TW, Davies NG, Kucharski AJ, group CC-w, Edmunds WJ, et al. Estimates of severity and transmissibility of novel South Africa SARS-CoV-2 variant 501Y.V2. Centre for Mathematical Modelling of Infectious Diseases. CMMID Repository [Preprint]. 2021.
108. Wibmer CK, Ayres F, Hermanus T, Madzivhandila M, Kgagudi P, Oosthuysen B, et al. SARS-CoV-2 501Y.V2 escapes neutralization by South African COVID-19 donor plasma. Nat Med. 2021;27(4):622-5.
109. Sinha S, Tam B, Wang SM. Altered interaction between RBD and ACE2 receptor contributes towards the increased transmissibility of SARS CoV-2 delta, kappa, beta, and gamma strains with RBD double mutations. BioRxiv [Preprint]. 2021.
110. Campbell F, Archer B, Laurenson-Schafer H, Jinnai Y, Konings F, Batra N, et al. Increased transmissibility and global spread of SARS-CoV-2 variants of concern as at June 2021. Euro Surveill. 2021;26(24).
111. Ecdc.europa.eu [Internet]. Risk assessment: SARS-CoV-2 - increased circulation of variants of concern and vaccine rollout in the EU/EEA, 14th update. European Centre for Disease Prevention and Control. [15 February 2021; cited 8 October 2021] Available from: https://www.ecdc.europa.eu/en/publications-data/covid-19-risk-assessment-variants-vaccine-fourteenth-update-february-2021
112. Khan A, Zia T, Suleman M, Khan T, Ali SS, Abbasi AA, et al. Higher infectivity of the SARS-CoV-2 new variants is associated with K417N/T, E484K, and N501Y mutants: An insight from structural data. J Cell Physiol. 2021;236(10):7045-57.
113. Baum A, Fulton BO, Wloga E, Copin R, Pascal KE, Russo V, et al. Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies. Science. 2020;369(6506):1014-8.
114. Curran J, Dol J, Boulos L, Somerville M, McCulloch H, MacDonald M, et al. Transmission characteristics of SARS-CoV-2 variants of concern. MedRxiv [Preprint]. 2021.
115. de Faria E, Guedes AR, Oliveira MS, de Godoy Moreira MV, Maia FL, dos Santos Barboza A, et al. Performance of vaccination with CoronaVac in a cohort of healthcare workers (HCW) - preliminary report. MedRxiv [Preprint]. 2021.
116. Freitas ARR, Beckedorff OA, Cavalcanti LPG, Siqueira AM, Castro DB, Costa CFD, et al. The emergence of novel SARS-CoV-2 variant P.1 in Amazonas (Brazil) was temporally associated with a change in the age and sex profile of COVID-19 mortality: A population based ecological study. Lancet Reg Health Am. 2021;1:100021.
117. Funk T, Pharris A, Spiteri G, Bundle N, Melidou A, Carr M, et al. Characteristics of SARS-CoV-2 variants of concern B.1.1.7, B.1.351 or P.1: data from seven EU/EEA countries, weeks 38/2020 to 10/2021. Euro Surveill. 2021;26(16).
118. Sabino EC, Buss LF, Carvalho MPS, Prete CA, Jr., Crispim MAE, Fraiji NA, et al. Resurgence of COVID-19 in Manaus, Brazil, despite high seroprevalence. Lancet. 2021;397(10273):452-5.
119. Dejnirattisai W, Zhou D, Supasa P, Liu C, Mentzer AJ, Ginn HM, et al. Antibody evasion by the P.1 strain of SARS-CoV-2. Cell. 2021;184(11):2939-54 e9.
120. Korber B, Fischer WM, Gnanakaran S, Yoon H, Theiler J, Abfalterer W, et al. Tracking Changes in SARS-CoV-2 Spike: Evidence that D614G Increases Infectivity of the COVID-19 Virus. Cell. 2020;182(4):812-27 e19.
121. Volz E, Hill V, McCrone JT, Price A, Jorgensen D, O'Toole A, et al. Evaluating the Effects of SARS-CoV-2 Spike Mutation D614G on Transmissibility and Pathogenicity. Cell. 2021;184(1):64-75 e11.

122. Augusto G, Mohsen MO, Zinkhan S, Liu X, Vogel M, Bachmann MF. In vitro data suggest that Indian delta variant B.1.617 of SARS-CoV-2 escapes neutralization by both receptor affinity and immune evasion. Allergy. 2021.
123. Tchesnokova V, Kulakesara H, Larson L, Bowers V, Rechkina E, Kisiela D, et al. Acquisition of the L452R mutation in the ACE2-binding interface of Spike protein triggers recent massive expansion of SARS-Cov-2 variants. BioRxiv [Preprint]. 2021.
124. Li Q, Wu J, Nie J, Zhang L, Hao H, Liu S, et al. The Impact of Mutations in SARS-CoV-2 Spike on Viral Infectivity and Antigenicity. Cell. 2020;182(5):1284-94 e9.
125. Di Giacomo S, Mercatelli D, Rakhimov A, Giorgi FM. Preliminary report on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Spike mutation T478K. J Med Virol. 2021;93(9):5638-43.
126. Torjesen I. Covid-19: Delta variant is now UK's most dominant strain and spreading through schools. BMJ. 2021;373:n1445.
127. Reuters.com [Internet]. Delta COVID variant now dominant strain worldwide, U.S. deaths surge -officials. O'donnell C, Mason J, Reuters. [16 July 2021; cited 6 January 2022]. Available from: www.reuters.com
128. Euro.who.int [Internet]. SARS-CoV-2 Delta variant now dominant in much of European region; efforts must be reinforced to prevent transmission, warns WHO Regional Office for Europe and ECDC. World Health Organisation. [23 July 2021; cited 11 October 2021]. Available from: https://www.euro.who.int/en/media-centre/sections/press-releases/2021/sars-cov-2-delta-variant-now-dominant-in-much-of-european-region-efforts-must-be-reinforced-to-prevent-transmission,-warns-who-regional-office-for-europe-and-ecdc
129. Li B, Deng A, Li K, Hu Y, Li Z, Xiong Q, et al. Viral infection and transmission in a large, well-traced outbreak caused by the SARS-CoV-2 Delta variant MedRxiv [Preprint]. 2021.
130. Teyssou E, Delagreverie H, Visseaux B, Lambert-Niclot S, Brichler S, Ferre V, et al. The Delta SARS-CoV-2 variant has a higher viral load than the Beta and the historical variants in nasopharyngeal samples from newly diagnosed COVID-19 patients. J Infect. 2021;83(4):e1-e3.
131. Kumar A, Asghar A, Raza K, Narayan RK, Jha RK, Satyam A, et al. Demographic characteristics of SARS-CoV-2 B.1.617.2 (Delta) variant infections in Indian population. MedRxiv [Preprint]. 2021.
132. Planas D, Veyer D, Baidaliuk A, Staropoli I, Guivel-Benhassine F, Rajah MM, et al. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. Nature. 2021;596(7871):276-80.
133. Sheikh A, McMenamin J, Taylor B, Robertson C, Public Health S, the EIIC. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. Lancet. 2021;397(10293):2461-2.
134. Fisman DN, Tuite AR. Progressive Increase in Virulence of Novel SARS-CoV-2 Variants in Ontario, Canada. MedRxiv [Preprint]. 2021.
135. Cameroni E, Saliba C, Bowen JE, Rosen LE, Culap K, Pinto D, et al. Broadly neutralizing antibodies overcome SARS-CoV-2 Omicron antigenic shift. BioRxiv [Preprint]. 2021.
136. Shah M, Woo HG. Omicron: A heavily mutated SARS-CoV-2 variant exhibits stronger binding to ACE2 and potently escape approved COVID-19 therapeutic antibodies. BioRxiv [Preprint]. 2021.
137. Wolter N, Jassat W, Walaza S, Welch R, Moultrie H, Groome M, et al. Early assessment of the clinical severity of the SARS-CoV-2 Omicron variant in South Africa. MedRxiv [Preprint]. 2021.
138. Gov.uk [Internet]. Omicron daily overview: 24 December 2021. UK Health Security Agency. [24 December 2021; cited 4 January 2022]. Available from:

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1043866/20211224_OS_Daily_Omicron_Overview.pdf

139. Who.int [Internet]. Enhancing readiness for Omicron (B.1.1.529): Technical brief and priority actions for Member States. World Health Organisation. [23 December 2021; cited 4 January 2022]. Available from: https://www.who.int/docs/default-source/coronaviruse/2021-12-23-global-technical-brief-and-priority-action-on-omicron.pdf?sfvrsn=d0e9fb6c_8
140. Med.hku.hk [Internet]. HKUMed finds Omicron SARS-CoV-2 can infect faster and better than Delta in human bronchus but with less severe infection in lung. The University of Hong Kong, LKS Faculty of Medicine. [15 December 2021; cited 5 January 2022]. Available from: https://www.med.hku.hk/en/news/press/20211215-omicron-sars-cov-2-infection
141. Sheikh A, Kerr S, Woolhouse M, McMenamin J, C. R. Severity of Omicron variant of concern and vaccine effectiveness against symptomatic disease: national cohort with nested test negative design study in Scotland. 2021.
142. Pulliam JRC, van Schalkwyk C, Govender N, von Gottberg A, Cohen C, Groome MJ, et al. Increased risk of SARS-CoV-2 reinfection associated with emergence of the Omicron variant in South Africa. MedRxiv [Preprint]. 2021.
143. Sandile Cele, Laurelle Jackson, Khadija Khan, David Khoury, Thandeka Moyo-Gwete, Houriiyah Tegally, et al. SARS-CoV-2 Omicron has extensive but incomplete escape of Pfizer BNT162b2 elicited neutralization and requires ACE2 for infection. MedRxiv [Preprint]. 2021.
144. Planas D, Saunders N, Maes P, Guivel-Benhassine F, Planchais C, Buchrieser J, et al. Considerable escape of SARS-CoV-2 variant Omicron to antibody neutralization. BioRxiv [Preprint]. 2021.
145. Meng B, Ferreira IATM, Abdullahi A, Saito A, Kimura I, Yamasoba D, et al. SARS-CoV-2 Omicron spike mediated immune escape, infectivity and cell-cell fusion. BioRxiv [Preprint]. 2021.
146. Pfizer.com [Internet]. Pfizer and BioNTech Provide Update on Omicron Variant. Pfizer. [8 December 2021; cited 4 January 2022]. Available from: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-provide-update-omicron-variant
147. Keeton R, Tincho MB, Ngomti A, Baguma R, Benede N, Suzuki A, et al. SARS-CoV-2 spike T cell responses induced upon vaccination or infection remain robust against Omicron. MedRxiv [Preprint]. 2021.
148. Sacoronavirus.co.za [Internet]. Cabinet approves changes to covid-19 regulations. South Africa Department of Health. [30 December 2021; cited 7 January 2022]. Available from: https://sacoronavirus.co.za/2021/12/30/media-release-cabinet-approves-changes-to-covid-19-regulations/
149. Taylor L. Covid-19: Omicron drives weekly record high in global infections. BMJ. 2022;376:o66.
150. Tada T, Zhou H, Dcosta BM, Samanovic MI, Mulligan MJ, Landau NR. SARS-CoV-2 Lambda Variant Remains Susceptible to Neutralization by mRNA Vaccine-elicited Antibodies and Convalescent Serum. BioRxiv [Preprint]. 2021.
151. Acevedo ML, Alonso-Palomares L, Bustamante A, Gaggero A, Paredes F, Cortés CP, et al. Infectivity and immune escape of the new SARS-CoV-2 variant of interest Lambda. MedRxiv [Preprint]. 2021.
152. Laiton-Donato K, Franco-Munoz C, Alvarez-Diaz DA, Ruiz-Moreno HA, Usme-Ciro JA, Prada DA, et al. Characterization of the emerging B.1.621 variant of interest of SARS-CoV-2. Infect Genet Evol. 2021;95:105038.

153. Chen J, Gao K, Wang R, Wei GW. Revealing the Threat of Emerging SARS-CoV-2 Mutations to Antibody Therapies. J Mol Biol. 2021;433(18):167155.
154. Amanat F, Krammer F. SARS-CoV-2 vaccines: status report. Immunity. 2020;52(4):583-9.
155. [dataset] Who.int. COVID-19 vaccine tracker and landscape. World Health Organisation. [25 January 2022; cited 26 January 2022]. Available from: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines
156. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020;383(27):2603-15.
157. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh C-L, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020;367(6483):1260-3.
158. Who.int [Internet]. Coronavirus disease (COVID-19): Vaccines. World Health Organisation. [20 January 2022; cited 26 January 2022]. Available from: https://www.who.int/news-room/questions-and-answers/item/coronavirus-disease-(covid-19)-vaccines
159. Sahin U, Muik A, Vogler I, Derhovanessian E, Kranz LM, Vormehr M, et al. BNT162b2 vaccine induces neutralizing antibodies and poly-specific T cells in humans. Nature. 2021;595(7868):572-7.
160. Arunachalam PS, Scott MKD, Hagan T, Li C, Feng Y, Wimmers F, et al. Systems vaccinology of the BNT162b2 mRNA vaccine in humans. Nature. 2021;596(7872):410-6.
161. Walsh EE, Frenck RW, Jr., Falsey AR, Kitchin N, Absalon J, Gurtman A, et al. Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates. N Engl J Med. 2020;383(25):2439-50.
162. Appelman B, van der Straten K, Lavell AHA, Schinkel M, Slim MA, Poniman M, et al. Time since SARS-CoV-2 infection and humoral immune response following BNT162b2 mRNA vaccination. EBioMedicine. 2021;72:103589.
163. Beatty AL, Peyser ND, Butcher XE, Cocohoba JM, Lin F, Olgin JE, et al. Analysis of COVID-19 Vaccine Type and Adverse Effects Following Vaccination. JAMA Netw Open. 2021;4(12):e2140364.
164. Vizcarra P, Haemmerle J, Velasco H, Velasco T, Fernandez-Escribano M, Vallejo A, et al. BNT162b2 mRNA COVID-19 vaccine Reactogenicity: The key role of immunity. Vaccine. 2021;39(51):7367-74.
165. Salmeron Rios S, Mas Romero M, Cortes Zamora EB, Tabernero Sahuquillo MT, Romero Rizos L, Sanchez-Jurado PM, et al. Immunogenicity of the BNT162b2 vaccine in frail or disabled nursing home residents: COVID-A study. J Am Geriatr Soc. 2021;69(6):1441-7.
166. Barda N, Dagan N, Ben-Shlomo Y, Kepten E, Waxman J, Ohana R, et al. Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. N Engl J Med. 2021;385(12):1078-90.
167. Sharma O, Sultan AA, Ding H, Triggle CR. A Review of the Progress and Challenges of Developing a Vaccine for COVID-19. Front Immunol. 2020;11:585354.
168. Who.int [Internet]. WHO lists two additional COVID-19 vaccines for emergency use and COVAX roll-out. World Health Organisation. [15 February 2021; cited 13 October 2021]. Available rom: https://www.who.int/news/item/15-02-2021-who-lists-two-additional-covid-19-vaccines-for-emergency-use-and-covax-roll-out
169. Ewer KJ, Barrett JR, Belij-Rammerstorfer S, Sharpe H, Makinson R, Morter R, et al. T cell and antibody responses induced by a single dose of ChAdOx1 nCoV-19 (AZD1222) vaccine in a phase 1/2 clinical trial. Nat Med. 2021;27(2):270-8.

170. Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij-Rammerstorfer S, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. Lancet. 2020;396(10249):467-78.
171. Al Khames Aga QA, Alkhaffaf WH, Hatem TH, Nassir KF, Batineh Y, Dahham AT, et al. Safety of COVID-19 vaccines. J Med Virol. 2021;93(12):6588-94.
172. Sadoff J, Gray G, Vandebosch A, Cardenas V, Shukarev G, Grinsztejn B, et al. Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19. N Engl J Med. 2021;384(23):2187-201.
173. Alter G, Yu J, Liu J, Chandrashekar A, Borducchi EN, Tostanoski LH, et al. Immunogenicity of Ad26.COV2.S vaccine against SARS-CoV-2 variants in humans. Nature. 2021;596(7871):268-72.
174. Sadoff J, Le Gars M, Shukarev G, Heerwegh D, Truyers C, de Groot AM, et al. Interim Results of a Phase 1-2a Trial of Ad26.COV2.S Covid-19 Vaccine. N Engl J Med. 2021;384(19):1824-35.
175. Keeton R, Richardson SI, Moyo-Gwete T, Hermanus T, Tincho MB, Benede N, et al. Prior infection with SARS-CoV-2 boosts and broadens Ad26.COV2.S immunogenicity in a variant-dependent manner. Cell Host Microbe. 2021;29(11):1611-9 e5.
176. See I, Su JR, Lale A, Woo EJ, Guh AY, Shimabukuro TT, et al. US Case Reports of Cerebral Venous Sinus Thrombosis With Thrombocytopenia After Ad26.COV2.S Vaccination, March 2 to April 21, 2021. JAMA. 2021;325(24):2448-56.
177. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2021;384(5):403-16.
178. Mukhopadhyay L, Yadav PD, Gupta N, Mohandas S, Patil DY, Shete-Aich A, et al. Comparison of the immunogenicity & protective efficacy of various SARS-CoV-2 vaccine candidates in non-human primates. Indian J Med Res. 2021;153(1 & 2):93-114.
179. Anderson EJ, Rouphael NG, Widge AT, Jackson LA, Roberts PC, Makhene M, et al. Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults. N Engl J Med. 2020;383(25):2427-38.
180. Jackson LA, Anderson EJ, Rouphael NG, Roberts PC, Makhene M, Coler RN, et al. An mRNA Vaccine against SARS-CoV-2 - Preliminary Report. N Engl J Med. 2020;383(20):1920-31.
181. Chu L, McPhee R, Huang W, Bennett H, Pajon R, Nestorova B, et al. A preliminary report of a randomized controlled phase 2 trial of the safety and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine. Vaccine. 2021;39(20):2791-9.
182. Who.int [Internet]. Interim recommendations for use of the inactivated COVID-19 vaccine BIBP developed by China National Biotec Group (CNBG), Sinopharm. World Health Organisation. [28 October 2021; cited 7 January 2022]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-BIBP
183. Who.int [Internet]. Background document on the inactivated vaccine Sinovac-CoronaVac against COVID-19. World Health Organisation. [1 June 2021; cited 13 October 2021]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-Sinovac-CoronaVac-background-2021.1
184. Who.int [Internet]. Background document on the Bharat Biotech BBV152 COVAXIN® (COVID-19) vaccine. World Health Organisation. [3 November 2021; cited 7 January 2022]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-bbv152-covaxin-background

185. Who.int [Internet]. WHO issues emergency use listing for eighth COVID-19 vaccine. World Health Organisation. [3 November 2021; cited 7 January 2022]. Available from: https://www.who.int/news/item/03-11-2021-who-issues-emergency-use-listing-for-eighth-covid-19-vaccine
186. Who.int [Internet]. WHO lists 9th COVID-19 vaccine for emergency use with aim to increase access to vaccination in lower-income countries. World Health Organisation. [17 December 2021; cited 7 January 2022]. Available from: https://www.who.int/news/item/17-12-2021-who-lists-9th-covid-19-vaccine-for-emergency-use-with-aim-to-increase-access-to-vaccination-in-lower-income-countries
187. Who.int [Internet]. WHO lists 10th COVID-19 vaccine for emergency use: Nuvaxovid. World Health Organisation. [21 December 2021; cited 7 January 2022]. Available from: https://www.who.int/news/item/21-12-2021-who-lists-10th-covid-19-vaccine-for-emergency-use-nuvaxovid
188. Who.int [Internet]. Interim recommendations for use of the Novavax NVX-CoV2373 vaccine against COVID-19. World Health Organisation. [20 December 2021; cited 7 January 2022]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-novavax-nvx-cov2373
189. Mishra SK, Pradhan SK, Pati S, Sahu S, Nanda RK. Waning of Anti-spike Antibodies in AZD1222 (ChAdOx1) Vaccinated Healthcare Providers: A Prospective Longitudinal Study. Cureus. 2021;13(11):e19879.
190. Tre-Hardy M, Cupaiolo R, Wilmet A, Antoine-Moussiaux T, Della Vecchia A, Horeanga A, et al. Immunogenicity of mRNA-1273 COVID vaccine after 6 months surveillance in health care workers; a third dose is necessary. J Infect. 2021;83(5):559-64.
191. Shrotri M, Navaratnam AMD, Nguyen V, Byrne T, Geismar C, Fragaszy E, et al. Spike-antibody waning after second dose of BNT162b2 or ChAdOx1. Lancet. 2021;398(10298):385-7.
192. Chemaitelly H, Tang P, Hasan MR, AlMukdad S, Yassine HM, Benslimane FM, et al. Waning of BNT162b2 Vaccine Protection against SARS-CoV-2 Infection in Qatar. N Engl J Med. 2021.
193. Mizrahi B, Lotan R, Kalkstein N, Peretz A, Perez G, Ben-Tov A, et al. Correlation of SARS-CoV-2 Breakthrough Infections to Time-from-vaccine; Preliminary Study. MedRxiv [Preprint]. 2021.
194. Thomas SJ, Moreira ED, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Six Month Safety and Efficacy of the BNT162b2 mRNA COVID-19 Vaccine. MedRxiv [Preprint]. 2021.
195. Tre-Hardy M, Cupaiolo R, Wilmet A, Antoine-Moussiaux T, Della Vecchia A, Horeanga A, et al. Six-month interim analysis of ongoing immunogenicity surveillance of the mRNA-1273 vaccine in healthcare workers: A third dose is expected. J Infect. 2021.
196. Almendro-Vazquez P, Laguna-Goya R, Ruiz-Ruigomez M, Utrero-Rico A, Lalueza A, Maestro de la Calle G, et al. Longitudinal dynamics of SARS-CoV-2-specific cellular and humoral immunity after natural infection or BNT162b2 vaccination. PLoS Pathog. 2021;17(12):e1010211.
197. Cohen KW, Linderman SL, Moodie Z, Czartoski J, Lai L, Mantus G, et al. Longitudinal analysis shows durable and broad immune memory after SARS-CoV-2 infection with persisting antibody responses and memory B and T cells. Cell Rep Med. 2021;2(7):100354.
198. Zeng G, Wu Q, Pan H, Li M, Yang J, Wang L, et al. Immunogenicity and safety of a third dose of CoronaVac, and immune persistence of a two-dose schedule, in healthy adults: interim results from two single-centre, double-blind, randomised, placebo-controlled phase 2 clinical trials. Lancet Infect Dis. 2021.

199. Choi A, Koch M, Wu K, Chu L, Ma L, Hill A, et al. Safety and immunogenicity of SARS-CoV-2 variant mRNA vaccine boosters in healthy adults: an interim analysis. Nat Med. 2021.
200. Flaxman A, Marchevsky NG, Jenkin D, Aboagye J, Aley PK, Angus B, et al. Reactogenicity and immunogenicity after a late second dose or a third dose of ChAdOx1 nCoV-19 in the UK: a substudy of two randomised controlled trials (COV001 and COV002). Lancet. 2021;398(10304):981-90.
201. Iketani S, Liu L, Nair MS, Mohri H, Wang M, Huang Y, et al. A third COVID-19 vaccine shot markedly boosts neutralizing antibody potency and breadth MedRxiv [Preprint]. 2021.
202. Garcia-Beltran WF, St Denis KJ, Hoelzemer A, Lam EC, Nitido AD, Sheehan ML, et al. mRNA-based COVID-19 vaccine boosters induce neutralizing immunity against SARS-CoV-2 Omicron variant. MedRxiv [Preprint]. 2021.
203. Yorsaeng R, Suntronwong N, Phowatthanasathian H, Assawakosri S, Kanokudom S, Thongmee T, et al. Immunogenicity of a third dose viral-vectored COVID-19 vaccine after receiving two-dose inactivated vaccines in healthy adults. Vaccine. 2022;40(3):524-30.
204. Munro APS, Janani L, Cornelius V, Aley PK, Babbage G, Baxter D, et al. Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial. Lancet. 2021;398(10318):2258-76.
205. Madelon N, Heikkilä N, Sabater Royo I, Fontannaz P, Breville G, Lauper K, et al. Omicron-specific cytotoxic T-cell responses are boosted following a third dose of mRNA COVID-19 vaccine in anti-CD20-treated multiple sclerosis patients MedRxiv [Preprint]. 2021.
206. Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Kalkstein N, et al. Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel. N Engl J Med. 2021;385(15):1393-400.
207. Barda N, Dagan N, Cohen C, Hernan MA, Lipsitch M, Kohane IS, et al. Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. Lancet. 2021;398(10316):2093-100.
208. Arbel R, Hammerman A, Sergienko R, Friger M, Peretz A, Netzer D, et al. BNT162b2 Vaccine Booster and Mortality Due to Covid-19. N Engl J Med. 2021;385(26):2413-20.
209. Spitzer A, Angel Y, Marudi O, Zeltser D, Saiag E, Goldshmidt H, et al. Association of a Third Dose of BNT162b2 Vaccine With Incidence of SARS-CoV-2 Infection Among Health Care Workers in Israel. JAMA. 2022.
210. Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Alroy-Preis S, et al. Protection against Covid-19 by BNT162b2 Booster across Age Groups. N Engl J Med. 2021;385(26):2421-30.
211. Levine-Tiefenbrun M, Yelin I, Alapi H, Katz R, Herzel E, Kuint J, et al. Viral loads of Delta-variant SARS-CoV-2 breakthrough infections after vaccination and booster with BNT162b2. Nat Med. 2021;27(12):2108-10.
212. Andrews N, Stowe J, Kirsebom F, Toffa S, Rickeard T, Gallagher E, et al. Effectiveness of COVID-19 vaccines against the Omicron (B.1.1.529) variant of concern. medRxiv [Preprint]. 2021.
213. Hansen CH, Schelde AB, Moustsen-Helm IR, Emborg H-D, Krause TG, Mølbak K, et al. Vaccine effectiveness against SARS-CoV-2 infection with the Omicron or Delta variants following a two-dose or booster BNT162b2 or mRNA-1273 vaccination series: A Danish cohort study MedRxiv [Preprint]. 2021.
214. Lusvarghi S, Pollett SD, Neerukonda SN, Wang W, Wang R, Vassell R, et al. SARS-CoV-2 Omicron neutralization by therapeutic antibodies, convalescent sera, and post-mRNA vaccine booster. BioRxiv [Preprint]. 2021.

215. Cdc.gov [Internet]. CDC Recommends Pfizer Booster at 5 Months, Additional Primary Dose for Certain Immunocompromised Children. Centers for Disease Control and Prevention. [4 January 2022; cited 7 January 2022]. Available from: https://www.cdc.gov/media/releases/2022/s0104-Pfizer-Booster.html
216. Wu K, Choi A, Koch M, Elbashir S, Ma L, Lee D, et al. Variant SARS-CoV-2 mRNA vaccines confer broad neutralization as primary or booster series in mice. Vaccine. 2021;39(51):7394-400.
217. Covid19-trials.com [Internet]. Global Coronavirus COVID-19 Clinical Trial Tracker. Cytel Inc. [cited 12 January 2022]. Available from: https://www.covid19-trials.com/
218. Gov.uk [Internet]. First oral antiviral for COVID-19, Lagevrio (molnupiravir), approved by MHRA. Medicines and Healthcare products Regulatory Agency. [4 November 2021; cited 12 January 2022]. Available from: https://www.gov.uk/government/news/first-oral-antiviral-for-covid-19-lagevrio-molnupiravir-approved-by-mhra
219. Gov.uk [Internet]. Oral COVID-19 antiviral, Paxlovid, approved by UK regulator. Medicines and Healthcare products Regulatory Agency. [31 December 2021; cited 12 January 2022]. Available from: https://www.gov.uk/government/news/oral-covid-19-antiviral-paxlovid-approved-by-uk-regulator
220. Fda.gov [Internet]. Coronavirus (COVID-19) Update: FDA Authorizes Additional Oral Antiviral for Treatment of COVID-19 in Certain Adults. U.S. Food and Drug Administration. [23 December 2021; cited 12 January 2022]. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-oral-antiviral-treatment-covid-19-certain
221. Fda.gov [Internet]. Coronavirus (COVID-19) Update: FDA Authorizes First Oral Antiviral for Treatment of COVID-19. U.S. Food and Drug Administration. [22 December 2021; cited 12 January 2022]. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-oral-antiviral-treatment-covid-19
222. ema.europa.eu [Internet]. EMA issues advice on use of Lagevrio (molnupiravir) for the treatment of COVID-19. European Medicines Agency. [19 November 2021.; cited 12 January 2022]. Available from: https://www.ema.europa.eu/en/news/ema-issues-advice-use-lagevrio-molnupiravir-treatment-covid-19
223. ema.europa.eu [Internet]. EMA issues advice on use of Paxlovid (PF-07321332 and ritonavir) for the treatment of COVID-19: rolling review starts in parallel. European Medicines Agency. [16 December 2021.; cited 12 January 2022]. Available from: https://www.ema.europa.eu/en/news/ema-issues-advice-use-paxlovid-pf-07321332-ritonavir-treatment-covid-19-rolling-review-starts
224. Gov.uk [Internet]. MHRA approves Xevudy (sotrovimab), a COVID-19 treatment found to cut hospitalisation and death by 79%. Medicines and Healthcare products Regulatory Agency. [2 December 2021; cited 12 January 2022]. Available from: https://www.gov.uk/government/news/mhra-approves-xevudy-sotrovimab-a-covid-19-treatment-found-to-cut-hospitalisation-and-death-by-79#:~:text=and%20licensing%20guidance-,MHRA%20approves%20Xevudy%20(sotrovimab)%2C%20a%20COVID%2D19%20treatment,risk%20of%20developing%20severe%20disease.
225. Fda.gov [Internet]. Coronavirus (COVID-19) Update: FDA Authorizes Additional Monoclonal Antibody for Treatment of COVID-19. U.S. Food and Drug Administration. [26 May 2021; cited 12 January 2022]. Available from: https://www.fda.gov/news-events/press-

announcements/coronavirus-covid-19-update-fda-authorizes-additional-monoclonal-antibody-treatment-covid-19

226. ema.europa.eu [Internet]. COVID-19: EMA recommends authorisation of antibody medicine Xevudy. European Medicines Agency. [16 December 2021.; cited 12 January 2022]. Available from: https://www.ema.europa.eu/en/news/covid-19-ema-recommends-authorisation-antibody-medicine-xevudy#:~:text=EMA's%20human%20medicines%20committee%20(CHMP,medicine%20together%20with%20Vir%20Biotechnology.
227. Who.int [Internet]. Therapeutics and COVID-19: living guideline. World Health Organisation. [14 January 2022; cited 21 January 2022] Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022.1
228. Nice.org.uk [Internet]. COVID-19 rapid guideline: managing COVID-19 NICE guideline [NG191]. National Institute for Health and Care Excellence. [16 December 2021; cited 21 January 2022]. Available from: https://www.nice.org.uk/guidance/ng191
229. Gov.uk [Internet]. MHRA guidance on coronavirus (COVID-19). Medicines and Healthcare products Regulatory Agency. [16 September 2021; cited 21 January 2022]. Available from: https://www.gov.uk/government/collections/mhra-guidance-on-coronavirus-covid-19
230. ecdc.europa.eu [Internet]. All resources on COVID-19 – Guidance and technical reports. [2022; cited 21 January 2022]. Available from: https://www.ecdc.europa.eu/en/covid-19/all-reports-covid-19
231. Nih.gov [Internet]. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health [19 January 2022; cited 21 January 2022]. Available from: https://www.covid19treatmentguidelines.nih.gov/
232. Cdc.gov [Internet]. Guidance for COVID-19. Centers for Disease Control and Prevention. [15 March 2021; cited 21 January 2022]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/communication/guidance.html
233. Blundell R, Costa Dias M, Joyce R, Xu X. COVID-19 and Inequalities. Fisc Stud. 2020.
234. Chadeau-Hyam M, Bodinier B, Elliott J, Whitaker MD, Tzoulaki I, Vermeulen R, et al. Risk factors for positive and negative COVID-19 tests: a cautious and in-depth analysis of UK biobank data. Int J Epidemiol. 2020;49(5):1454-67.
235. Patel JA, Nielsen FBH, Badiani AA, Assi S, Unadkat VA, Patel B, et al. Poverty, inequality and COVID-19: the forgotten vulnerable. Public Health. 2020;183:110-1.
236. Cohen J, Rodgers YVM. Contributing factors to personal protective equipment shortages during the COVID-19 pandemic. Prev Med. 2020;141:106263.
237. Who.int [Internet]. Vaccine Equity. World Health Organisation. [cited 10 January 2022]. Available from: https://www.who.int/campaigns/vaccine-equity
238. parliament.uk [Internet]. Coronavirus: lessons learned to date. The House of Commons, Science and Technology Committee, and Health and Social Care Committee. [12 October 2021; cited 10 January 2022]. Available from: https://publications.parliament.uk/pa/cm5802/cmselect/cmsctech/92/9203.htm
239. Ball P. The lightning-fast quest for COVID vaccines - and what it means for other diseases. Nature. 2021;589(7840):16-8.
240. Summers J, Cheng HY, Lin HH, Barnard LT, Kvalsvig A, Wilson N, et al. Potential lessons from the Taiwan and New Zealand health responses to the COVID-19 pandemic. Lancet Reg Health West Pac. 2020;4:100044.

241. Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. N Engl J Med. 2021;384(15):1412-23.
242. Lopez Bernal J, Andrews N, Gower C, Gallagher E, Simmons R, Thelwall S, et al. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. N Engl J Med. 2021;385(7):585-94.
243. Abu-Raddad LJ, Chemaitelly H, Butt AA, National Study Group for C-V. Effectiveness of the BNT162b2 Covid-19 Vaccine against the B.1.1.7 and B.1.351 Variants. N Engl J Med. 2021;385(2):187-9.
244. Chung H, He S, Nasreen S, Sundaram ME, Buchan SA, Wilson SE, et al. Effectiveness of BNT162b2 and mRNA-1273 covid-19 vaccines against symptomatic SARS-CoV-2 infection and severe covid-19 outcomes in Ontario, Canada: test negative design study. BMJ. 2021;374:n1943.
245. Nasreen S, Chung H, He S, Brown KA, Gubbay JB, Buchan SA, et al. Effectiveness of mRNA and ChAdOx1 COVID-19 vaccines against symptomatic SARS CoV-2 infection and severe outcomes with variants of concern in Ontario. MedRxiv [Preprint]. 2021.
246. Puranik A, Lenehan PJ, Silvert E, Niesen MJM, Corchado-Garcia J, O'Horo JC, et al. Comparison of two highly-effective mRNA vaccines for COVID-19 during periods of Alpha and Delta variant prevalence. MedRxiv [Preprint]. 2021.
247. Julia Stowe, Nick Andrews, Charlotte Gower, Eileen Gallagher, Lara Utsi, Ruth Simmons, et al. Effectiveness of COVID-19 vaccines against hospital admission with the Delta (B.1.617.2) variant. Public Health England [preprint]. 2021.
248. Lopez Bernal J, Andrews N, Gower C, Robertson C, Stowe J, Tessier E, et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. BMJ. 2021;373:n1088.
249. Skowronski DM, Setayeshgar S, Zou M, Prystajecky N, Tyson JR, Galanis E, et al. Single-dose mRNA vaccine effectiveness against SARS-CoV-2, including Alpha and Gamma variants: a test-negative design in adults 70 years and older in British Columbia, Canada. Clin Infect Dis. 2021.
250. Carazo S, Talbot D, Boulianne N, Brisson M, Gilca R, Deceuninck G, et al. Single-dose mRNA vaccine effectiveness against SARS-CoV-2 in healthcare workers extending 16 weeks post-vaccination: a test-negative design from Quebec, Canada. Clin Infect Dis. 2021.
251. Charmet T, Schaeffer L, Grant R, Galmiche S, Cheny O, Von Platen C, et al. Impact of original, B.1.1.7, and B.1.351/P.1 SARS-CoV-2 lineages on vaccine effectiveness of two doses of COVID-19 mRNA vaccines: Results from a nationwide case-control study in France. Lancet Reg Health Eur. 2021;8:100171.
252. Tang P, Hasan MR, Chemaitelly H, Yassine HM, Benslimane FM, Al Khatib HA, et al. BNT162b2 and mRNA-1273 COVID-19 vaccine effectiveness against the SARS-CoV-2 Delta variant in Qatar. Nat Med. 2021;27(12):2136-43.
253. Hall VJ, Foulkes S, Saei A, Andrews N, Oguti B, Charlett A, et al. COVID-19 vaccine coverage in health-care workers in England and effectiveness of BNT162b2 mRNA vaccine against infection (SIREN): a prospective, multicentre, cohort study. Lancet. 2021;397(10286):1725-35.
254. Haas EJ, Angulo FJ, McLaughlin JM, Anis E, Singer SR, Khan F, et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. Lancet. 2021;397(10287):1819-29.

255. Nanduri S, Pilishvili T, Derado G, Soe MM, Dollard P, Wu H, et al. Effectiveness of Pfizer-BioNTech and Moderna Vaccines in Preventing SARS-CoV-2 Infection Among Nursing Home Residents Before and During Widespread Circulation of the SARS-CoV-2 B.1.617.2 (Delta) Variant - National Healthcare Safety Network, March 1-August 1, 2021. MMWR Morb Mortal Wkly Rep. 2021;70(34):1163-6.
256. Fowlkes A, Gaglani M, Groover K, Thiese MS, Tyner H, Ellingson K, et al. Effectiveness of COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Frontline Workers Before and During B.1.617.2 (Delta) Variant Predominance - Eight U.S. Locations, December 2020-August 2021. MMWR Morb Mortal Wkly Rep. 2021;70(34):1167-9.
257. Lefevre B, Tondeur L, Madec Y, Grant R, Lina B, van der Werf S, et al. Beta SARS-CoV-2 variant and BNT162b2 vaccine effectiveness in long-term care facilities in France. Lancet Healthy Longev. 2021.
258. Pouwels KB, Pritchard E, Matthews PC, Stoesser N, Eyre DW, Vihta K-D, et al. Effect of Delta variant on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK. Nature Medicine. 2021.
259. Williams C, Al-Bargash D, Macalintal C, Stuart R, Seth A, Latham J, et al. COVID-19 Outbreak Associated with a SARS-CoV-2 P.1 Lineage in a Long-Term Care Home after Implementation of a Vaccination Program - Ontario, April-May 2021. Clin Infect Dis. 2021.
260. Fabiani M, Ramigni M, Gobbetto V, Mateo-Urdiales A, Pezzotti P, Piovesan C. Effectiveness of the Comirnaty (BNT162b2, BioNTech/Pfizer) vaccine in preventing SARS-CoV-2 infection among healthcare workers, Treviso province, Veneto region, Italy, 27 December 2020 to 24 March 2021. Euro Surveill. 2021;26(17).
261. Thomas SJ, Moreira ED, Jr., Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months. N Engl J Med. 2021;385(19):1761-73.
262. Angel Y, Spitzer A, Henig O, Saiag E, Sprecher E, Padova H, et al. Association Between Vaccination With BNT162b2 and Incidence of Symptomatic and Asymptomatic SARS-CoV-2 Infections Among Health Care Workers. JAMA. 2021;325(24):2457-65.
263. Bjork J, Inghammar M, Moghaddassi M, Rasmussen M, Malmqvist U, Kahn F. High level of protection against COVID-19 after two doses of BNT162b2 vaccine in the working age population - first results from a cohort study in Southern Sweden. Infect Dis (Lond). 2022;54(2):128-33.
264. Cabezas C, Coma E, Mora-Fernandez N, Li X, Martinez-Marcos M, Fina F, et al. Associations of BNT162b2 vaccination with SARS-CoV-2 infection and hospital admission and death with covid-19 in nursing homes and healthcare workers in Catalonia: prospective cohort study. BMJ. 2021;374:n1868.
265. Emborg H-D, Valentiner-Branth P, Schelde AB, Nielsen KF, Gram MA, Moustsen-Helms IR, et al. Vaccine effectiveness of the BNT162b2 mRNA COVID-19 vaccine against RT-PCR confirmed SARS-CoV2 infections, hospitalisations and mortality in prioritised risk groups. MedRxiv [Preprint]. 2021.
266. Gras-Valenti P, Chico-Sanchez P, Algado-Selles N, Jimenez-Sepulveda NJ, Gomez-Sotero IL, Fuster-Perez M, et al. [Effectiveness of the first dose of BNT162b2 vaccine to preventing covid-19 in healthcare personnel.]. Rev Esp Salud Publica. 2021;95.
267. Mason TFD, Whitston M, Hodgson J, Watkinson RE, Lau YS, Abdulrazeg O, et al. Effects of BNT162b2 mRNA vaccine on COVID-19 infection and hospitalisation amongst older people: matched case control study for England. BMC Med. 2021;19(1):275.

268. Monge S, Olmedo C, Alejos B, Lapena MF, Sierra MJ, Limia A, et al. Direct and Indirect Effectiveness of mRNA Vaccination against Severe Acute Respiratory Syndrome Coronavirus 2 in Long-Term Care Facilities, Spain. Emerg Infect Dis. 2021;27(10):2595-603.
269. Pritchard E, Matthews PC, Stoesser N, Eyre DW, Gethings O, Vihta KD, et al. Impact of vaccination on new SARS-CoV-2 infections in the United Kingdom. Nat Med. 2021;27(8):1370-8.
270. Regev-Yochay G, Amit S, Bergwerk M, Lipsitch M, Leshem E, Kahn R, et al. Decreased infectivity following BNT162b2 vaccination: A prospective cohort study in Israel. Lancet Reg Health Eur. 2021;7:100150.
271. Shrotri M, Krutikov M, Palmer T, Giddings R, Azmi B, Subbarao S, et al. Vaccine effectiveness of the first dose of ChAdOx1 nCoV-19 and BNT162b2 against SARS-CoV-2 infection in residents of long-term care facilities in England (VIVALDI): a prospective cohort study. Lancet Infect Dis. 2021;21(11):1529-38.
272. Swift MD, Breeher LE, Tande AJ, Tommaso CP, Hainy CM, Chu H, et al. Effectiveness of Messenger RNA Coronavirus Disease 2019 (COVID-19) Vaccines Against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in a Cohort of Healthcare Personnel. Clin Infect Dis. 2021;73(6):e1376-e9.
273. Thompson MG, Burgess JL, Naleway AL, Tyner H, Yoon SK, Meece J, et al. Prevention and Attenuation of Covid-19 with the BNT162b2 and mRNA-1273 Vaccines. N Engl J Med. 2021;385(4):320-9.
274. Frenck RW, Jr., Klein NP, Kitchin N, Gurtman A, Absalon J, Lockhart S, et al. Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents. N Engl J Med. 2021;385(3):239-50.
275. June Choe Y, Yi S, Hwang I, Kim J, Park YJ, Cho E, et al. Safety and effectiveness of BNT162b2 mRNA Covid-19 vaccine in adolescents. Vaccine. 2021.
276. Lutrick K, Rivers P, Yoo YM, Grant L, Hollister J, Jovel K, et al. Interim Estimate of Vaccine Effectiveness of BNT162b2 (Pfizer-BioNTech) Vaccine in Preventing SARS-CoV-2 Infection Among Adolescents Aged 12-17 Years - Arizona, July-December 2021. MMWR Morb Mortal Wkly Rep. 2021;70(5152):1761-5.
277. Glatman-Freedman A, Bromberg M, Dichtiar R, Hershkovitz Y, Keinan-Boker L. The BNT162b2 vaccine effectiveness against new COVID-19 cases and complications of breakthrough cases: A nation-wide retrospective longitudinal multiple cohort analysis using individualised data. EBioMedicine. 2021;72:103574.
278. Pilishvili T, Fleming-Dutra KE, Farrar JL, Gierke R, Mohr NM, Talan DA, et al. Interim Estimates of Vaccine Effectiveness of Pfizer-BioNTech and Moderna COVID-19 Vaccines Among Health Care Personnel - 33 U.S. Sites, January-March 2021. MMWR Morb Mortal Wkly Rep. 2021;70(20):753-8.
279. Martinez-Baz I, Miqueleiz A, Casado I, Navascues A, Trobajo-Sanmartin C, Burgui C, et al. Effectiveness of COVID-19 vaccines in preventing SARS-CoV-2 infection and hospitalisation, Navarre, Spain, January to April 2021. Euro Surveill. 2021;26(21).
280. Vasileiou E, Simpson CR, Shi T, Kerr S, Agrawal U, Akbari A, et al. Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study. Lancet. 2021;397(10285):1646-57.
281. ecdc.europa.eu [Internet]. Interim analysis of COVID-19 vaccine effectiveness against Severe Acute Respiratory Infection due to laboratory-confirmed SARS-CoV-2 among individuals aged 50 years and older, ECDC multi-country study – first update. European Centre for Disease Prevention and Control. [20 January 2022; cited 24 January 2022]. Available from:

https://www.ecdc.europa.eu/en/publications-data/interim-analysis-covid-19-vaccine-effectiveness-against-severe-acute-respiratory

282. Rosenberg ES, Dorabawila V, Easton D, Bauer UE, Kumar J, Hoen R, et al. Covid-19 Vaccine Effectiveness in New York State. N Engl J Med. 2022;386(2):116-27.
283. Olson SM, Newhams MM, Halasa NB, Price AM, Boom JA, Sahni LC, et al. Effectiveness of BNT162b2 Vaccine against Critical Covid-19 in Adolescents. N Engl J Med. 2022.
284. Zambrano LD, Newhams MM, Olson SM, Halasa NB, Price AM, Boom JA, et al. Effectiveness of BNT162b2 (Pfizer-BioNTech) mRNA Vaccination Against Multisystem Inflammatory Syndrome in Children Among Persons Aged 12-18 Years - United States, July-December 2021. MMWR Morb Mortal Wkly Rep. 2022;71(2):52-8.
285. Emary KRW, Golubchik T, Aley PK, Ariani CV, Angus B, Bibi S, et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B.1.1.7): an exploratory analysis of a randomised controlled trial. Lancet. 2021;397(10282):1351-62.
286. astrazeneca.com [Internet]. AZD1222 US Phase III trial met primary efficacy endpoint in preventing COVID-19 at interim analysis. AstraZeneca. [22 March 2021; cited 15 October 2021]. Available from: https://www.astrazeneca.com/media-centre/press-releases/2021/astrazeneca-us-vaccine-trial-met-primary-endpoint.html
287. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet. 2021;397(10269):99-111.
288. Madhi SA, Baillie V, Cutland CL, Voysey M, Koen AL, Fairlie L, et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant. N Engl J Med. 2021;384(20):1885-98.
289. Pramod S, Govindan D, Ramasubramani P, Kar SS, Aggarwal R, Manoharan N, et al. Effectiveness of Covishield vaccine in preventing Covid-19 – A test-negative case control study. MedRxiv [Preprint]. 2021.
290. Falsey AR, Sobieszczyk ME, Hirsch I, Sproule S, Robb ML, Corey L, et al. Phase 3 Safety and Efficacy of AZD1222 (ChAdOx1 nCoV-19) Covid-19 Vaccine. N Engl J Med. 2021;385(25):2348-60.
291. Clemens SAC, Folegatti PM, Emary KRW, Weckx LY, Ratcliff J, Bibi S, et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 lineages circulating in Brazil. Nat Commun. 2021;12(1):5861.
292. Voysey M, Costa Clemens SA, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. Lancet. 2021;397(10277):881-91.
293. Bhattacharya A, Ranjan P, Ghosh T, Agarwal H, Seth S, Maher GT, et al. Evaluation of the dose-effect association between the number of doses and duration since the last dose of COVID-19 vaccine, and its efficacy in preventing the disease and reducing disease severity: A single centre, cross-sectional analytical study from India. Diabetes Metab Syndr. 2021;15(5):102238.
294. Malathi Murugesan, Prasad Mathews, Hema Paul, Rajiv Karthik, Joy John Mammen, Rupali. P. Protective Effect Conferred by Prior Infection and Vaccination on COVID-19 in a Healthcare Worker Cohort in South India. SSRN [Preprint]. 2021.
295. Alencar CH, Cavalcanti LPG, Almeida MM, Barbosa PPL, Cavalcante KKS, Melo DN, et al. High Effectiveness of SARS-CoV-2 Vaccines in Reducing COVID-19-Related Deaths in over 75-Year-Olds, Ceara State, Brazil. Trop Med Infect Dis. 2021;6(3).

296. Cerqueira-Silva T, Oliveira VdA, Pescarini J, Bertoldo Júnior J, Machado TM, Flores-Ortiz R, et al. The effectiveness of Vaxzevria and CoronaVac vaccines: A nationwide longitudinal retrospective study of 61 million Brazilians (VigiVac-COVID19). . MedRxiv [Preprint]. 2021.
297. Otavio T Ranzani, Rogério dos Santos Leite, Larissa Domingues Castilho, Crhistinne Cavalheiro Maymone Gonçalves, Geraldo Resende, Rosana Leite de Melo, et al. Vaccine effectiveness of Ad26.COV2.S against symptomatic COVID-19 and clinical outcomes in Brazil: a test-negative study design. MedRxiv [Preprint]. 2021.
298. Corchado-Garcia J, Puyraimond-Zemmour D, Hughes T, Cristea-Platon T, Lenehan P, Pawlowski C, et al. Real-world effectiveness of Ad26.COV2.S adenoviral vector vaccine for COVID-19. MedRxiv [Preprint]. 2021.
299. Barlow RS, Jian K, Larson L. Effectiveness of COVID-19 Vaccines Against SARS-CoV-2 Infection During a Delta Variant Epidemic Surge in Multnomah County, Oregon, July 2021. MedRxiv [Preprint]. 2021.
300. Polinski JM, Weckstein AR, Batech M, Kabelac C, Kamath T, Harvey R, et al. Effectiveness of the Single-Dose Ad26.COV2.S COVID Vaccine. MedRxiv [Preprint]. 2021.
301. Corchado-Garcia J, Zemmour D, Hughes T, Bandi H, Cristea-Platon T, Lenehan P, et al. Analysis of the Effectiveness of the Ad26.COV2.S Adenoviral Vector Vaccine for Preventing COVID-19. JAMA Netw Open. 2021;4(11):e2132540.
302. Chin ET, Leidner D, Zhang Y, Long E, Prince L, Li Y, et al. Effectiveness of the mRNA-1273 Vaccine during a SARS-CoV-2 Delta Outbreak in a Prison. N Engl J Med. 2021;385(24):2300-1.
303. Gupta K, O'Brien WJ, Bellino P, Linsenmeyer K, Doshi SJ, Sprague RS, et al. Incidence of SARS-CoV-2 Infection in Health Care Workers After a Single Dose of mRNA-1273 Vaccine. JAMA Netw Open. 2021;4(6):e2116416.
304. Chemaitelly H, Yassine HM, Benslimane FM, Al Khatib HA, Tang P, Hasan MR, et al. mRNA-1273 COVID-19 vaccine effectiveness against the B.1.1.7 and B.1.351 variants and severe COVID-19 disease in Qatar. Nat Med. 2021;27(9):1614-21.
305. Herlihy R, Bamberg W, Burakoff A, Alden N, Severson R, Bush E, et al. Rapid Increase in Circulation of the SARS-CoV-2 B.1.617.2 (Delta) Variant - Mesa County, Colorado, April-June 2021. MMWR Morb Mortal Wkly Rep. 2021;70(32):1084-7.
306. Bruxvoort KJ, Sy LS, Qian L, Ackerson BK, Luo Y, Lee GS, et al. Real-world effectiveness of the mRNA-1273 vaccine against COVID-19: Interim results from a prospective observational cohort study. Lancet Reg Health Am. 2021:100134.
307. Bruxvoort KJ, Sy LS, Qian L, Ackerson BK, Luo Y, Lee GS, et al. Effectiveness of mRNA-1273 against delta, mu, and other emerging variants of SARS-CoV-2: test negative case-control study. BMJ. 2021;375:e068848.
308. El Sahly HM, Baden LR, Essink B, Doblecki-Lewis S, Martin JM, Anderson EJ, et al. Efficacy of the mRNA-1273 SARS-CoV-2 Vaccine at Completion of Blinded Phase. N Engl J Med. 2021;385(19):1774-85.
309. Li XN, Huang Y, Wang W, Jing QL, Zhang CH, Qin PZ, et al. Effectiveness of inactivated SARS-CoV-2 vaccines against the Delta variant infection in Guangzhou: a test-negative case-control real-world study. Emerg Microbes Infect. 2021;10(1):1751-9.
310. Min Kang, Yao Yi, Yan Li, Limei Sun, Aiping Deng, Ting Hu, et al. Effectiveness of Inactivated COVID-19 Vaccines Against COVID-19 Pneumonia and Severe Illness Caused by the B.1.617.2 (Delta) Variant: Evidence from an Outbreak in Guangdong, China. SSRN [Preprint]. 2021.

311. Silva-Valencia Javier, Soto-Becerra Percy, Escobar-Agreda Stefan, Fernández-Navarro Manuel, Moscoso-Porras Miguel, Solari Lely, et al. Effectiveness of the BBIPB-CorV Vaccine in Preventing Infection and Death in Health Care Workers in Peru 2021. SSRN [Preprint]. 2021.
312. Al Kaabi N, Zhang Y, Xia S, Yang Y, Al Qahtani MM, Abdulrazzaq N, et al. Effect of 2 Inactivated SARS-CoV-2 Vaccines on Symptomatic COVID-19 Infection in Adults: A Randomized Clinical Trial. JAMA. 2021;326(1):35-45.
313. Farida Ismail AlHosani, Anderson Eduardo Stanciole, Bashir Aden, Andrey Timoshkin, Omar Najim, Walid Abbas Zaher, et al. Sinopharm's BBIBP-CorV vaccine effectiveness on preventing hospital admission and deaths: results from a retrospective study in the Emirate of Abu Dhabi, United Arab Emirates (UAE). SSRN [Preprint]. 2021.
314. AlQahtani M, Bhattacharyya S, Alawadi A, Mahmeed HA, Sayed JA, Justman J, et al. Morbidity and mortality from COVID-19 postvaccination breakthrough infections in association with vaccines and the emergence of variants in Bahrain. Research Square [Preprint]. 2021.
315. Jara A, Undurraga EA, Gonzalez C, Paredes F, Fontecilla T, Jara G, et al. Effectiveness of an Inactivated SARS-CoV-2 Vaccine in Chile. N Engl J Med. 2021;385(10):875-84.
316. Ranzani OT, Hitchings MDT, Dorion M, D'Agostini TL, de Paula RC, de Paula OFP, et al. Effectiveness of the CoronaVac vaccine in older adults during a gamma variant associated epidemic of covid-19 in Brazil: test negative case-control study. BMJ. 2021;374:n2015.
317. Hitchings MDT, Ranzani OT, Torres MSS, de Oliveira SB, Almiron M, Said R, et al. Effectiveness of CoronaVac among healthcare workers in the setting of high SARS-CoV-2 Gamma variant transmission in Manaus, Brazil: A test-negative case-control study. Lancet Reg Health Am. 2021;1:100025.
318. Enny S. Paixao, Kerry LM Wong, Flavia Jôse Oliveira Alves, Vinicius de Araújo Oliveira, Thiago Cerqueira-Silva, Juracy Bertoldo Júnior, et al. Effectiveness of the CoronaVac vaccine in prevention of symptomatic and progression to severe Covid-19 in pregnant women in Brazil. SSRN [Preprint]. 2021.
319. Hitchings MDT, Ranzani OT, Scaramuzzini Torres MS, de Oliveira SB, Almiron M, Said R, et al. Effectiveness of CoronaVac in the setting of high SARS-CoV-2 P.1 variant transmission in Brazil: A test-negative case-control study. MedRxiv [Preprint]. 2021.
320. Tanriover MD, Doganay HL, Akova M, Guner HR, Azap A, Akhan S, et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. Lancet. 2021;398(10296):213-22.
321. Palacios R, Batista AP, Albuquerque CSN, Patiño EG, Santos JdP, Tilli Reis Pessoa Conde M, et al. Efficacy and Safety of a COVID-19 Inactivated Vaccine in Healthcare Professionals in Brazil: The PROFISCOV Study. SSRN [Preprint]. 2021.
322. Ella R, Reddy S, Blackwelder W, Potdar V, Yadav P, Sarangi V, et al. Efficacy, safety, and lot-to-lot immunogenicity of an inactivated SARS-CoV-2 vaccine (BBV152): interim results of a randomised, double-blind, controlled, phase 3 trial. Lancet. 2021;398(10317):2173-84.
323. Desai D, Khan AR, Soneja M, Mittal A, Naik S, Kodan P, et al. Effectiveness of an inactivated virus-based SARS-CoV-2 vaccine, BBV152, in India: a test-negative, case-control study. Lancet Infect Dis. 2021.
324. Malhotra S, Mani K, Lodha R, Bakhshi S, Mathur VP, Gupta P, et al. SARS-CoV-2 Reinfection Rate and Estimated Effectiveness of the Inactivated Whole Virion Vaccine BBV152 Against Reinfection Among Health Care Workers in New Delhi, India. JAMA Netw Open. 2022;5(1):e2142210.

325. Heath PT, Galiza EP, Baxter DN, Boffito M, Browne D, Burns F, et al. Safety and Efficacy of NVX-CoV2373 Covid-19 Vaccine. N Engl J Med. 2021;385(13):1172-83.
326. Dunkle LM, Kotloff KL, Gay CL, Anez G, Adelglass JM, Barrat Hernandez AQ, et al. Efficacy and Safety of NVX-CoV2373 in Adults in the United States and Mexico. N Engl J Med. 2021.
327. Toback S, Galiza E, Cosgrove C, Galloway J, Goodman AL, Swift PA, et al. Safety, immunogenicity, and efficacy of a COVID-19 vaccine (NVX-CoV2373) co-administered with seasonal influenza vaccines: an exploratory substudy of a randomised, observer-blinded, placebo-controlled, phase 3 trial. Lancet Respir Med. 2021.
328. Shinde V, Bhikha S, Hoosain Z, Archary M, Bhorat Q, Fairlie L, et al. Efficacy of NVX-CoV2373 Covid-19 Vaccine against the B.1.351 Variant. N Engl J Med. 2021;384(20):1899-909.

COVID-19: Virology, variants, and vaccinations

Keywords: Covid-19, Coronavirus, Virology, SARS-CoV-2 variants, Vaccines.

Megan Young[1†], Harry Crook[1†], Janet Scott[2], Paul Edison[1,3,*]

[1] Faculty of Medicine, Imperial College London, London, UK.
[2] Medical Research Council-University of Glasgow Centre for Virus Research, University of Glasgow, UK
[3] School of Medicine, Cardiff University, Cardiff, UK.

† Both authors contributed equally to the manuscript

*Corresponding author:
Dr Paul Edison, MD, MRCP, PhD, FRCP, FRCPI,
Clinical Senior Lecturer and Professor,
Clinical Senior Lecturer, Imperial College London and Honorary Professor, Cardiff University, UK
Division of Neurology, Faculty of Medicine, Imperial College London
Level 2, Commonwealth Building,
Hammersmith Campus, Imperial College London,
Du Cane Road, London, W12 0NN, UK

Tel: +442075941081
E-mail: paul.edison@imperial.ac.uk

No authors have any competing interests.

Abstract

As of 25th January 2022, there have been over 349 million confirmed cases of COVID-19, with over 5.59 million confirmed deaths associated with the SARS-CoV-2 virus. The COVID-19 pandemic has prompted an extensive, global effort to study the molecular evolution of the virus and develop vaccines to combat its spread. Although rigorous determination of SARS-CoV-2 infectivity remains elusive, due to the continuous evolution of the virus, steps have been made to understand its genome, structure, and emerging genetic mutations. The SARS-CoV-2 genome is composed of a number of open reading frames (ORFs) and structural proteins, including the spike protein, which is essential for entry into host cells. As of 25th January 2022, the WHO reports five variants of concern (VOC) two variants of interest (VOI) and three variants under monitoring (VUM). The mutations harboured in these variants confer an increased transmissibility, severity of disease, and escape from neutralising antibodies compared to the primary strain. The current vaccine strategy, including booster doses, provides protection from severe disease. As of 24th January 2022, there are 33 approved vaccines in use in 197 countries. In this review, we discuss the genetics, structure and transmission methods of SARS-CoV-2 and its variants, highlighting how mutations provide enhanced abilities to spread and inflict disease. We also outline the vaccines currently in use around the world, providing evidence for the immunogenicity and effectiveness of each.

1. Introduction

There are seven coronaviruses that infect humans, all belonging to either alpha- or beta-coronavirus subgroups, including 229E (alpha), NL63 (alpha), OC43 (beta), and HKU1 (beta)(1). Over the last two decades, three notable beta-coronaviruses, severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002, Middle East respiratory syndrome coronavirus (MERS-CoV) in 2011, and most recently, severe acute respiratory syndrome 2 (SARS-CoV-2) in 2019, have emerged and caused severe illness resulting in debilitating disease and worldwide fatalities. SARS-CoV-2 is the pathogen responsible for the current Coronavirus 2019 (COVID-19) pandemic and has caused more than 5.59 million deaths in approximately two years and resulted in multisystem illness in several million people(2).

All viruses change and mutate over time, with most changes having little to no impact. However, some mutations may alter its pathogenic or transmission potential and could, therefore, increase disease severity or hinder the effectiveness of vaccines and therapeutic strategies. The World Health Organisation (WHO) classify SARS-CoV-2 variants that increase transmissibility, disease severity or virulence, or decrease the effectiveness of public health measures, diagnostics, therapeutics, or vaccines as variants of concern (VOC). Variants with genetic changes that are predicted to enhance the virulence and transmissibility of the virus which have been identified to cause community transmission in multiple countries posing a possible risk to global public health are defined as variants of interest (VOI). Lastly, the WHO defines variants with genetic changes that are suspected to affect virus characteristics and have currently unclear phenotypic or epidemiological effects as variants under monitoring (VUM). VUM are not typically assigned a name until they are upgraded to VOI or VOC. The full working definitions of VOC, VOI and VUM can be found on the WHO 'tracking SARS-CoV-2 variants' website: www.who.int/en/activities/tracking-SARS-CoV-2-variants/(3). As of 25th January 2022, the WHO reports five VOC; Alpha, Beta, Gamma, Delta and Omicron, two VOI; Lambda and Mu, and three VUM(3). Former VOC/VOI/VUM have been reclassified as 'formerly monitored variants' due to them either no longer circulating, having little impact on the epidemiological situation, or having no concerning properties(3). Since the beginning of the COVID-19 pandemic, the rapid

development of effective COVID-19 vaccines has taken place around the world. As of 24th January 2022, there are 33 approved vaccines in use in 197 countries, with ten vaccines having gained emergency use listing approval from the WHO(4).

In this review, we provide an overview of the genome and structure of SARS-CoV-2, describing how these elements allow the virus to infect and replicate inside of host cells, before outlining how certain mutations harboured by SARS-CoV-2 variants enhance these abilities. Next, we examine the current state of vaccine development around the world and provide evidence of the effectiveness of booster doses.

2. Methods

We searched PubMed and Embase databases for COVID-19-related articles published between 1st January 2020 and 25th January 2022 and for general coronavirus-related articles published from 1st January 2000 onwards. Our search terms included SARS-CoV-2, COVID-19, and specific terms including virology, genome, variants, and vaccine. Additional, specific search terms are outlined in supplementary file 1. We performed further manual searching for additional articles and data using relevant databases, including who.int, gov.uk, and ecdc.europa.eu/en. Due to the rapidly evolving nature of the literature involving SARS-CoV-2, we also searched preprint databases including MedRxiv and BioRxiv. Due to the various topics addressed here, studies were selected through different criteria, details of which can be found in supplementary file 1. Overall, studies were selected based on quality and journal reputation, with real-world studies with large sample sizes of greatest interest.

3. Viral transmission, clinical presentation, and genetic susceptibility of COVID-19

SARS-CoV-2 is predominantly spread via respiratory droplet transmission, spreading between people through close contact, coughing, or sneezing. It has been documented that the virus can also spread through airborne transmission, fomite transmission, and via other modes, such as through biological material including urine and faeces, and through (5, 6). The SARS-CoV-2 virus may survive on surfaces or suspended in air droplets for some time. Indeed, on plastic, stainless steel, and glass surfaces, the half-life of the virus is around 5.3, 4.4, and 4.2 hours, respectively(7), with no difference seen between SARS-CoV-2 variants(8). Although SARS-CoV-2 can be detected on inanimate surfaces for hours and days, due to the evaporation of water droplets, the viruses' living environment, the concentration of the virus plummets rapidly(9). Protective measures, including using personal protective equipment (PPE), maintaining indoor ventilation, and disinfecting hands and surfaces, can effectively limit the spread of SARS-CoV-2(10).

Once inside the airways, SARS-CoV-2 can directly or indirectly infect ciliated, mucus-secreting, and club cells of bronchial epithelium, type 1 pneumocytes within the lungs, and the conjunctival mucosa(11). The clinical presentation of COVID-19 is non-specific, heterogeneous, and infection can result in a wide spectrum of symptoms. Following an incubation period of 4-14 days, symptoms develop ranging from mild to severe disease and, in some cases, can result in death(12). The most common COVID-19 symptoms include fever, cough, dyspnoea, and fatigue(13, 14), while myalgia, gastrointestinal issues, cognitive deficits, and other symptoms are reported. Asymptomatic individuals can also test positive for COVID-19(15, 16). Although the entire population is susceptible to COVID-19 infection, some subgroups within the general population exist that are more susceptible to developing poorer clinical outcomes.

Risk factors associated with increased risk of hospitalisation, severe disease, and fatal outcome with COVID-19 have been identified. Older age(17-19), male sex(20, 21), non-white

ethnicity(21, 22), comorbidities including diabetes, hypertension, and lung disease(18, 23-25), malignancy and immunodeficiency(26-28) have all been associated with more severe COVID-19. The duration of symptoms endured by COVID-19 patients, as well as the treatment they receive will also have profound influences on the severity of disease they experience and both the acute and long-term outcomes following recovery. The host genetic background is thought to have an influence on the susceptibility and severity of COVID-19, possibly explaining the broad spectrum of clinical manifestations that can develop in seemingly similar individuals. A study examining individuals with COVID-19 across numerous ancestry groups identified four gene loci associated with susceptibility to COVID-19; SLC6A20, RPL24, ABO, PLEKHA4, and nine associated with increased risk of severe COVID-19; LZTFL1, FOXP4, TMEM65, OAS1, KANSL1, TAC4 , DPP9, RAVER1, and IFNAR2(29). Meanwhile, genome-wide association studies spanning across Europe, the United States (US), and the United Kingdom (UK) identified a gene cluster on chromosome three (chr3p21.31) as being strongly linked with susceptibility and severity of COVID-19(30, 31). Polymorphisms in the angiotensin-converting enzyme 2 (ACE2) receptor and transmembrane protease serine 2 (TMPRSS2) have also been shown to enhance SARS-CoV-2 viral entry(32, 33), with differential polymorphisms seen across ethnic populations, which may partly explain why certain ethnic groups are more susceptible to severe COVID-19. Increased ACE2 receptor levels have also been associated with other risk factors of COVID-19 including smoking and increasing age(34). The utilisation of polygenetic risk scores (PRS) may be useful in determining an individual's risk for developing severe disease caused by COVID-19(35). A PRS infers a person's risk of susceptibility to, or development of a certain disease based on the total number of genomic variations they possess. Determining PRS with the inclusion of comorbidities, such as chronic obstructive pulmonary disease(36), or other aspects, such as coagulation factors(37), may improve the usefulness of PRS in determining a person's risk of severe COVID-19.

4. Virology of SARS-CoV-2

SARS-CoV-2 is a positive-stranded ribonucleic acid (RNA) virus belonging to Coronaviridae family. Coronaviruses, which have crownlike appearances, are the largest known RNA viruses and are thought to primarily infect vertebrates(38, 39). SARS-CoV-2 belongs to the beta genus of the coronaviruses and has a genome varying from 29.8kb to 29.9kb in size(40). Human coronaviruses (HCoV) genomes consist of a variable number of open reading frames (ORFs). Following the typical 5'-3' order, the beginning two-thirds of the SARS-CoV-2 genome contains two ORFs, ORF1a and ORF1b which, inside the host cell, are translated at the rough endoplasmic reticulum into polyprotein 1a (pp1a) and polyprotein 1ab (pp1ab), respectively(40). These polyproteins are cleaved into 16 non-structural proteins (nsp); nsp1-11, from pp1a and nsp12-16, from pp1ab. The proteolytic release of nsp1 occurs rapidly, which enables it to interfere with translation processes of the host cell by inducing cellular mRNA degradation(41-43). Nsp2-16 contain the viruses' replication and transcription complex (RTC) and encode multiple enzymes with many functions including, proteases, helicase, polymerase, exo- and endo-nuclease, N7- and 2'O-methyltransferases, and de-ubiquitination enzymes(44, 45). The final third of HCoV genomes contain genes that encode structural and accessory proteins. The four major structural proteins encoded here are the nucleocapsid (N), membrane (M), envelope (E), and spike glycoprotein (S) proteins(46, 47). The N protein is associated with the viral RNA genome and is involved in RNA synthesis regulation and interacts with the M protein during viral budding(39, 48). The M protein is important for viral assembly, it contains a short N-terminal domain that projects onto the external surface of the envelope and a long internal C terminus(39). The E protein function is largely unknown; however, along with the N and M proteins, it is required for viral assembly and

release(47) . Lastly, the S protein gives coronaviruses their characteristic spikes that compose their crownlike appearance. This protein projects through the viral envelope, is heavily glycosylated, and regulates host cell membrane receptor binding and fusion of the viral and cellular membrane(49). The functions of the eleven accessory proteins encoded within the one-third closest to the 3' end of the SARS-CoV-2 genome are not fully understood. These accessory proteins are encoded by the ORF3a, ORF3b, ORF3c, ORF3d, ORF6, ORF7a, ORF7b, ORF8, ORF9b, ORC9c, and ORF10 genes. Some of these proteins, including ORF3b, ORF6, ORF7a and ORF8 are interferon antagonists which impair the host cell immune response(50-53), while ORF3a may promote virus release(54) and is involved in apoptosis of host cells through caspase-3 activation(55). ORF9b and ORF9c are known to supress the host antiviral response by interacting with host cell organelles(56-58), while a clear understanding of the functions of ORF3c, ORF7b, and ORF10 remains elusive(59). ***Figure 1*** (A and B) depicts the genome and structure of SARS-CoV-2.

The S glycoprotein is composed of two functionally distinct subunits (S1 and S2) and is essential for viral entry into host cells. The N-terminal S1 domain of the protein contains the receptor-binding domain (RBD) that directly interacts with the ACE2 receptor on the host cell, the primary receptor that SARS-Cov-2 utilises for cell entry(60). The C-terminal S2 domain fuses the host and viral membranes to allow for entry of the viral genome into the host cell(61). The subunits of the trimeric S complex are either in a closed (pre-fusion stage) or open (post-fusion stage) conformation(62), with one subunit always in an open conformation to allow for ACE2 recognition and binding(63). The RBD itself consists of five anti-parallel β-strands surrounded by several α-helices(64). From closed to open conformation, the RBD undergoes structural rearrangement whereby the globular head region rotates clockwise, which alters is elecropotential surface(64). Once positioned, numerous residues within the RBD form either hydrogen bonds or salt bridges with residues of the ACE2 receptor, allowing for tight binding(65), while the concave structure of the RBD allows for three distinct binding regions(64). Following binding between the S protein and the host cell receptor, host cell proteases cleave the S protein, causing the release of the S2 domain which allows for fusion and cell entry(66). ***Figure 1*** (C and D) demonstrate the structure and function of the S protein.

The ACE2 receptor is expressed in numerous cell types throughout the human body, including in the lungs, oral and nasal mucosa, heart, gastrointestinal tract, kidneys, liver, spleen, and brain(67), highlighting the widespread infection that SARS-CoV-2 can inflict. Meanwhile, TMPRSS2, a host cell protease, facilitates fusion of the viral and host cell membranes(68), and may play a role in the spread of the virus in the airways(68). Host cell cathepsin L may also aid in SARS-CoV-2 cell entry by cleaving the S protein(69). Indeed, a clinically approved protease inhibitor has been shown to block SARS-CoV-2 cell entry(70). ***Figure 2*** depicts the mechanism by which SARS-CoV-2 gains entry into and replicates inside host cells, and overviews the host cell immune response.

5. Variants of SARS-CoV-2

Most viral mutations have a limited impact on the viruses' ability to infect, replicate, escape host immunity, and transmit, however, certain mutations may give a viral strain a competitive advantage and, through natural selection, give it the ability to become dominant. Many of the mutations observed in SARS-CoV-2 variants are found within the RBD or the N-terminal domain of the S protein, which alters the three-dimensional structure of the S protein. Not only can these changes affect the transmission abilities of the virus but can also allow it to better escape the immune response, including from neutralising antibodies either elicited through vaccine administration or natural infection. The SARS-CoV-2 virus has mutated numerous times, with estimates suggesting that

circulating lineages acquire nucleotide mutations at rates of around one to two mutations per month(71). The current method of identifying variants relies on the use of genomic testing such as whole genome sequencing, partial S-gene sequencing, or nucleic acid amplification technique (NAAT)-based assays(72). The aspects of different variants that most people experience, however, is the clinical symptoms they inflict. Certain variants induce a greater risk of severe disease and death, such as Alpha and Delta(73), while others are more likely to induce milder symptoms, such as Omicron(74, 75). Moreover, individual symptoms can differ between variants. For example, the Gamma variant is associated inflicting anosmia and dysgeusia(76), which is less commonly seen in Omicron infections. Moving forward, the clinical themes and symptoms associated with emerging variants should be elucidated rapidly in order for the public and healthcare professionals to rapidly identify possible cases of COVID-19.

The WHO have tracked and monitored SARS-CoV-2 variants since the COVID-19 pandemic began to identify VOCs. As of 25th January 2022, the WHO reports five VOC, two VOI, and three VUM(3) (***Table 1***). Herein, we report studies that compare SARS-CoV-2 variants to the 'primary' virus strain. 'Primary strain' refers to the strain of the virus that first emerged in Wuhan, China at the end of 2019 and spread around the world in the first wave of infections, which is often also referred to as the Wuhan-Hu-1, B.1, or wild-type strain.

5.1 Variants of concern

5.1.1 Alpha

The Alpha SARS-CoV-2 variant, of the B.1.1.7 lineage, was first documented in the UK in September 2020 and classified as a VOC on 18th December 2020(3, 77). This variant contains S protein mutations which have potential biological effects. Firstly, the S protein residue 501, a key contact residue within the RBD, forms a portion of the binding loop in the contact region of the ACE2 receptor, forms a hydrogen bond with the Y41 residue of the ACE2 receptor, and stabilises the ACE2 K353 residue(65, 78, 79). Alpha harbours an N501Y mutation which increases the binding affinity of the RBD to the ACE2 receptor(80). Next, the P681H mutation contained within the Alpha variant is located immediately adjacent to the 682-685 furin cleavage site, at the interface of the S1 and S2 domains(81). The S1/S2 furin cleavage site prompts entry into respiratory epithelial cells and partly determines the transmissibility of the virus(82-84), while the P681H mutation makes the furin cleavage site less acidic, meaning it is more effectively recognised and cleaved(85, 86). Alpha also contains a D614G mutation, located within the S1/S2 furin cleavage site, which increases SARS-CoV-2 binding affinity to the ACE2 receptor and increases infectivity(87). Other mutations harboured within the Alpha variant enhance the ability of the virus to escape antibody detection, such as the two amino acid deletion at the sites 69-70 in the N-terminal domain of the S protein(88, 89), while other mutations demonstrate limited or no effects(90). In February 2021, viruses of the B.1.1.7 lineage with the added S protein mutation E484K were identified, which may have threatened vaccine effectiveness due to the mutation conferring an increased resistance to neutralising vaccine-elicited and monoclonal antibodies(91). This mutation had limited effects, however, and variants containing it failed to dominate.

Epidemiological studies explored the Alpha variant, with a study in Madrid, Spain finding that the probability of admission to an intensive care unit (ICU) was twice as high in patients infected with the Alpha variant compared to those infected with the primary strain, while this variant became the dominant strain within four months, and led to an increase in disease burden as a result(92). Meanwhile in Cannes, France, infection with the Alpha variant was associated with a 3.8-fold higher

risk of transfer to an ICU or death compared to the primary strain(93). During the third COVID-19 wave in Ontario, Canada, where 91% of infections were caused by the Alpha variant, the risk of both hospitalisation (adjusted odds ratio (aOR)=1.57) and death (aOR=1.52) was higher compared to primary strain infections(94). Overall, the Alpha variant was approximately 50-70% more transmissible and was associated with a 30-60% increased risk of hospitalisation and death compared to the primary strain(95-100).

The Alpha variant was found to have a minimal impact on the effectiveness of current vaccines(101, 102), while the risk of reinfection remained similar for this variant as with previous ones(103). On 3rd September 2021, the European Centre for Disease Prevention and Control (ECDC) reclassified the Alpha, and the Alpha+E484K mutation variants from a VOC to a 'de-escalated variant' (104).

5.1.2 Beta

The Beta SARS-CoV-2 variant, of the B.1.351 lineage, was first documented in South Africa in May 2020(3). This variant contains five S protein mutations of interest: N501Y, E484K, D614G, K417N, and A701V. Like the Alpha variant, Beta contains the mutations N501Y, E484K, and D614G, which increase ACE2 receptor binding affinity(80, 87), increase virulence(105), and enhance resistance to neutralising antibodies(91, 106). The K417 residue of the SARS-CoV-2 S protein interacts with the D30 residue of the ACE2 receptor, forming a salt bridge across the central contact region(65, 78), however, the K417N mutation appears to have a limited impact on ACE2 receptor binding(80). The A701V mutation is located close to the furin cleavage site but has a minimal impact on transmissibility or antibody resistance(101).

In a genomic and epidemiological study, it was concluded that the Beta SARS-CoV-2 variant had a selective advantage over previous variants from its increased transmissibility and immune escape abilities(107, 108), while the E484K/N501K mutations significantly enhanced the binding affinity of Beta and, hence, increased its transmissibility(109). A retrospective cohort study found that infection with the Beta variant was associated with an increased hospitalisation risk compared to an infection with a non-VOC (hazard ratio (HR)=2.30)(100). Overall, Beta is approximately 25-50% more transmissible, is associated with a possible increase in risk of hospital mortality, and has enhanced resistance to antibody neutralisation compared to previous variants(107, 108, 110).

5.1.3 Gamma

The Gamma variant is of the P.1 lineage and was first reported in November 2020 from travellers returning to Japan from Brazil, and was later discovered in Brazil(3, 111). This variant contains the S protein mutations of interest; K417T, E484K, N501Y, D614G, and H655Y(104). As mentioned, the N501Y and D614G mutations increase ACE2 receptor binding affinity and increase infectivity of the virus(80, 87). The N501Y, K417N/T, and E484K mutation trinity, meanwhile, is shared by both Gamma and Beta variants, and is associated with enhanced infectivity and lethality compared to the N501Y mutation alone, possibly due to tighter binding of the S protein to the ACE2 receptor due to increased electrostatic contribution(112). Gamma also possesses the H655Y mutation which was found to provide enhanced viral escape abilities from multiple human monoclonal antibodies *in vitro*(113).

The Gamma variant is associated with heightened transmissibility(109, 110, 114), with one study concluding that it possesses a 1.7- to 2.4-fold increased transmissibility compared to previous variants(115). Additionally, the wave of infections caused by the Gamma variant in Brazil was

associated with a 13% increase in death rate compared to the previous wave, suggesting the greater virulence held by Gamma compared to previous viral strains(116). A surveillance study from seven European countries concluded that the Gamma variant was associated with a higher risk of hospitalisation (aOR=2.6) and admission to an ICU (aOR=2.2) when compared to non-VOC cases(117). In Manaus, Brazil the resurgence of COVID-19, despite high seroprevalence, suggested that the Gamma variant had a moderate resistance to neutralising antibodies(118), however, Gamma has been shown to be significantly less resistant to neutralising antibodies, compared to other variants, including Beta(119).

5.1.4 Delta

The Delta variant, from the B.1.617.2 lineage, was first documented in India in October 2020 and was classified as a VOC on 11th May 2021(3). Of the S protein mutations of interest, the aforementioned P681H and D614G are also harboured by the Delta variant(104) and similarly impacts its ACE2 receptor binding affinity and transmissibility(106, 120, 121). Unlike the E484K mutation seen in previous variants, Delta contains the E484Q mutation which, along with a L452R mutation also located within the RBD, causes significantly higher affinity for the ACE2 receptor than the primary strain or the E484K mutation alone(122). The L452R mutation alone results in greater RBD-ACE2 receptor binding affinity and enhanced escape from neutralising antibodies(123, 124). Lastly, the Delta variant contains the T478K mutation, located on the interface between the S protein and the ACE2 receptor when bound, which increases the electrostatic potential of the S protein and enhances binding affinity(125).

The Delta variant quickly became the dominant variant in the UK(126), US(127), Europe, and around the world(128). The mutations present in the Delta variant, enhanced the transmissibility of the virus as a result of increased binding affinity to the ACE2 receptor(109). It was estimated that the reproduction number of the Delta variant is 97% greater than non-VOC/VOI and approximately three times that of the Alpha, Beta, and Gamma variants(110), which highlights the competitive advantage that this variant had over earlier ones and how it rapidly became the dominant strain globally. The fast replication rate of Delta likely contributes to its increased transmissibility compared to Alpha, Beta, and Gamma. From infected individuals, the Delta variant has been able to be detected by polymerase chain reaction (PCR) within the first four days from exposure, while non-Delta infections could only be detected after six days(129). Furthermore, viral loads of people infected with the Delta variant were found to be significantly higher than people infected with other strains(129), including Beta(130). Delta is also thought to better escape neutralisation, with the frequency of post-vaccination infections much higher for the Delta variant than infections with the primary strain in India(131) and blood sera samples from individuals who had received one dose of a COVID-19 vaccine showing minimal neutralisation of the Delta variant(132).

The Delta variant is also associated with an increased disease severity. In Scotland, infection with the Delta variant was associated with an increased risk of hospitalisation (HR=1.85) compared to infection with the Alpha variant(133). Compared to non-VOC infections, North American studies demonstrated that infection with Delta was associated with a 108%(134) or HR=2.3(100) increased risk of hospitalisation, a 234% increased risk for admission to an ICU, and a 132% increased risk of death(134). Lastly, a study in India found that the risk of death was around 1.8 times higher for Delta infections, while Delta also infected and induced symptoms in a greater proportion of younger people (0-19 years old), compared to the primary strain(131).

5.1.5 Omicron

The Omicron variant is of the B.1.1.529 lineage and was first discovered in November 2021 in South Africa and Botswana before being detected in multiple countries and classified as a VOC on 26th November 2021(3). This variant contains over 30 S protein mutations(104), 23 of which have been previously identified, including K417N, T478K, E484A, D614G, H655Y, P681H, and N501Y(135). 15 Omicron mutations are contained within the RBD(17) providing the variant with a significantly enhanced binding affinity to the ACE2 receptor(135, 136). In addition, various single mutations harboured with the RBD of the Omicron variant impair the effectiveness of neutralising antibodies, including K417N, N440K, G446S, E484A, Q493K, G496S, G339D, S371L, and S375F(17).

The emergence of Omicron has been followed by a tidal wave of infections worldwide. Early data from South Africa demonstrated that the proportion of COVID-19 cases caused by the Omicron variant rose from 3% in early October, to 98% by early December(137). In late December 2021, meanwhile, the doubling time for number of positive Omicron cases was between two and three in the UK, US, and much of Europe(138, 139), highlighting the transmissibility of this variant. The mutations harboured by Omicron that enhance its binding affinity(135, 136) and ability to escape neutralising antibodies(17) likely drove its rapid spread, as did its fast replication rate, which is around 70 times faster than the Delta and primary strains(140). The reinfection rate of Omicron has also been found to be significantly higher than that of previous variants in studies from Scotland(141) and South Africa(142).

The Omicron variant has extensive but incomplete escape from naturally acquired and vaccine-induced immunity(143, 144). Compared to the Delta variant, Omicron requires around a ten-fold increased antibody titre to be neutralised, following vaccination with either Oxford-AstraZeneca or Pfizer/BioNtech vaccines(145). Indeed, blood sera from individuals who had received two doses of the Pfizer/BioNtech vaccine exhibited more than a 25-fold reduction in neutralising antibody titres against the Omicron variant compared to the primary strain(146). T-cell responses to Omicron may remain intact, however. One preprint study demonstrated that 70-80% of the T-cell response targeting the S protein was maintained in those vaccinated or with prior infection, while the magnitude of Omicron cross-reactive T-cells was like that of both Delta and Beta variants(147). Furthermore, data from Pfizer/BioNtech revealed that 80% of the epitopes in the Omicron variant S protein that are recognised by CD8+ T-cells were not affected by this variant's mutations, following two-doses of the vaccine(146). T-cell responses induced from vaccine administration or prior infection may, therefore, provide some protection from severe disease.

Recent real-world evidence has implied that Omicron infection is milder in severity than previous variants. In an early South African analysis, the risk of hospitalisation (aOR=0.2) was lower for Omicron infections compared to non-Omicron SARS-CoV-2 infections(137) while, compared to earlier infections associated with the Delta variant, Omicron-infected individuals had a lower risk of severe disease (aOR=0.3)(137). In December 2021 in England, Omicron cases were found to induce a significantly reduced risk of hospitalisation or presentation for emergency care in comparison to Delta cases(74, 75). The decreased disease severity inflicted by Omicron may be due to its reduced capacity for replication in lung tissue, which was found to be more than ten times less in lung tissue compared to Delta(140). Concordantly, the S protein of the Omicron variant is less efficient at cleaving the ACE2 receptor and entering cells of lung organoids(145), while is also less able to cause fusion between lung cells compared to Delta(145), which is often observed in cases of severe COVID-19. The reduction in replication within the lungs, and the preservation of T-cell responses likely contribute to the milder disease exerted by the Omicron variant.

Although the Omicron variant appears to manifest in mild disease, high case numbers may still result in many hospitalisations and deaths in those vulnerable to the virus. Omicron case numbers may be beginning to peak, however. In South Africa, a 29.7% decrease in weekly COVID-19 cases were reported in the week ending 25th December 2021, compared to the previous week, and the Omicron wave is said to have passed(148). Concerningly, global case numbers continue to rise rapidly(149) and many countries will continue to feel the pressure exerted by the wave of Omicron infections.

5.2 Variants of interest

5.2.1 Lambda

The Lambda variant, of the C.37 lineage, was first documented in Peru in December 2020 and was designated as a VOI on 14th June 2021(3). This variant contains the S protein mutations; D614G, L452Q, and F490S(104). The L452Q mutation, located within the RBD, enhances binding affinity to the ACE2 receptor and increases the infectivity of Lambda(150), while, together L452Q and F490S increase the resistance of this variant to vaccine-elicited antibody neutralisation(150). Furthermore, F490S was identified as being a high-risk mutation for enhancing abilities to escape neutralisation(150).

Infectivity of the Lambda variant may be higher than that of Alpha, Gamma, and other D614G containing variants(151), suggesting that Lambda could potentially spread more rapidly and effectively. Additionally, compared to the primary SARS-CoV-2 virus, antibody neutralisation was found to be decreased by 3.05-fold for the Lambda variant, higher than that for Gamma (2.33-fold) and Alpha (2.03-fold) variants(151). However, findings suggest that the Lambda variant can be neutralised by monoclonal antibodies and current vaccines are protective against this variant(150).

5.2.2 Mu

The Mu variant, from the B.1.621 lineage, was first documented in Columbia in January 2021 before receiving designation as a VOI on 30th August 2021(3). This variant contains the aforementioned S protein mutations E484K, N501Y, D614G, and P681H(104). Mu also contains the S protein mutation R346K, located within the RBD(104, 152), which may induce large binding free energy changes that disrupt the binding of antibodies to the S protein and enhance the ability of the variant to escape neutralisation(153). As discussed, the E484K, N501Y, D614G, and P681H mutations have been shown to increase transmissibility(80, 85, 87, 105, 109, 112, 120, 121) and neutralisation escape(91, 106) suggesting that the Mu SARS-CoV-2 variant is likely to be more infectious than the primary strain.

Although the Lambda and Mu variants have been outcompeted by Delta and now Omicron, the development and spread of VOIs will need to be closely monitored and studied to appreciate their pathogenicity, transmissibility, and virulence.

5.3 VUM

As of 25th January 2022, there are three VUM listed by the WHO(3) ***(table 1)***.

6. Vaccinations

The COVID-19 pandemic prompted a rapid international search for safe and effective vaccines against the SARS-CoV-2 virus. In line with previous vaccine development, including for both SARS-CoV

and MERS-CoV, the S protein was a key target for COVID-19 vaccine development(154). As of 24th January 2022, 33 approved vaccines are in use in 197 countries, with ten vaccines having gained emergency use listing approval from the WHO(4), (***table 2***). As of 25th January 2022 there are 194 vaccines in pre-clinical development and 140 in clinical development(155). Numerous studies have explored the effectiveness of approved vaccines, however, large variations in vaccine effectiveness are reported. This variability is likely due to several factors in the studies including, the country, date, and population size of the study, as well as the SARS-CoV-2 variants circulating during the study period. These factors, along with how the effectiveness is reported, mean that it is difficult to compare vaccines and fully understand how effective each vaccine is. Here, we review the COVID-19 vaccines in use around the world.

6.1 Pfizer/BioNtech - BNT162b2

The BNT162b2 vaccine (Comirnaty) is a lipid nanoparticle-formulated, nucleoside-modified mRNA vaccine encoding a modified SARS-CoV-2 S protein which was developed through a collaborative effort between Pfizer (New York, US) and BioNTech (Mainz, Germany)(156, 157). BNT162b2 gained WHO emergency use listing on 31st December 2020(158) and, as of 24th January 2022, has been approved for use in 136 countries(4).

Following administration of BNT162b2, a Th1-biased response is observed, with tumour necrosis factor alpha (TNFα), interferon gamma (IFNγ), and interleukin-2 (IL-2) all elevated following vaccination, compared to placebo(159, 160). Highest neutralisation titres are found between seven and fourteen days following the second dose(161), while those previously infected with COVID-19 showed a four-fold increase in antibody binding and a 18-fold increase in neutralisation titres compared to previously uninfected individuals following two-doses(162). The BNT162b vaccine is well tolerated, with limited reactogenicity. Redness and swelling at injection site have been reported, however mild or moderate pain at the injection site is the most commonly reported reaction to vaccination(161). Fatigue, muscle pain, headache and chills are other commonly reported symptoms following BNT162b2 administration(163). The rate of systemic reactions after a second dose of BNT162b has been found to be 1.7 to 2 times higher than after a first dose, possibly suggesting an immunity-boosting effect(164). Many safety reports of this vaccine describe no serious adverse events(161, 164, 165), however, a large study found that BNT162b2 was associated with an increased risk of myocarditis, lymphadenopathy, appendicitis, and herpes zoster infection(166). Although rare, allergic reaction or anaphylaxis has also been reported following administration of the BNT162b2 vaccine(163). ***Table 2*** outlines clinical trial and real-world data for vaccine effectiveness.

6.2 Oxford-AstraZeneca – AZD1222

The AZD1222 vaccine (Vaxzevria) is a non-replicating vector of the chimpanzee adenovirus ChAdOx1, modified to encode the SARS-CoV-2 S protein(167). Developed through collaboration between the University of Oxford and AstraZeneca (Cambridge, UK), this vaccine was given WHO emergency use listing on 16th February 2021(158) and has been approved for use in 137 countries, as of 24th January 2022(4). The WHO has granted emergency use listing to two versions of this vaccine (AZD1222 and Covishield) in order to utilise Covishield as part of their worldwide COVAX initiate, which is being produced by the Serum Institute of India and AstraZeneca-SKBio (Republic of Korea)(168).

Following administration of AZD1222, significant antibody production, predominantly of IgG1 and IgG3 subclasses, and a Th-1 cell response, with increased expression of IFNγ and TNFα, is seen(122, 169). One dose of AZD1222 has been shown to produce a neutralising antibody response in

91% of participants, while a second dose resulted in 100% of participants producing neutralising antibodies(170). Mild and moderate itch, pain, redness, swelling, tenderness, and warmth are common local reactions, while chills, fatigue, fever, headache, muscle ache, and nausea are commonly reported systemic reactions following AZD1222 administration(170). Rare symptoms, including severe chest pain, nasal bleeding, and allergic reaction have been reported following AZD1222 administration(171). ***Table 2*** outlines clinical trial and real-world data for vaccine effectiveness.

6.3 Johnson & Johnson - Ad26.COV.2.S

The Ad26.COV.2.S vaccine is a non-replicating adenovirus vector, modified to contain the SARS-CoV-2 S protein in a prefusion-stabilised conformation and requires a single dose(172). This vector was developed from the recombinant human adenovirus type 26 by the Janssen pharmaceutical company of Johnson & Johnson (New Brunswick, New Jersey, US)(172) and was listed for WHO emergency use listing on 12th March 2021(158). As of 24th January 2022, Ad26.COV.2.S has been approved for use in 106 countries(4).

The Ad26.COV.2.S vaccine induces the production of a variety of antibody subclasses, such as IgG, IgM, and IgA, and promotes several non-neutralising antibody responses, including activation of CD4+ and CD8+ Th1-cells and production if IFNγ, IL-2, and TNFα(173, 174). Although neutralising antibody responses induced by Ad26.COV2.S are reduced against SARS-CoV-2 variants, non-neutralising antibody and T-cell responses have been found to be preserved against VOC(173), while a prior COVID-19 infection significantly increases levels of S protein-binding antibodies, antibody-dependent cellular cytotoxicity, and neutralising antibodies against VOCs including Beta and Delta(175). Ad26.COV.2.S is safe and well tolerated, with a large clinical trial demonstrating that headache, fatigue, and myalgia, are the most common systemic reactions, while injection-site pain is the most common local reaction following administration(172). Like other vaccines, Ad26.COV.2.S has been associated with serious adverse events, such as allergic reactions and cerebral venous sinus thrombosis, however, these are rare(163, 176). ***Table 2*** outlines clinical trial and real-world data for vaccine effectiveness.

6.4 Moderna – mRNA-1273

The mRNA-1273 vaccine (Spikevax) developed by Moderna (Massachusetts, US) is a lipid-nanoparticle-encapsulated mRNA vaccine expressing the SARS-CoV-2 S protein that has been prefusion-stabilised(177). This vaccine gained WHO emergency use listing on 30th April 2021(158), and as of 24th January 2022, has been approved for use in 85 countries(4).

The mRNA-1273 vaccine elicits a strong CD4+ Th-1 cell response, with TNFα, IFNγ, and IL-2 expression increased following administration(178-180), while neutralising antibody titres have been shown to significantly increase up until around 28 days following the second dose of the vaccine, and afterwards remain consistently high(181). Fatigue, muscle pain, headache, chills, joint pain, and injection-site pain/reaction are common adverse effects caused by the mRNA-1273 vaccine(163, 177), while serious adverse effects are often avoided(177, 181). Serious adverse events, including allergic reaction and anaphylaxis are rare, but not inconceivable following mRNA-1273 administration(163). ***Table 2*** outlines clinical trial and real-world data for vaccine effectiveness.

6.5 Other WHO emergency use listed COVID-19 vaccines

In addition to the five COVID-19 vaccines described previously, five other vaccines have gained emergency use listing by the WHO. First, the Sinopharm BBIBP-CorV COVID-19 vaccine (Covilo) was

developed by the Beijing Bio-Institute of Biological Products, a subsidiary of China National Biotec Group, and was given WHO emergency use listing on 7th May 2021(158). This vaccine is a 19nCoV-CDC-Tan-HB02 strain SARS-CoV-2 antigen that is produced in Vero cells, inactivated by β-propiolactone, and then purified and absorbed with aluminium hydroxide(182). Next, the CoronaVac vaccine, developed by Sinovac Biotech (Beijing, China), was listed for WHO emergency use on 1st June 2021(158). Like the BBIBP-CorV vaccine, this vaccine is a Vero cell-based, aluminium hydroxide-adjuvanted, β-propiolactone-inactivated vaccine, however, it is based on the SARS-CoV-2 CZ02 strain(183). Covaxin (BBV152) is a whole virion inactivated SARS-CoV-2 vaccine formula developed by Bharat Biotech International ltd (India)(184) which gained emergency use listing from the WHO On 3rd November 2021(185). Lastly, Covovax and its originator, Nuvaxovid (NVX-CoV2372), were both developed by Novavax (Maryland, United States) and the Coalition for Epidemic Preparedness Innovations (Oslo, Norway), and gained emergency use listing on 17st and 21th December 2021, respectively(186, 187). Both vaccines are manufactured using the same technology, and consist of a recombinant SARS-CoV-2 S protein nanoparticle administered with the adjuvant Matrix-M as a co-formulation(188). These vaccines produce similar immune responses to those already discussed. Studies assessing the efficacy of these vaccines are outlined in ***table 2***.

6.10 Other approved vaccines

In addition to the vaccines that have received emergency use listing from the WHO, around the world, vaccines have been developed, tested, and approved to combat COVID-19. As of 24th January 2022, 33 vaccines, including the ten described above, have been approved in at least one country(4). The remaining 23 approved vaccines are outlined in ***table 3***.

6.11 Waning immunity and boosters

Throughout the COVID-19 pandemic, emerging variants have threatened the effectiveness of vaccines (***table 2***). Simultaneously, waning immunity following vaccination questions how long vaccines remain effective and highlights the importance of booster doses. Indeed, protection against SARS-CoV-2 following vaccination decreases over time, both in terms of antibody titres(189-191) and vaccine effectiveness(192-195). Cellular responses, such as T-cell immunity, may persist for longer periods, however(196, 197). With a gradual loss of protection from SARS-CoV-2 following COVID-19 vaccination, many countries are now rolling out booster programmes with the aim of raising levels of immunity.

Since booster programmes began, evidence that a booster vaccine dose enhances antibody and cellular responses has accumulated. Following a third dose of vaccine, neutralising antibody titres increase significantly(198-201) and, in some cases, to higher levels than after the primary two doses(198). Additionally, boosters have also been found to increase neutralising antibody titres against Beta, Gamma, Delta, and Omicron variants(199, 202, 203). T-cell response is also enhanced following a third dose(200, 204, 205). Together, enhancing neutralising antibody and cellular responses with a booster vaccine dose is likely to provide a greater level of protection than relying on immunity built through a primary regimen.

The antibody and cellular responses observed following booster vaccinations have been found to correlate with increased levels of protection against SAR-CoV-2 infection and severe illness. On 30th July 2021, Israel was the first country to offer a third dose of BNT162b2 to certain groups. Subsequently, several studies have revealed that those who received a third vaccine dose were significantly less likely to be infected or have severe disease with SARS-CoV-2 compared to those who

received two-doses(206-209). In those aged 60 or older, an observational study demonstrated that the rate of severe COVID-19 and death was lower in the boosted group by a factor of 17.9 and 14.7, respectively, compared to the non-boosted group(210). Booster doses of COVID-19 vaccine have been shown to be effective against infection with Delta(211, 212) and, to a lesser degree, Omicron variants(75, 145, 146, 212-214) despite the numerous mutations harboured by these variants. Overall, increasing evidence is pointing towards the benefits of booster doses of COVID-19 vaccines, therefore it is expected that booster programmes will continue to roll out across the globe. Based on current evidence, the CDC recommend that the time interval for receiving a booster following the primary regiment is five months for Pfizer/BioNTech BNT162b2 primary regimen, six months for Moderna mRNA-1273 primary regimen, and two months for Johnson & Johnson Ad26.COV2.S primary regimen(215). As the pandemic progresses and new variants emerge, variant-specific vaccines may require development, with pre-clinical studies demonstrating their efficacy(216) and pharmaceutical companies, such as Pfizer, advancing in variant-specific vaccine development(146). Policy makers should also consider when vaccine boosters will be given in the future and who will receive booster doses in the long-term.

7. Emerging Treatments

As more is learnt about the virus, the therapeutic strategy against COVID-19 develops. There are currently over two thousand ongoing trials assessing certain treatment strategies for COVID-19(217). Recently, antivirals including molnupiravir (Lagevrio) and nirmatrelvir/ritonavir (Paxlovid) have been approved in the UK(218, 219), US(220, 221), and Europe(222, 223) for treating COVID-19 in certain risk groups. Similarly, sotrovimab (Xevudy), a monoclonal antibody treatment, has recently been approved for use in treating certain COVID-19 patients in the UK(224), US(225), and Europe(226). These drugs have been shown to be effective at preventing poor clinical outcomes, including death, in those vulnerable to severe COVID-19 infection. Other drug treatments, such as janus kinase inhibitors, corticosteroids, and anti-inflammatories have contrasting evidence to support their use, and therefore, the use of specific drugs is either recommended for or against by certain treatment and management guidelines, which are discussed below.

8. Guidelines

The treatment and management of COVID-19 is a continually evolving topic, however, health authorities have published and continue to update guidelines and recommendations for treating COVID-19. The WHO living guideline on COVID-19 and therapeutics is regularly updated, with the latest version, published on 14th January 2022 containing 14 recommendations on COVID-19 treatment(227). In the UK, the National Institute for Health and Care Excellence (NICE)(228) and Medicines and Healthcare products Regulatory Agency (MHRA)(229) provide updated guidelines on COVID-19 treatment, while in Europe, the ECDC regularly publishes several guidelines providing recommendations on a range of COVID-19 related topics(230). In the US, the National Institutes of Health (NIH)(231) and the CDC(232) provide guidance on COVID-19 treatment and management, with the CDC supplying guidelines for specific groups including, employers, schools, health departments, and governments.

9. Considerations for the future

Novel infectious diseases and pandemics are an unpredictable but inevitable aspect of nature and it is, therefore, important that we learn from past pandemics to prepare for future ones. Firstly,

the COVID-19 pandemic has highlighted and amplified the existing inequalities within society(233), with non-white ethnicity, social disadvantage, and unemployment all risk factors for testing positive for COVID-19(234) and those most economically deprived found to be particularly vulnerable(235). These inequalities require addressing to be better prepared for similar situations in the future. Next, to progress through a pandemic we should be racing the pathogen, not each other. This statement becomes apparent when you consider the problems countries faced when seeking out PPE(236), and the vaccine inequity seen around the world(237), with developed countries often better placed to be able to purchase these items. Initiatives such as the WHO's COVAX programme are vital to protect those most vulnerable and reduce the global spread of disease. In October 2021, the UK government released a publication outlining where the policies implemented to reduce the impact of the COVID-19 pandemic failed, and the lessons learned from these failures (238). Here, it is clear that there is room for improvement, with the publication presenting conclusions and recommendations on how to enhance pandemic preparedness, lockdown and social distancing measures, testing and contact tracing, social care, and vaccines. In countries such as the UK, US, and much of Europe, where the COVID-19 death rate has been high, steps need to be taken and lessons need to be learnt in order to be better prepared for the next pandemic. The responsibility of improving pandemic response lies with policy makers, the medical/scientific community, and the public, and will ultimately require a collaborative approach.

Certain aspects of the response to the COVID-19 pandemic have been a triumph, however. One of the major victories was the rapid development and rollout of vaccines(239), which continue to be effective. The rollout of rapid testing and quarantine for positive cases was also important to at least disrupt the spread of the virus, especially given that asymptomatic individuals can contribute to the spread. Furthermore, the swift identification and sharing of knowledge of SARS-CoV-2 variants between countries should be applauded. Lessons can be learned from countries where COVID-19 was controlled. In Taiwan, managing the pandemic as directed by pre-COVID-19 pandemic plans prompted an immediate response; screening of all airline passengers arriving from Wuhan and high risk areas, restricting entry for non-Taiwanese citizens, 14-day quarantine period for contacts of confirmed cases or returning travellers, a ban on large gatherings, and widespread mask wearing were some of the quickly implemented management strategies(240). New Zealand implemented similarly effective restrictions, with the addition of a national lockdown(240). Many of the pandemic control components that kept case and death numbers low in Taiwan and New Zealand could be adopted by other countries in the future and may lead to greater outcomes in terms of protecting both health of individuals and the health and wellbeing of the country. Overall, there is much to be learnt from the COVID-19 pandemic and, as we emerge from it, inspection of which policies failed, and which succeeded are imperative.

10. Conclusion

COVID-19 remains prevalent and life-threatening. Although rollout of vaccines has been successful, we must aim to address unmet goals, such as attaining a high global vaccination coverage and ensuring that all healthcare systems have the capacity to cope with seasonal waves. With Omicron highly prevalent, we must continue to learn, develop therapeutics, and remain vigilant to new VOCs. Here, we have provided an overview of the virology of SARS-CoV-2, including the mutations harboured by variants of the virus and how these mutations effect its transmissibility and virulence. Lastly, we discussed the vaccines that have been developed and administered around the world and provided

evidence supporting the rollout of booster doses. Future priorities should focus on continuing vaccination programmes and developing variant-specific vaccines as new mutations emerge. This, along with the expansion of our knowledge of SARS-CoV-2 and which therapies are most successful to treat infections with it will ultimately lead to favourable outcomes moving forward.

Research Questions

1) How will the SARS-CoV-2 virus mutate in the future, and which mutations will give a competitive advantage that will allow the virus to inflict disease to many people?
2) How do we keep up with the rapidly changing SARS-CoV-2 environment and ensure that vaccines remain effective?
3) How do we manage the booster programme and when will future booster vaccinations be required in order to maintain high levels of immunity?
4) How can we learn from the current and past pandemics so that we are better prepared for the next one?

Patient Involvement: Patients who had been infected with covid-19 were contacted and requested to review the initial drafts of this manuscript. The received feedback was mostly positive and assisted in developing and focusing our review. Final drafts were also reviewed by patients who had had covid-19 and similar positive feedback was received.

Contributorship statement and guarantor: MY and HC performed the literature search and drafted the manuscript. HC revised and finalised the manuscript. JS reviewed and revised the manuscript. PE was responsible for the concept and design of the work. PE reviewed, revised, and finalised the manuscript. PE is the guarantor.

Competing interests: We have read and understood the BMJ policy on declaration of interests and declare the following interests: PE was funded by the Medical Research Council and now by Higher Education Funding Council for England (HEFCE). He has also received grants from Alzheimer's Research, UK, Alzheimer's Drug Discovery Foundation, Alzheimer's Society, UK, Medical Research Council, Alzheimer's Association US, Van-Geest foundation, and European Union grants. PE is a consultant to Roche, Pfizer, and Novo Nordisk. He has received educational and research grants from GE Healthcare, Novo Nordisk, Piramal Life Science/Life Molecular Imaging, Avid Radiopharmaceuticals and Eli Lilly. He is a member of the Scientific Advisory Board at Novo Nordisk. None of these were related to COVID-19

Figure Legends:

Figure 1: Genome and structure of SARS-CoV-2. A) SARS-CoV-2 genome and S protein amino acid composition. The SARS-CoV-2 genome is approximately 30,000 base pairs (bp) long and consists of open reading frames (ORF) and elements that are essential for the virus' structure. The spike S

protein is responsible for binding and entry into host cells. SARS-CoV-2 variants of concern (VOC) contain various S protein non-synonymous mutations that result in amino acid changes in the receptor binding domain (orange text) and the S1/S2 subunit interface (black text) which have been demonstrated to enhance transmissibility of the virus. VOC include Alpha (α), Beta (β), Gamma (γ), and Delta (δ). **B) SARS-CoV-2 structure.** SARS-CoV-2 is a RNA virus that has a crown-like appearance and contains four major structural proteins: nucleocapsid (N), spike (S), envelope (E), and membrane (M). **C) S and ACE2 interaction.** The SARS-CoV-2 S protein directly interacts with human angiotensin-converting enzyme 2 (ACE2) receptors in order to gain entry into host cells. The receptor binding domain (RBD) of the S protein tightly binds to ACE2. **D) Spike protein structure.** The S protein protrudes out from the main SARS-CoV-2 bulk and is comprised of two subunits: S1 and S2. S1 contains the RBD which directly interacts with the human ACE2 receptor, while the S1/S2 interface contains a furin cleavage site which is cleaved to allow S2 to fuse with the host cell membrane. Both the RBD and the S1/S2 interface contain transmissibility increasing mutations that are harboured in variants of concern.

Figure 2: Viral entry and host response. A) At the alveolar epithelial cell layer. Epithelial cells in the lungs express both angiotensin-converting enzyme 2 (ACE2) receptors and transmembrane protease serine 2 (TMPRSS2), allowing for infection by SARS-CoV-2. Replication of the virus within these cells induces an intense immune response that attracts monocytes, T-cells and macrophages and, in some cases, can result in a cytokine storm. **B) Within nearby blood vessels.** Cytokines produced by the epithelial cell layer are released into blood vessels supplying the infected tissue, which causes the recruitment of further immune cells to the area, driving the damaging inflammatory response further. Circulating cytokines also create a systemic inflammatory environment. **C) Adaptive immune response.** Circulating lymphocytes carry viral antigens to lymph nodes and bone marrow to begin the adaptive immune system processes whereby B-cells, and later antibodies, are activated. **D) SARS-CoV2 host replication.** The SARS-CoV-2 virus utilises the ACE2 receptor and TMPRSS2 to gain entry into human cells. Following release of the viral RNA within the host cell, the virus utilises the host endoplasmic reticulum (ER) and Golgi apparatus to produce and manufacture new viral particles, which are released out of the cell to infect other cells and new hosts.

Table 1: SARS-CoV-2 variants and their S protein mutations. *first detection worldwide. Information correct as of 24th January 2022.

Table 2: Vaccine effectiveness of vaccines that have gained WHO emergency use listing. *Adjusted for covariates when reported by study, dates are reported in dd/mm/yyyy format. Vaccine effectiveness days/months refers to days/months since vaccination dose. Information correct as of reported conclusion date of each study.

Table 3: COVID-19 vaccines approved in at least one country. Information correct as of 24th January 2022.

References

1. CDC.org [Internet]. Human Coronavirus Types. Centres for Disease Control and Prevention. [15 February 2020; cited 12 October 2021]. Available from: https://www.cdc.gov/coronavirus/types.html
2. Who.int [Internet]. Weekly operational update on COVID-19 - 25 January 2022. World Health Organisation. [25 January 2022; cited 26 January 2022]. Available from: https://www.who.int/publications/m/item/weekly-operational-update-on-covid-19---25-january-2022

3. Who.int [Internet]. Tracking SARS-CoV-2 variants. World Health Organisation. [25 January 2022; cited 26 January 2022]. Available from: https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/
4. covid19.trackvaccines.org [Internet]. COVID-19 Vaccine Tracker. [24 January 2022; cited 26 January 2022]. Available from: https://covid19.trackvaccines.org/
5. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet. 2020;395(10223):514-23.
6. Who.int [Internet]. Transmission of SARS-CoV-2: implications for infection prevention precautions - Scientific Brief. World Health Organisation. [9 July 2020; cited 28 October 2021]. Available from: https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions
7. Gidari A, Sabbatini S, Bastianelli S, Pierucci S, Busti C, Bartolini D, et al. SARS-CoV-2 Survival on Surfaces and the Effect of UV-C Light. Viruses. 2021;13(3).
8. Pottage T, Garratt I, Onianwa O, Spencer A, Paton S, Verlander NQ, et al. A comparison of persistence of SARS-CoV-2 variants on stainless steel. J Hosp Infect. 2021;114:163-6.
9. Guo L, Wang M, Zhang L, Mao N, An C, Xu L, et al. Transmission risk of viruses in large mucosalivary droplets on the surface of objects: A time-based analysis. Infect Dis Now. 2021;51(3):219-27.
10. Carraturo F, Del Giudice C, Morelli M, Cerullo V, Libralato G, Galdiero E, et al. Persistence of SARS-CoV-2 in the environment and COVID-19 transmission risk from environmental matrices and surfaces. Environ Pollut. 2020;265(Pt B):115010.
11. Hui KP, Cheung M-C, Perera RA, Ng K-C, Bui CH, Ho JC, et al. Tropism, replication competence, and innate immune responses of the coronavirus SARS-CoV-2 in human respiratory tract and conjunctiva: an analysis in ex-vivo and in-vitro cultures. The Lancet Respiratory Medicine. 2020;8(7):687-95.
12. McAloon C, Collins A, Hunt K, Barber A, Byrne AW, Butler F, et al. Incubation period of COVID-19: a rapid systematic review and meta-analysis of observational research. BMJ Open. 2020;10(8):e039652.
13. Bliddal S, Banasik K, Pedersen OB, Nissen J, Cantwell L, Schwinn M, et al. Acute and persistent symptoms in non-hospitalized PCR-confirmed COVID-19 patients. Sci Rep. 2021;11(1):13153.
14. Grant MC, Geoghegan L, Arbyn M, Mohammed Z, McGuinness L, Clarke EL, et al. The prevalence of symptoms in 24,410 adults infected by the novel coronavirus (SARS-CoV-2; COVID-19): A systematic review and meta-analysis of 148 studies from 9 countries. PLoS One. 2020;15(6):e0234765.
15. Kronbichler A, Kresse D, Yoon S, Lee KH, Effenberger M, Shin JI. Asymptomatic patients as a source of COVID-19 infections: A systematic review and meta-analysis. Int J Infect Dis. 2020;98:180-6.
16. Arons MM, Hatfield KM, Reddy SC, Kimball A, James A, Jacobs JR, et al. Presymptomatic SARS-CoV-2 Infections and Transmission in a Skilled Nursing Facility. N Engl J Med. 2020;382(22):2081-90.
17. Cao Y, Wang J, Jian F, Xiao T, Song W, Yisimayi A, et al. B.1.1.529 escapes the majority of SARS-CoV-2 neutralizing antibodies of diverse epitopes. BioRxiv [Preprint]. 2021.
18. Wolff D, Nee S, Hickey NS, Marschollek M. Risk factors for Covid-19 severity and fatality: a structured literature review. Infection. 2021;49(1):15-28.
19. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62.

20. Zhang J, Wang X, Jia X, Li J, Hu K, Chen G, et al. Risk factors for disease severity, unimprovement, and mortality in COVID-19 patients in Wuhan, China. Clin Microbiol Infect. 2020;26(6):767-72.
21. Ebinger JE, Achamallah N, Ji H, Claggett BL, Sun N, Botting P, et al. Pre-existing traits associated with Covid-19 illness severity. PLoS One. 2020;15(7):e0236240.
22. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;584(7821):430-6.
23. Li R, Tian J, Yang F, Lv L, Yu J, Sun G, et al. Clinical characteristics of 225 patients with COVID-19 in a tertiary Hospital near Wuhan, China. J Clin Virol. 2020;127:104363.
24. Guo L, Shi Z, Zhang Y, Wang C, Do Vale Moreira NC, Zuo H, et al. Comorbid diabetes and the risk of disease severity or death among 8807 COVID-19 patients in China: A meta-analysis. Diabetes Res Clin Pract. 2020;166:108346.
25. Feng Y, Ling Y, Bai T, Xie Y, Huang J, Li J, et al. COVID-19 with Different Severities: A Multicenter Study of Clinical Features. Am J Respir Crit Care Med. 2020;201(11):1380-8.
26. Tian J, Yuan X, Xiao J, Zhong Q, Yang C, Liu B, et al. Clinical characteristics and risk factors associated with COVID-19 disease severity in patients with cancer in Wuhan, China: a multicentre, retrospective, cohort study. Lancet Oncol. 2020;21(7):893-903.
27. Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020;21(3):335-7.
28. Vizcarra P, Perez-Elias MJ, Quereda C, Moreno A, Vivancos MJ, Dronda F, et al. Description of COVID-19 in HIV-infected individuals: a single-centre, prospective cohort. Lancet HIV. 2020;7(8):e554-e64.
29. Baillie JK, Wilson JF, Bulteel N, Hayward C, Klaric L, Porteous DJ, et al. Mapping the human genetic architecture of COVID-19. Nature. 2021.
30. Shelton JF, Shastri AJ, Ye C, Weldon CH, Filshtein-Somnez T, Coker D, et al. Trans-ethnic analysis reveals genetic and non-genetic associations with COVID-19 susceptibility and severity. MedRxiv [Preprint]. 2020.
31. Ellinghaus D, Degenhardt F, Bujanda L, Buti M, Albillos A, Invernizzi P, et al. Genomewide association study of severe covid-19 with respiratory failure/[...]. New England Journal of Medicine Boston: Massachusetts Medical Society, 2020, vol 383, no 16. 2020.
32. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. cell. 2020;181(2):271-80. e8.
33. Hou Y, Zhao J, Martin W, Kallianpur A, Chung MK, Jehi L, et al. New insights into genetic susceptibility of COVID-19: an ACE2 and TMPRSS2 polymorphism analysis. BMC medicine. 2020;18(1):1-8.
34. Barbry P, Muus C, Luecken M, Eraslan G, Waghray A, Heimberg G, et al. Integrated analyses of single-cell atlases reveal age, gender, and smoking status associations with cell type-specific expression of mediators of SARS-CoV-2 viral entry and highlights inflammatory programs in putative target cells. BioRxiv [Preprint]. 2020.
35. Prakrithi P, Lakra P, Sundar D, Kapoor M, Mukerji M, Gupta I, et al. Genetic Risk Prediction of COVID-19 Susceptibility and Severity in the Indian Population. Front Genet. 2021;12:714185.
36. Huang QM, Zhang PD, Li ZH, Zhou JM, Liu D, Zhang XR, et al. Genetic Risk and Chronic Obstructive Pulmonary Disease Independently Predict the Risk of Incident Severe COVID-19. Ann Am Thorac Soc. 2022;19(1):58-65.
37. Zhou Y, Qian X, Liu Z, Yang H, Liu T, Chen K, et al. Coagulation factors and the incidence of COVID-19 severity: Mendelian randomization analyses and supporting evidence. Signal Transduct Target Ther. 2021;6(1):222.

38. Payne S. Family Coronaviridae. Viruses 2017. p. 149-58.
39. Masters PS, Kuo L, Ye R, Hurst KR, Koetzner CA, Hsue B. Genetic and molecular biological analysis of protein-protein interactions in coronavirus assembly. Adv Exp Med Biol. 2006;581:163-73.
40. Khailany RA, Safdar M, Ozaslan M. Genomic characterization of a novel SARS-CoV-2. Gene Rep. 2020;19:100682.
41. Thoms M, Buschauer R, Ameismeier M, Koepke L, Denk T, Hirschenberger M, et al. Structural basis for translational shutdown and immune evasion by the Nsp1 protein of SARS-CoV-2. Science. 2020;369(6508):1249-55.
42. Schubert K, Karousis ED, Jomaa A, Scaiola A, Echeverria B, Gurzeler LA, et al. SARS-CoV-2 Nsp1 binds the ribosomal mRNA channel to inhibit translation. Nat Struct Mol Biol. 2020;27(10):959-66.
43. Huang C, Lokugamage KG, Rozovics JM, Narayanan K, Semler BL, Makino S. SARS coronavirus nsp1 protein induces template-dependent endonucleolytic cleavage of mRNAs: viral mRNAs are resistant to nsp1-induced RNA cleavage. PLoS Pathog. 2011;7(12):e1002433.
44. Snijder EJ, Decroly E, Ziebuhr J. The Nonstructural Proteins Directing Coronavirus RNA Synthesis and Processing. Adv Virus Res. 2016;96:59-126.
45. V'Kovski P, Gerber M, Kelly J, Pfaender S, Ebert N, Braga Lagache S, et al. Determination of host proteins composing the microenvironment of coronavirus replicase complexes by proximity-labeling. Elife. 2019;8.
46. Masters PS. The molecular biology of coronaviruses. Advances in virus research. 2006;66:193-292.
47. Siu Y, Teoh K, Lo J, Chan C, Kien F, Escriou N, et al. The M, E, and N structural proteins of the severe acute respiratory syndrome coronavirus are required for efficient assembly, trafficking, and release of virus-like particles. Journal of virology. 2008;82(22):11318-30.
48. Kuo L, Masters PS. Genetic evidence for a structural interaction between the carboxy termini of the membrane and nucleocapsid proteins of mouse hepatitis virus. J Virol. 2002;76(10):4987-99.
49. Hulswit RJ, de Haan CA, Bosch BJ. Coronavirus Spike Protein and Tropism Changes. Adv Virus Res. 2016;96:29-57.
50. Konno Y, Kimura I, Uriu K, Fukushi M, Irie T, Koyanagi Y, et al. SARS-CoV-2 ORF3b Is a Potent Interferon Antagonist Whose Activity Is Increased by a Naturally Occurring Elongation Variant. Cell Rep. 2020;32(12):108185.
51. Kopecky-Bromberg SA, Martinez-Sobrido L, Frieman M, Baric RA, Palese P. Severe acute respiratory syndrome coronavirus open reading frame (ORF) 3b, ORF 6, and nucleocapsid proteins function as interferon antagonists. J Virol. 2007;81(2):548-57.
52. Xia H, Cao Z, Xie X, Zhang X, Chen JY, Wang H, et al. Evasion of Type I Interferon by SARS-CoV-2. Cell Rep. 2020;33(1):108234.
53. Wong HH, Fung TS, Fang S, Huang M, Le MT, Liu DX. Accessory proteins 8b and 8ab of severe acute respiratory syndrome coronavirus suppress the interferon signaling pathway by mediating ubiquitin-dependent rapid degradation of interferon regulatory factor 3. Virology. 2018;515:165-75.
54. Azad GK, Khan PK. Variations in Orf3a protein of SARS-CoV-2 alter its structure and function. Biochem Biophys Rep. 2021;26:100933.
55. Ren Y, Shu T, Wu D, Mu J, Wang C, Huang M, et al. The ORF3a protein of SARS-CoV-2 induces apoptosis in cells. Cell Mol Immunol. 2020;17(8):881-3.
56. Kreimendahl S, Rassow J. The Mitochondrial Outer Membrane Protein Tom70-Mediator in Protein Traffic, Membrane Contact Sites and Innate Immunity. Int J Mol Sci. 2020;21(19).

57. Gordon DE, Jang GM, Bouhaddou M, Xu J, Obernier K, White KM, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. Nature. 2020;583(7816):459-68.
58. Dominguez Andres A, Feng Y, Campos AR, Yin J, Yang CC, James B, et al. SARS-CoV-2 ORF9c Is a Membrane-Associated Protein that Suppresses Antiviral Responses in Cells. BioRxiv [Preprint]. 2020.
59. Redondo N, Zaldivar-Lopez S, Garrido JJ, Montoya M. SARS-CoV-2 Accessory Proteins in Viral Pathogenesis: Knowns and Unknowns. Front Immunol. 2021;12:708264.
60. Bosch BJ, van der Zee R, de Haan CA, Rottier PJ. The coronavirus spike protein is a class I virus fusion protein: structural and functional characterization of the fusion core complex. J Virol. 2003;77(16):8801-11.
61. Li F. Structure, Function, and Evolution of Coronavirus Spike Proteins. Annu Rev Virol. 2016;3(1):237-61.
62. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020;367(6483):1260-3.
63. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. Cell. 2020;181(2):281-92 e6.
64. Khare S, Azevedo M, Parajuli P, Gokulan K. Conformational Changes of the Receptor Binding Domain of SARS-CoV-2 Spike Protein and Prediction of a B-Cell Antigenic Epitope Using Structural Data. Front Artif Intell. 2021;4:630955.
65. Lan J, Ge J, Yu J, Shan S, Zhou H, Fan S, et al. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. Nature. 2020;581(7807):215-20.
66. Millet JK, Whittaker GR. Host cell proteases: Critical determinants of coronavirus tropism and pathogenesis. Virus Res. 2015;202:120-34.
67. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004;203(2):631-7.
68. Glowacka I, Bertram S, Muller MA, Allen P, Soilleux E, Pfefferle S, et al. Evidence that TMPRSS2 activates the severe acute respiratory syndrome coronavirus spike protein for membrane fusion and reduces viral control by the humoral immune response. J Virol. 2011;85(9):4122-34.
69. Zhao MM, Yang WL, Yang FY, Zhang L, Huang WJ, Hou W, et al. Cathepsin L plays a key role in SARS-CoV-2 infection in humans and humanized mice and is a promising target for new drug development. Signal Transduct Target Ther. 2021;6(1):134.
70. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020;181(2):271-80 e8.
71. Duchene S, Featherstone L, Haritopoulou-Sinanidou M, Rambaut A, Lemey P, Baele G. Temporal signal and the phylodynamic threshold of SARS-CoV-2. Virus Evol. 2020;6(2):veaa061.
72. Ecdc.europa.eu [Internet]. Methods for the detection and characterisation of SARS-CoV-2 variants - first update. European Centre for Disease Prevention and Control. [20 December 2021; cited 7 January 2022]. Available from: https://www.ecdc.europa.eu/en/publications-data/methods-detection-and-characterisation-sars-cov-2-variants-first-update
73. Cdc.gov [Internet]. COVID-19: About Variants. Centers for Disease Control and Prevention. [13 December 2021; cited 7 January 2022]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/variants/about-variants.html
74. Imperial.ac.uk [Internet]. Report 50 - Hospitalisation risk for Omicron cases in England. Imperial College London, MRC Centre for Global Infectious Disease Analysis. [22 December

2021; cited 10 January 2022]. Available from: https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/covid-19/report-50-severity-omicron/

75. Gov.uk [Internet]. SARS-CoV-2 variants of concern and variants under investigation in England - Technical briefing 33. UK Health Security Agency. [23 December 2021; cited 10 January 2022]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1043807/technical-briefing-33.pdf
76. Luna-Muschi A, Borges IC, de Faria E, Barboza AS, Maia FL, Leme MD, et al. Clinical features of COVID-19 by SARS-CoV-2 Gamma variant: A prospective cohort study of vaccinated and unvaccinated healthcare workers. J Infect. 2021.
77. Gov.uk [Internet]. Investigation of novel SARS-CoV-2 variant - Variant of Concern 202012/01 - Technical briefing 5. UK Health Security Agency (formerly Public Health England). [14 January 2021; cited 10 January 2022]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/959426/Variant_of_Concern_VOC_202012_01_Technical_Briefing_5.pdf
78. Wang Y, Liu M, Gao J. Enhanced receptor binding of SARS-CoV-2 through networks of hydrogen-bonding and hydrophobic interactions. Proc Natl Acad Sci U S A. 2020;117(25):13967-74.
79. Yi C, Sun X, Ye J, Ding L, Liu M, Yang Z, et al. Key residues of the receptor binding motif in the spike protein of SARS-CoV-2 that interact with ACE2 and neutralizing antibodies. Cell Mol Immunol. 2020;17(6):621-30.
80. Starr TN, Greaney AJ, Hilton SK, Ellis D, Crawford KHD, Dingens AS, et al. Deep Mutational Scanning of SARS-CoV-2 Receptor Binding Domain Reveals Constraints on Folding and ACE2 Binding. Cell. 2020;182(5):1295-310 e20.
81. Huang Y, Yang C, Xu XF, Xu W, Liu SW. Structural and functional properties of SARS-CoV-2 spike protein: potential antivirus drug development for COVID-19. Acta Pharmacol Sin. 2020;41(9):1141-9.
82. Hoffmann M, Kleine-Weber H, Pohlmann S. A Multibasic Cleavage Site in the Spike Protein of SARS-CoV-2 Is Essential for Infection of Human Lung Cells. Mol Cell. 2020;78(4):779-84 e5.
83. Peacock TP, Goldhill DH, Zhou J, Baillon L, Frise R, Swann OC, et al. The furin cleavage site of SARS-CoV-2 spike protein is a key determinant for transmission due to enhanced replication in airway cells. BioRxiv [Preprint]. 2020.
84. Zhu Y, Feng F, Hu G, Wang Y, Yu Y, Zhu Y, et al. The S1/S2 boundary of SARS-CoV-2 spike protein modulates cell entry pathways and transmission. BioRxiv [Preprint]. 2020.
85. Scudellari M. How the coronavirus infects cells - and why Delta is so dangerous. Nature. 2021;595(7869):640-4.
86. Wang Q, Qiu Y, Li JY, Zhou ZJ, Liao CH, Ge XY. A Unique Protease Cleavage Site Predicted in the Spike Protein of the Novel Pneumonia Coronavirus (2019-nCoV) Potentially Related to Viral Transmissibility. Virol Sin. 2020;35(3):337-9.
87. Yurkovetskiy L, Wang X, Pascal KE, Tomkins-Tinch C, Nyalile TP, Wang Y, et al. Structural and Functional Analysis of the D614G SARS-CoV-2 Spike Protein Variant. Cell. 2020;183(3):739-51 e8.
88. McCarthy KR, Rennick LJ, Nambulli S, Robinson-McCarthy LR, Bain WG, Haidar G, et al. Natural deletions in the SARS-CoV-2 spike glycoprotein drive antibody escape. BioRxiv [Preprint]. 2021.
89. Kemp SA, Collier DA, Datir R, Ferreira I, Gayed S, Jahun A, et al. Neutralising antibodies in Spike mediated SARS-CoV-2 adaptation. MedRxiv [Preprint]. 2020.

90. Gamage AM, Tan KS, Chan WOY, Liu J, Tan CW, Ong YK, et al. Infection of human Nasal Epithelial Cells with SARS-CoV-2 and a 382-nt deletion isolate lacking ORF8 reveals similar viral kinetics and host transcriptional profiles. PLoS Pathog. 2020;16(12):e1009130.
91. Collier DA, De Marco A, Ferreira I, Meng B, Datir RP, Walls AC, et al. Sensitivity of SARS-CoV-2 B.1.1.7 to mRNA vaccine-elicited antibodies. Nature. 2021;593(7857):136-41.
92. Martínez-García L, Espinel MA, Abreu M, González-Alba JM, Gijón D, McGee A, et al. Emergence and Spread of B. 1.1. 7 Lineage in Primary Care and Clinical Impact in the Morbi-Mortality among Hospitalized Patients in Madrid, Spain. Microorganisms. 2021;9(7):1517.
93. Vassallo M, Manni S, Klotz C, Fabre R, Pini P, Blanchouin E, et al. Patients Admitted for Variant Alpha COVID-19 Have Poorer Outcomes than Those Infected with the Old Strain. J Clin Med. 2021;10(16).
94. McAlister FA, Nabipoor M, Chu A, Lee DS, Saxinger L, Bakal JA. Lessons from the COVID-19 third wave in Canada: the impact of variants of concern and shifting demographics. MedRxiv [Preprint]. 2021.
95. Davies NG, Abbott S, Barnard RC, Jarvis CI, Kucharski AJ, Munday JD, et al. Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. Science. 2021;372(6538).
96. Leung K, Shum MH, Leung GM, Lam TT, Wu JT. Early transmissibility assessment of the N501Y mutant strains of SARS-CoV-2 in the United Kingdom, October to November 2020. Euro Surveill. 2021;26(1).
97. Zhao S, Lou J, Cao L, Zheng H, Chong MKC, Chen Z, et al. Quantifying the transmission advantage associated with N501Y substitution of SARS-CoV-2 in the UK: an early data-driven analysis. J Travel Med. 2021;28(2).
98. Gov.uk [Internet]. NERVTAG paper on COVID-19 variant of concern B.1.1.7. NERVTAG - COVID-19 Public statements. [22 January 2021; cited 7 October 2021] Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/961037/NERVTAG_note_on_B.1.1.7_severity_for_SAGE_77__1_.pdf
99. Challen R, Brooks-Pollock E, Read JM, Dyson L, Tsaneva-Atanasova K, Danon L. Risk of mortality in patients infected with SARS-CoV-2 variant of concern 202012/1: matched cohort study. BMJ. 2021;372:n579.
100. Paredes MI, Lunn SM, Famulare M, Frisbie LA, Painter I, Burstein R, et al. Associations between SARS-CoV-2 variants and risk of COVID-19 hospitalization among confirmed cases in Washington State: a retrospective cohort study. MedRxiv [Preprint]. 2021.
101. Wang P, Nair MS, Liu L, Iketani S, Luo Y, Guo Y, et al. Antibody Resistance of SARS-CoV-2 Variants B.1.351 and B.1.1.7. BioRxiv [Preprint]. 2021:2021.01.25.428137.
102. Wu K, Werner AP, Moliva JI, Koch M, Choi A, Stewart-Jones GBE, et al. mRNA-1273 vaccine induces neutralizing antibodies against spike mutants from global SARS-CoV-2 variants. BioRxiv [Preprint]. 2021.
103. Gallais F, Gantner P, Bruel T, Velay A, Planas D, Wendling M-J, et al. Anti-SARS-CoV-2 Antibodies Persist for up to 13 Months and Reduce Risk of Reinfection. MedRxiv [Preprint]. 2021.
104. Ecdc.europa.eu [Internet]. SARS-CoV-2 variants of concern as of 20 January 2022. European Centre for Disease Prevention and Control. [20 January 2022; cited 24 January 2022] Available from: https://www.ecdc.europa.eu/en/covid-19/variants-concern
105. Gu H, Chen Q, Yang G, He L, Fan H, Deng YQ, et al. Adaptation of SARS-CoV-2 in BALB/c mice for testing vaccine efficacy. Science. 2020;369(6511):1603-7.
106. Plante JA, Liu Y, Liu J, Xia H, Johnson BA, Lokugamage KG, et al. Spike mutation D614G alters SARS-CoV-2 fitness. Nature. 2021;592(7852):116-21.

107. Pearson CA, Russell TW, Davies NG, Kucharski AJ, group CC-w, Edmunds WJ, et al. Estimates of severity and transmissibility of novel South Africa SARS-CoV-2 variant 501Y.V2. Centre for Mathematical Modelling of Infectious Diseases. CMMID Repository [Preprint]. 2021.
108. Wibmer CK, Ayres F, Hermanus T, Madzivhandila M, Kgagudi P, Oosthuysen B, et al. SARS-CoV-2 501Y.V2 escapes neutralization by South African COVID-19 donor plasma. Nat Med. 2021;27(4):622-5.
109. Sinha S, Tam B, Wang SM. Altered interaction between RBD and ACE2 receptor contributes towards the increased transmissibility of SARS CoV-2 delta, kappa, beta, and gamma strains with RBD double mutations. BioRxiv [Preprint]. 2021.
110. Campbell F, Archer B, Laurenson-Schafer H, Jinnai Y, Konings F, Batra N, et al. Increased transmissibility and global spread of SARS-CoV-2 variants of concern as at June 2021. Euro Surveill. 2021;26(24).
111. Ecdc.europa.eu [Internet]. Risk assessment: SARS-CoV-2 - increased circulation of variants of concern and vaccine rollout in the EU/EEA, 14th update. European Centre for Disease Prevention and Control. [15 February 2021; cited 8 October 2021] Available from: https://www.ecdc.europa.eu/en/publications-data/covid-19-risk-assessment-variants-vaccine-fourteenth-update-february-2021
112. Khan A, Zia T, Suleman M, Khan T, Ali SS, Abbasi AA, et al. Higher infectivity of the SARS-CoV-2 new variants is associated with K417N/T, E484K, and N501Y mutants: An insight from structural data. J Cell Physiol. 2021;236(10):7045-57.
113. Baum A, Fulton BO, Wloga E, Copin R, Pascal KE, Russo V, et al. Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies. Science. 2020;369(6506):1014-8.
114. Curran J, Dol J, Boulos L, Somerville M, McCulloch H, MacDonald M, et al. Transmission characteristics of SARS-CoV-2 variants of concern. MedRxiv [Preprint]. 2021.
115. de Faria E, Guedes AR, Oliveira MS, de Godoy Moreira MV, Maia FL, dos Santos Barboza A, et al. Performance of vaccination with CoronaVac in a cohort of healthcare workers (HCW) - preliminary report. MedRxiv [Preprint]. 2021.
116. Freitas ARR, Beckedorff OA, Cavalcanti LPG, Siqueira AM, Castro DB, Costa CFD, et al. The emergence of novel SARS-CoV-2 variant P.1 in Amazonas (Brazil) was temporally associated with a change in the age and sex profile of COVID-19 mortality: A population based ecological study. Lancet Reg Health Am. 2021;1:100021.
117. Funk T, Pharris A, Spiteri G, Bundle N, Melidou A, Carr M, et al. Characteristics of SARS-CoV-2 variants of concern B.1.1.7, B.1.351 or P.1: data from seven EU/EEA countries, weeks 38/2020 to 10/2021. Euro Surveill. 2021;26(16).
118. Sabino EC, Buss LF, Carvalho MPS, Prete CA, Jr., Crispim MAE, Fraiji NA, et al. Resurgence of COVID-19 in Manaus, Brazil, despite high seroprevalence. Lancet. 2021;397(10273):452-5.
119. Dejnirattisai W, Zhou D, Supasa P, Liu C, Mentzer AJ, Ginn HM, et al. Antibody evasion by the P.1 strain of SARS-CoV-2. Cell. 2021;184(11):2939-54 e9.
120. Korber B, Fischer WM, Gnanakaran S, Yoon H, Theiler J, Abfalterer W, et al. Tracking Changes in SARS-CoV-2 Spike: Evidence that D614G Increases Infectivity of the COVID-19 Virus. Cell. 2020;182(4):812-27 e19.
121. Volz E, Hill V, McCrone JT, Price A, Jorgensen D, O'Toole A, et al. Evaluating the Effects of SARS-CoV-2 Spike Mutation D614G on Transmissibility and Pathogenicity. Cell. 2021;184(1):64-75 e11.

122. Augusto G, Mohsen MO, Zinkhan S, Liu X, Vogel M, Bachmann MF. In vitro data suggest that Indian delta variant B.1.617 of SARS-CoV-2 escapes neutralization by both receptor affinity and immune evasion. Allergy. 2021.
123. Tchesnokova V, Kulakesara H, Larson L, Bowers V, Rechkina E, Kisiela D, et al. Acquisition of the L452R mutation in the ACE2-binding interface of Spike protein triggers recent massive expansion of SARS-Cov-2 variants. BioRxiv [Preprint]. 2021.
124. Li Q, Wu J, Nie J, Zhang L, Hao H, Liu S, et al. The Impact of Mutations in SARS-CoV-2 Spike on Viral Infectivity and Antigenicity. Cell. 2020;182(5):1284-94 e9.
125. Di Giacomo S, Mercatelli D, Rakhimov A, Giorgi FM. Preliminary report on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Spike mutation T478K. J Med Virol. 2021;93(9):5638-43.
126. Torjesen I. Covid-19: Delta variant is now UK's most dominant strain and spreading through schools. BMJ. 2021;373:n1445.
127. Reuters.com [Internet]. Delta COVID variant now dominant strain worldwide, U.S. deaths surge -officials. O'donnell C, Mason J, Reuters. [16 July 2021; cited 6 January 2022]. Available from: www.reuters.com
128. Euro.who.int [Internet]. SARS-CoV-2 Delta variant now dominant in much of European region; efforts must be reinforced to prevent transmission, warns WHO Regional Office for Europe and ECDC. World Health Organisation. [23 July 2021; cited 11 October 2021]. Available from: https://www.euro.who.int/en/media-centre/sections/press-releases/2021/sars-cov-2-delta-variant-now-dominant-in-much-of-european-region-efforts-must-be-reinforced-to-prevent-transmission,-warns-who-regional-office-for-europe-and-ecdc
129. Li B, Deng A, Li K, Hu Y, Li Z, Xiong Q, et al. Viral infection and transmission in a large, well-traced outbreak caused by the SARS-CoV-2 Delta variant MedRxiv [Preprint]. 2021.
130. Teyssou E, Delagreverie H, Visseaux B, Lambert-Niclot S, Brichler S, Ferre V, et al. The Delta SARS-CoV-2 variant has a higher viral load than the Beta and the historical variants in nasopharyngeal samples from newly diagnosed COVID-19 patients. J Infect. 2021;83(4):e1-e3.
131. Kumar A, Asghar A, Raza K, Narayan RK, Jha RK, Satyam A, et al. Demographic characteristics of SARS-CoV-2 B.1.617.2 (Delta) variant infections in Indian population. MedRxiv [Preprint]. 2021.
132. Planas D, Veyer D, Baidaliuk A, Staropoli I, Guivel-Benhassine F, Rajah MM, et al. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. Nature. 2021;596(7871):276-80.
133. Sheikh A, McMenamin J, Taylor B, Robertson C, Public Health S, the EIIC. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. Lancet. 2021;397(10293):2461-2.
134. Fisman DN, Tuite AR. Progressive Increase in Virulence of Novel SARS-CoV-2 Variants in Ontario, Canada. MedRxiv [Preprint]. 2021.
135. Cameroni E, Saliba C, Bowen JE, Rosen LE, Culap K, Pinto D, et al. Broadly neutralizing antibodies overcome SARS-CoV-2 Omicron antigenic shift. BioRxiv [Preprint]. 2021.
136. Shah M, Woo HG. Omicron: A heavily mutated SARS-CoV-2 variant exhibits stronger binding to ACE2 and potently escape approved COVID-19 therapeutic antibodies. BioRxiv [Preprint]. 2021.
137. Wolter N, Jassat W, Walaza S, Welch R, Moultrie H, Groome M, et al. Early assessment of the clinical severity of the SARS-CoV-2 Omicron variant in South Africa. MedRxiv [Preprint]. 2021.
138. Gov.uk [Internet]. Omicron daily overview: 24 December 2021. UK Health Security Agency. [24 December 2021; cited 4 January 2022]. Available from:

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1043866/20211224_OS_Daily_Omicron_Overview.pdf

139. Who.int [Internet]. Enhancing readiness for Omicron (B.1.1.529): Technical brief and priority actions for Member States. World Health Organisation. [23 December 2021; cited 4 January 2022]. Available from: https://www.who.int/docs/default-source/coronaviruse/2021-12-23-global-technical-brief-and-priority-action-on-omicron.pdf?sfvrsn=d0e9fb6c_8
140. Med.hku.hk [Internet]. HKUMed finds Omicron SARS-CoV-2 can infect faster and better than Delta in human bronchus but with less severe infection in lung. The University of Hong Kong, LKS Faculty of Medicine. [15 December 2021; cited 5 January 2022]. Available from: https://www.med.hku.hk/en/news/press/20211215-omicron-sars-cov-2-infection
141. Sheikh A, Kerr S, Woolhouse M, McMenamin J, C. R. Severity of Omicron variant of concern and vaccine effectiveness against symptomatic disease: national cohort with nested test negative design study in Scotland. 2021.
142. Pulliam JRC, van Schalkwyk C, Govender N, von Gottberg A, Cohen C, Groome MJ, et al. Increased risk of SARS-CoV-2 reinfection associated with emergence of the Omicron variant in South Africa. MedRxiv [Preprint]. 2021.
143. Sandile Cele, Laurelle Jackson, Khadija Khan, David Khoury, Thandeka Moyo-Gwete, Houriiyah Tegally, et al. SARS-CoV-2 Omicron has extensive but incomplete escape of Pfizer BNT162b2 elicited neutralization and requires ACE2 for infection. MedRxiv [Preprint]. 2021.
144. Planas D, Saunders N, Maes P, Guivel-Benhassine F, Planchais C, Buchrieser J, et al. Considerable escape of SARS-CoV-2 variant Omicron to antibody neutralization. BioRxiv [Preprint]. 2021.
145. Meng B, Ferreira IATM, Abdullahi A, Saito A, Kimura I, Yamasoba D, et al. SARS-CoV-2 Omicron spike mediated immune escape, infectivity and cell-cell fusion. BioRxiv [Preprint]. 2021.
146. Pfizer.com [Internet]. Pfizer and BioNTech Provide Update on Omicron Variant. Pfizer. [8 December 2021; cited 4 January 2022]. Available from: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-provide-update-omicron-variant
147. Keeton R, Tincho MB, Ngomti A, Baguma R, Benede N, Suzuki A, et al. SARS-CoV-2 spike T cell responses induced upon vaccination or infection remain robust against Omicron. MedRxiv [Preprint]. 2021.
148. Sacoronavirus.co.za [Internet]. Cabinet approves changes to covid-19 regulations. South Africa Department of Health. [30 December 2021; cited 7 January 2022]. Available from: https://sacoronavirus.co.za/2021/12/30/media-release-cabinet-approves-changes-to-covid-19-regulations/
149. Taylor L. Covid-19: Omicron drives weekly record high in global infections. BMJ. 2022;376:o66.
150. Tada T, Zhou H, Dcosta BM, Samanovic MI, Mulligan MJ, Landau NR. SARS-CoV-2 Lambda Variant Remains Susceptible to Neutralization by mRNA Vaccine-elicited Antibodies and Convalescent Serum. BioRxiv [Preprint]. 2021.
151. Acevedo ML, Alonso-Palomares L, Bustamante A, Gaggero A, Paredes F, Cortés CP, et al. Infectivity and immune escape of the new SARS-CoV-2 variant of interest Lambda. MedRxiv [Preprint]. 2021.
152. Laiton-Donato K, Franco-Munoz C, Alvarez-Diaz DA, Ruiz-Moreno HA, Usme-Ciro JA, Prada DA, et al. Characterization of the emerging B.1.621 variant of interest of SARS-CoV-2. Infect Genet Evol. 2021;95:105038.

153. Chen J, Gao K, Wang R, Wei GW. Revealing the Threat of Emerging SARS-CoV-2 Mutations to Antibody Therapies. J Mol Biol. 2021;433(18):167155.
154. Amanat F, Krammer F. SARS-CoV-2 vaccines: status report. Immunity. 2020;52(4):583-9.
155. [dataset] Who.int. COVID-19 vaccine tracker and landscape. World Health Organisation. [25 January 2022; cited 26 January 2022]. Available from: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines
156. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020;383(27):2603-15.
157. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh C-L, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020;367(6483):1260-3.
158. Who.int [Internet]. Coronavirus disease (COVID-19): Vaccines. World Health Organisation. [20 January 2022; cited 26 January 2022]. Available from: https://www.who.int/news-room/questions-and-answers/item/coronavirus-disease-(covid-19)-vaccines
159. Sahin U, Muik A, Vogler I, Derhovanessian E, Kranz LM, Vormehr M, et al. BNT162b2 vaccine induces neutralizing antibodies and poly-specific T cells in humans. Nature. 2021;595(7868):572-7.
160. Arunachalam PS, Scott MKD, Hagan T, Li C, Feng Y, Wimmers F, et al. Systems vaccinology of the BNT162b2 mRNA vaccine in humans. Nature. 2021;596(7872):410-6.
161. Walsh EE, Frenck RW, Jr., Falsey AR, Kitchin N, Absalon J, Gurtman A, et al. Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates. N Engl J Med. 2020;383(25):2439-50.
162. Appelman B, van der Straten K, Lavell AHA, Schinkel M, Slim MA, Poniman M, et al. Time since SARS-CoV-2 infection and humoral immune response following BNT162b2 mRNA vaccination. EBioMedicine. 2021;72:103589.
163. Beatty AL, Peyser ND, Butcher XE, Cocohoba JM, Lin F, Olgin JE, et al. Analysis of COVID-19 Vaccine Type and Adverse Effects Following Vaccination. JAMA Netw Open. 2021;4(12):e2140364.
164. Vizcarra P, Haemmerle J, Velasco H, Velasco T, Fernandez-Escribano M, Vallejo A, et al. BNT162b2 mRNA COVID-19 vaccine Reactogenicity: The key role of immunity. Vaccine. 2021;39(51):7367-74.
165. Salmeron Rios S, Mas Romero M, Cortes Zamora EB, Tabernero Sahuquillo MT, Romero Rizos L, Sanchez-Jurado PM, et al. Immunogenicity of the BNT162b2 vaccine in frail or disabled nursing home residents: COVID-A study. J Am Geriatr Soc. 2021;69(6):1441-7.
166. Barda N, Dagan N, Ben-Shlomo Y, Kepten E, Waxman J, Ohana R, et al. Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. N Engl J Med. 2021;385(12):1078-90.
167. Sharma O, Sultan AA, Ding H, Triggle CR. A Review of the Progress and Challenges of Developing a Vaccine for COVID-19. Front Immunol. 2020;11:585354.
168. Who.int [Internet]. WHO lists two additional COVID-19 vaccines for emergency use and COVAX roll-out. World Health Organisation. [15 February 2021; cited 13 October 2021]. Available rom: https://www.who.int/news/item/15-02-2021-who-lists-two-additional-covid-19-vaccines-for-emergency-use-and-covax-roll-out
169. Ewer KJ, Barrett JR, Belij-Rammerstorfer S, Sharpe H, Makinson R, Morter R, et al. T cell and antibody responses induced by a single dose of ChAdOx1 nCoV-19 (AZD1222) vaccine in a phase 1/2 clinical trial. Nat Med. 2021;27(2):270-8.

170. Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij-Rammerstorfer S, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. Lancet. 2020;396(10249):467-78.
171. Al Khames Aga QA, Alkhaffaf WH, Hatem TH, Nassir KF, Batineh Y, Dahham AT, et al. Safety of COVID-19 vaccines. J Med Virol. 2021;93(12):6588-94.
172. Sadoff J, Gray G, Vandebosch A, Cardenas V, Shukarev G, Grinsztejn B, et al. Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19. N Engl J Med. 2021;384(23):2187-201.
173. Alter G, Yu J, Liu J, Chandrashekar A, Borducchi EN, Tostanoski LH, et al. Immunogenicity of Ad26.COV2.S vaccine against SARS-CoV-2 variants in humans. Nature. 2021;596(7871):268-72.
174. Sadoff J, Le Gars M, Shukarev G, Heerwegh D, Truyers C, de Groot AM, et al. Interim Results of a Phase 1-2a Trial of Ad26.COV2.S Covid-19 Vaccine. N Engl J Med. 2021;384(19):1824-35.
175. Keeton R, Richardson SI, Moyo-Gwete T, Hermanus T, Tincho MB, Benede N, et al. Prior infection with SARS-CoV-2 boosts and broadens Ad26.COV2.S immunogenicity in a variant-dependent manner. Cell Host Microbe. 2021;29(11):1611-9 e5.
176. See I, Su JR, Lale A, Woo EJ, Guh AY, Shimabukuro TT, et al. US Case Reports of Cerebral Venous Sinus Thrombosis With Thrombocytopenia After Ad26.COV2.S Vaccination, March 2 to April 21, 2021. JAMA. 2021;325(24):2448-56.
177. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2021;384(5):403-16.
178. Mukhopadhyay L, Yadav PD, Gupta N, Mohandas S, Patil DY, Shete-Aich A, et al. Comparison of the immunogenicity & protective efficacy of various SARS-CoV-2 vaccine candidates in non-human primates. Indian J Med Res. 2021;153(1 & 2):93-114.
179. Anderson EJ, Rouphael NG, Widge AT, Jackson LA, Roberts PC, Makhene M, et al. Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults. N Engl J Med. 2020;383(25):2427-38.
180. Jackson LA, Anderson EJ, Rouphael NG, Roberts PC, Makhene M, Coler RN, et al. An mRNA Vaccine against SARS-CoV-2 - Preliminary Report. N Engl J Med. 2020;383(20):1920-31.
181. Chu L, McPhee R, Huang W, Bennett H, Pajon R, Nestorova B, et al. A preliminary report of a randomized controlled phase 2 trial of the safety and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine. Vaccine. 2021;39(20):2791-9.
182. Who.int [Internet]. Interim recommendations for use of the inactivated COVID-19 vaccine BIBP developed by China National Biotec Group (CNBG), Sinopharm. World Health Organisation. [28 October 2021; cited 7 January 2022]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-BIBP
183. Who.int [Internet]. Background document on the inactivated vaccine Sinovac-CoronaVac against COVID-19. World Health Organisation. [1 June 2021; cited 13 October 2021]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-Sinovac-CoronaVac-background-2021.1
184. Who.int [Internet]. Background document on the Bharat Biotech BBV152 COVAXIN® (COVID-19) vaccine. World Health Organisation. [3 November 2021; cited 7 January 2022]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-bbv152-covaxin-background

185. Who.int [Internet]. WHO issues emergency use listing for eighth COVID-19 vaccine. World Health Organisation. [3 November 2021; cited 7 January 2022]. Available from: https://www.who.int/news/item/03-11-2021-who-issues-emergency-use-listing-for-eighth-covid-19-vaccine
186. Who.int [Internet]. WHO lists 9th COVID-19 vaccine for emergency use with aim to increase access to vaccination in lower-income countries. World Health Organisation. [17 December 2021; cited 7 January 2022]. Available from: https://www.who.int/news/item/17-12-2021-who-lists-9th-covid-19-vaccine-for-emergency-use-with-aim-to-increase-access-to-vaccination-in-lower-income-countries
187. Who.int [Internet]. WHO lists 10th COVID-19 vaccine for emergency use: Nuvaxovid. World Health Organisation. [21 December 2021; cited 7 January 2022]. Available from: https://www.who.int/news/item/21-12-2021-who-lists-10th-covid-19-vaccine-for-emergency-use-nuvaxovid
188. Who.int [Internet]. Interim recommendations for use of the Novavax NVX-CoV2373 vaccine against COVID-19. World Health Organisation. [20 December 2021; cited 7 January 2022]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-novavax-nvx-cov2373
189. Mishra SK, Pradhan SK, Pati S, Sahu S, Nanda RK. Waning of Anti-spike Antibodies in AZD1222 (ChAdOx1) Vaccinated Healthcare Providers: A Prospective Longitudinal Study. Cureus. 2021;13(11):e19879.
190. Tre-Hardy M, Cupaiolo R, Wilmet A, Antoine-Moussiaux T, Della Vecchia A, Horeanga A, et al. Immunogenicity of mRNA-1273 COVID vaccine after 6 months surveillance in health care workers; a third dose is necessary. J Infect. 2021;83(5):559-64.
191. Shrotri M, Navaratnam AMD, Nguyen V, Byrne T, Geismar C, Fragaszy E, et al. Spike-antibody waning after second dose of BNT162b2 or ChAdOx1. Lancet. 2021;398(10298):385-7.
192. Chemaitelly H, Tang P, Hasan MR, AlMukdad S, Yassine HM, Benslimane FM, et al. Waning of BNT162b2 Vaccine Protection against SARS-CoV-2 Infection in Qatar. N Engl J Med. 2021.
193. Mizrahi B, Lotan R, Kalkstein N, Peretz A, Perez G, Ben-Tov A, et al. Correlation of SARS-CoV-2 Breakthrough Infections to Time-from-vaccine; Preliminary Study. MedRxiv [Preprint]. 2021.
194. Thomas SJ, Moreira ED, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Six Month Safety and Efficacy of the BNT162b2 mRNA COVID-19 Vaccine. MedRxiv [Preprint]. 2021.
195. Tre-Hardy M, Cupaiolo R, Wilmet A, Antoine-Moussiaux T, Della Vecchia A, Horeanga A, et al. Six-month interim analysis of ongoing immunogenicity surveillance of the mRNA-1273 vaccine in healthcare workers: A third dose is expected. J Infect. 2021.
196. Almendro-Vazquez P, Laguna-Goya R, Ruiz-Ruigomez M, Utrero-Rico A, Lalueza A, Maestro de la Calle G, et al. Longitudinal dynamics of SARS-CoV-2-specific cellular and humoral immunity after natural infection or BNT162b2 vaccination. PLoS Pathog. 2021;17(12):e1010211.
197. Cohen KW, Linderman SL, Moodie Z, Czartoski J, Lai L, Mantus G, et al. Longitudinal analysis shows durable and broad immune memory after SARS-CoV-2 infection with persisting antibody responses and memory B and T cells. Cell Rep Med. 2021;2(7):100354.
198. Zeng G, Wu Q, Pan H, Li M, Yang J, Wang L, et al. Immunogenicity and safety of a third dose of CoronaVac, and immune persistence of a two-dose schedule, in healthy adults: interim results from two single-centre, double-blind, randomised, placebo-controlled phase 2 clinical trials. Lancet Infect Dis. 2021.

199. Choi A, Koch M, Wu K, Chu L, Ma L, Hill A, et al. Safety and immunogenicity of SARS-CoV-2 variant mRNA vaccine boosters in healthy adults: an interim analysis. Nat Med. 2021.
200. Flaxman A, Marchevsky NG, Jenkin D, Aboagye J, Aley PK, Angus B, et al. Reactogenicity and immunogenicity after a late second dose or a third dose of ChAdOx1 nCoV-19 in the UK: a substudy of two randomised controlled trials (COV001 and COV002). Lancet. 2021;398(10304):981-90.
201. Iketani S, Liu L, Nair MS, Mohri H, Wang M, Huang Y, et al. A third COVID-19 vaccine shot markedly boosts neutralizing antibody potency and breadth MedRxiv [Preprint]. 2021.
202. Garcia-Beltran WF, St Denis KJ, Hoelzemer A, Lam EC, Nitido AD, Sheehan ML, et al. mRNA-based COVID-19 vaccine boosters induce neutralizing immunity against SARS-CoV-2 Omicron variant. MedRxiv [Preprint]. 2021.
203. Yorsaeng R, Suntronwong N, Phowatthanasathian H, Assawakosri S, Kanokudom S, Thongmee T, et al. Immunogenicity of a third dose viral-vectored COVID-19 vaccine after receiving two-dose inactivated vaccines in healthy adults. Vaccine. 2022;40(3):524-30.
204. Munro APS, Janani L, Cornelius V, Aley PK, Babbage G, Baxter D, et al. Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial. Lancet. 2021;398(10318):2258-76.
205. Madelon N, Heikkilä N, Sabater Royo I, Fontannaz P, Breville G, Lauper K, et al. Omicron-specific cytotoxic T-cell responses are boosted following a third dose of mRNA COVID-19 vaccine in anti-CD20-treated multiple sclerosis patients MedRxiv [Preprint]. 2021.
206. Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Kalkstein N, et al. Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel. N Engl J Med. 2021;385(15):1393-400.
207. Barda N, Dagan N, Cohen C, Hernan MA, Lipsitch M, Kohane IS, et al. Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. Lancet. 2021;398(10316):2093-100.
208. Arbel R, Hammerman A, Sergienko R, Friger M, Peretz A, Netzer D, et al. BNT162b2 Vaccine Booster and Mortality Due to Covid-19. N Engl J Med. 2021;385(26):2413-20.
209. Spitzer A, Angel Y, Marudi O, Zeltser D, Saiag E, Goldshmidt H, et al. Association of a Third Dose of BNT162b2 Vaccine With Incidence of SARS-CoV-2 Infection Among Health Care Workers in Israel. JAMA. 2022.
210. Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Alroy-Preis S, et al. Protection against Covid-19 by BNT162b2 Booster across Age Groups. N Engl J Med. 2021;385(26):2421-30.
211. Levine-Tiefenbrun M, Yelin I, Alapi H, Katz R, Herzel E, Kuint J, et al. Viral loads of Delta-variant SARS-CoV-2 breakthrough infections after vaccination and booster with BNT162b2. Nat Med. 2021;27(12):2108-10.
212. Andrews N, Stowe J, Kirsebom F, Toffa S, Rickeard T, Gallagher E, et al. Effectiveness of COVID-19 vaccines against the Omicron (B.1.1.529) variant of concern. medRxiv [Preprint]. 2021.
213. Hansen CH, Schelde AB, Moustsen-Helm IR, Emborg H-D, Krause TG, Mølbak K, et al. Vaccine effectiveness against SARS-CoV-2 infection with the Omicron or Delta variants following a two-dose or booster BNT162b2 or mRNA-1273 vaccination series: A Danish cohort study MedRxiv [Preprint]. 2021.
214. Lusvarghi S, Pollett SD, Neerukonda SN, Wang W, Wang R, Vassell R, et al. SARS-CoV-2 Omicron neutralization by therapeutic antibodies, convalescent sera, and post-mRNA vaccine booster. BioRxiv [Preprint]. 2021.

215. Cdc.gov [Internet]. CDC Recommends Pfizer Booster at 5 Months, Additional Primary Dose for Certain Immunocompromised Children. Centers for Disease Control and Prevention. [4 January 2022; cited 7 January 2022]. Available from: https://www.cdc.gov/media/releases/2022/s0104-Pfizer-Booster.html
216. Wu K, Choi A, Koch M, Elbashir S, Ma L, Lee D, et al. Variant SARS-CoV-2 mRNA vaccines confer broad neutralization as primary or booster series in mice. Vaccine. 2021;39(51):7394-400.
217. Covid19-trials.com [Internet]. Global Coronavirus COVID-19 Clinical Trial Tracker. Cytel Inc. [cited 12 January 2022]. Available from: https://www.covid19-trials.com/
218. Gov.uk [Internet]. First oral antiviral for COVID-19, Lagevrio (molnupiravir), approved by MHRA. Medicines and Healthcare products Regulatory Agency. [4 November 2021; cited 12 January 2022]. Available from: https://www.gov.uk/government/news/first-oral-antiviral-for-covid-19-lagevrio-molnupiravir-approved-by-mhra
219. Gov.uk [Internet]. Oral COVID-19 antiviral, Paxlovid, approved by UK regulator. Medicines and Healthcare products Regulatory Agency. [31 December 2021; cited 12 January 2022]. Available from: https://www.gov.uk/government/news/oral-covid-19-antiviral-paxlovid-approved-by-uk-regulator
220. Fda.gov [Internet]. Coronavirus (COVID-19) Update: FDA Authorizes Additional Oral Antiviral for Treatment of COVID-19 in Certain Adults. U.S. Food and Drug Administration. [23 December 2021; cited 12 January 2022]. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-oral-antiviral-treatment-covid-19-certain
221. Fda.gov [Internet]. Coronavirus (COVID-19) Update: FDA Authorizes First Oral Antiviral for Treatment of COVID-19. U.S. Food and Drug Administration. [22 December 2021; cited 12 January 2022]. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-oral-antiviral-treatment-covid-19
222. ema.europa.eu [Internet]. EMA issues advice on use of Lagevrio (molnupiravir) for the treatment of COVID-19. European Medicines Agency. [19 November 2021.; cited 12 January 2022]. Available from: https://www.ema.europa.eu/en/news/ema-issues-advice-use-lagevrio-molnupiravir-treatment-covid-19
223. ema.europa.eu [Internet]. EMA issues advice on use of Paxlovid (PF-07321332 and ritonavir) for the treatment of COVID-19: rolling review starts in parallel. European Medicines Agency. [16 December 2021.; cited 12 January 2022]. Available from: https://www.ema.europa.eu/en/news/ema-issues-advice-use-paxlovid-pf-07321332-ritonavir-treatment-covid-19-rolling-review-starts
224. Gov.uk [Internet]. MHRA approves Xevudy (sotrovimab), a COVID-19 treatment found to cut hospitalisation and death by 79%. Medicines and Healthcare products Regulatory Agency. [2 December 2021; cited 12 January 2022]. Available from: https://www.gov.uk/government/news/mhra-approves-xevudy-sotrovimab-a-covid-19-treatment-found-to-cut-hospitalisation-and-death-by-79#:~:text=and%20licensing%20guidance-,MHRA%20approves%20Xevudy%20(sotrovimab)%2C%20a%20COVID%2D19%20treatment,risk%20of%20developing%20severe%20disease.
225. Fda.gov [Internet]. Coronavirus (COVID-19) Update: FDA Authorizes Additional Monoclonal Antibody for Treatment of COVID-19. U.S. Food and Drug Administration. [26 May 2021; cited 12 January 2022]. Available from: https://www.fda.gov/news-events/press-

announcements/coronavirus-covid-19-update-fda-authorizes-additional-monoclonal-antibody-treatment-covid-19

226. ema.europa.eu [Internet]. COVID-19: EMA recommends authorisation of antibody medicine Xevudy. European Medicines Agency. [16 December 2021.; cited 12 January 2022]. Available from: https://www.ema.europa.eu/en/news/covid-19-ema-recommends-authorisation-antibody-medicine-xevudy#:~:text=EMA's%20human%20medicines%20committee%20(CHMP,medicine%20together%20with%20Vir%20Biotechnology.
227. Who.int [Internet]. Therapeutics and COVID-19: living guideline. World Health Organisation. [14 January 2022; cited 21 January 2022] Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022.1
228. Nice.org.uk [Internet]. COVID-19 rapid guideline: managing COVID-19 NICE guideline [NG191]. National Institute for Health and Care Excellence. [16 December 2021; cited 21 January 2022]. Available from: https://www.nice.org.uk/guidance/ng191
229. Gov.uk [Internet]. MHRA guidance on coronavirus (COVID-19). Medicines and Healthcare products Regulatory Agency. [16 September 2021; cited 21 January 2022]. Available from: https://www.gov.uk/government/collections/mhra-guidance-on-coronavirus-covid-19
230. ecdc.europa.eu [Internet]. All resources on COVID-19 – Guidance and technical reports. [2022; cited 21 January 2022]. Available from: https://www.ecdc.europa.eu/en/covid-19/all-reports-covid-19
231. Nih.gov [Internet]. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health [19 January 2022; cited 21 January 2022]. Available from: https://www.covid19treatmentguidelines.nih.gov/
232. Cdc.gov [Internet]. Guidance for COVID-19. Centers for Disease Control and Prevention. [15 March 2021; cited 21 January 2022]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/communication/guidance.html
233. Blundell R, Costa Dias M, Joyce R, Xu X. COVID-19 and Inequalities. Fisc Stud. 2020.
234. Chadeau-Hyam M, Bodinier B, Elliott J, Whitaker MD, Tzoulaki I, Vermeulen R, et al. Risk factors for positive and negative COVID-19 tests: a cautious and in-depth analysis of UK biobank data. Int J Epidemiol. 2020;49(5):1454-67.
235. Patel JA, Nielsen FBH, Badiani AA, Assi S, Unadkat VA, Patel B, et al. Poverty, inequality and COVID-19: the forgotten vulnerable. Public Health. 2020;183:110-1.
236. Cohen J, Rodgers YVM. Contributing factors to personal protective equipment shortages during the COVID-19 pandemic. Prev Med. 2020;141:106263.
237. Who.int [Internet]. Vaccine Equity. World Health Organisation. [cited 10 January 2022]. Available from: https://www.who.int/campaigns/vaccine-equity
238. parliament.uk [Internet]. Coronavirus: lessons learned to date. The House of Commons, Science and Technology Committee, and Health and Social Care Committee. [12 October 2021; cited 10 January 2022]. Available from: https://publications.parliament.uk/pa/cm5802/cmselect/cmsctech/92/9203.htm
239. Ball P. The lightning-fast quest for COVID vaccines - and what it means for other diseases. Nature. 2021;589(7840):16-8.
240. Summers J, Cheng HY, Lin HH, Barnard LT, Kvalsvig A, Wilson N, et al. Potential lessons from the Taiwan and New Zealand health responses to the COVID-19 pandemic. Lancet Reg Health West Pac. 2020;4:100044.

241. Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. N Engl J Med. 2021;384(15):1412-23.
242. Lopez Bernal J, Andrews N, Gower C, Gallagher E, Simmons R, Thelwall S, et al. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. N Engl J Med. 2021;385(7):585-94.
243. Abu-Raddad LJ, Chemaitelly H, Butt AA, National Study Group for C-V. Effectiveness of the BNT162b2 Covid-19 Vaccine against the B.1.1.7 and B.1.351 Variants. N Engl J Med. 2021;385(2):187-9.
244. Chung H, He S, Nasreen S, Sundaram ME, Buchan SA, Wilson SE, et al. Effectiveness of BNT162b2 and mRNA-1273 covid-19 vaccines against symptomatic SARS-CoV-2 infection and severe covid-19 outcomes in Ontario, Canada: test negative design study. BMJ. 2021;374:n1943.
245. Nasreen S, Chung H, He S, Brown KA, Gubbay JB, Buchan SA, et al. Effectiveness of mRNA and ChAdOx1 COVID-19 vaccines against symptomatic SARS CoV-2 infection and severe outcomes with variants of concern in Ontario. MedRxiv [Preprint]. 2021.
246. Puranik A, Lenehan PJ, Silvert E, Niesen MJM, Corchado-Garcia J, O'Horo JC, et al. Comparison of two highly-effective mRNA vaccines for COVID-19 during periods of Alpha and Delta variant prevalence. MedRxiv [Preprint]. 2021.
247. Julia Stowe, Nick Andrews, Charlotte Gower, Eileen Gallagher, Lara Utsi, Ruth Simmons, et al. Effectiveness of COVID-19 vaccines against hospital admission with the Delta (B.1.617.2) variant. Public Health England [preprint]. 2021.
248. Lopez Bernal J, Andrews N, Gower C, Robertson C, Stowe J, Tessier E, et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. BMJ. 2021;373:n1088.
249. Skowronski DM, Setayeshgar S, Zou M, Prystajecky N, Tyson JR, Galanis E, et al. Single-dose mRNA vaccine effectiveness against SARS-CoV-2, including Alpha and Gamma variants: a test-negative design in adults 70 years and older in British Columbia, Canada. Clin Infect Dis. 2021.
250. Carazo S, Talbot D, Boulianne N, Brisson M, Gilca R, Deceuninck G, et al. Single-dose mRNA vaccine effectiveness against SARS-CoV-2 in healthcare workers extending 16 weeks post-vaccination: a test-negative design from Quebec, Canada. Clin Infect Dis. 2021.
251. Charmet T, Schaeffer L, Grant R, Galmiche S, Cheny O, Von Platen C, et al. Impact of original, B.1.1.7, and B.1.351/P.1 SARS-CoV-2 lineages on vaccine effectiveness of two doses of COVID-19 mRNA vaccines: Results from a nationwide case-control study in France. Lancet Reg Health Eur. 2021;8:100171.
252. Tang P, Hasan MR, Chemaitelly H, Yassine HM, Benslimane FM, Al Khatib HA, et al. BNT162b2 and mRNA-1273 COVID-19 vaccine effectiveness against the SARS-CoV-2 Delta variant in Qatar. Nat Med. 2021;27(12):2136-43.
253. Hall VJ, Foulkes S, Saei A, Andrews N, Oguti B, Charlett A, et al. COVID-19 vaccine coverage in health-care workers in England and effectiveness of BNT162b2 mRNA vaccine against infection (SIREN): a prospective, multicentre, cohort study. Lancet. 2021;397(10286):1725-35.
254. Haas EJ, Angulo FJ, McLaughlin JM, Anis E, Singer SR, Khan F, et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. Lancet. 2021;397(10287):1819-29.

255. Nanduri S, Pilishvili T, Derado G, Soe MM, Dollard P, Wu H, et al. Effectiveness of Pfizer-BioNTech and Moderna Vaccines in Preventing SARS-CoV-2 Infection Among Nursing Home Residents Before and During Widespread Circulation of the SARS-CoV-2 B.1.617.2 (Delta) Variant - National Healthcare Safety Network, March 1-August 1, 2021. MMWR Morb Mortal Wkly Rep. 2021;70(34):1163-6.
256. Fowlkes A, Gaglani M, Groover K, Thiese MS, Tyner H, Ellingson K, et al. Effectiveness of COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Frontline Workers Before and During B.1.617.2 (Delta) Variant Predominance - Eight U.S. Locations, December 2020-August 2021. MMWR Morb Mortal Wkly Rep. 2021;70(34):1167-9.
257. Lefevre B, Tondeur L, Madec Y, Grant R, Lina B, van der Werf S, et al. Beta SARS-CoV-2 variant and BNT162b2 vaccine effectiveness in long-term care facilities in France. Lancet Healthy Longev. 2021.
258. Pouwels KB, Pritchard E, Matthews PC, Stoesser N, Eyre DW, Vihta K-D, et al. Effect of Delta variant on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK. Nature Medicine. 2021.
259. Williams C, Al-Bargash D, Macalintal C, Stuart R, Seth A, Latham J, et al. COVID-19 Outbreak Associated with a SARS-CoV-2 P.1 Lineage in a Long-Term Care Home after Implementation of a Vaccination Program - Ontario, April-May 2021. Clin Infect Dis. 2021.
260. Fabiani M, Ramigni M, Gobbetto V, Mateo-Urdiales A, Pezzotti P, Piovesan C. Effectiveness of the Comirnaty (BNT162b2, BioNTech/Pfizer) vaccine in preventing SARS-CoV-2 infection among healthcare workers, Treviso province, Veneto region, Italy, 27 December 2020 to 24 March 2021. Euro Surveill. 2021;26(17).
261. Thomas SJ, Moreira ED, Jr., Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months. N Engl J Med. 2021;385(19):1761-73.
262. Angel Y, Spitzer A, Henig O, Saiag E, Sprecher E, Padova H, et al. Association Between Vaccination With BNT162b2 and Incidence of Symptomatic and Asymptomatic SARS-CoV-2 Infections Among Health Care Workers. JAMA. 2021;325(24):2457-65.
263. Bjork J, Inghammar M, Moghaddassi M, Rasmussen M, Malmqvist U, Kahn F. High level of protection against COVID-19 after two doses of BNT162b2 vaccine in the working age population - first results from a cohort study in Southern Sweden. Infect Dis (Lond). 2022;54(2):128-33.
264. Cabezas C, Coma E, Mora-Fernandez N, Li X, Martinez-Marcos M, Fina F, et al. Associations of BNT162b2 vaccination with SARS-CoV-2 infection and hospital admission and death with covid-19 in nursing homes and healthcare workers in Catalonia: prospective cohort study. BMJ. 2021;374:n1868.
265. Emborg H-D, Valentiner-Branth P, Schelde AB, Nielsen KF, Gram MA, Moustsen-Helms IR, et al. Vaccine effectiveness of the BNT162b2 mRNA COVID-19 vaccine against RT-PCR confirmed SARS-CoV2 infections, hospitalisations and mortality in prioritised risk groups. MedRxiv [Preprint]. 2021.
266. Gras-Valenti P, Chico-Sanchez P, Algado-Selles N, Jimenez-Sepulveda NJ, Gomez-Sotero IL, Fuster-Perez M, et al. [Effectiveness of the first dose of BNT162b2 vaccine to preventing covid-19 in healthcare personnel.]. Rev Esp Salud Publica. 2021;95.
267. Mason TFD, Whitston M, Hodgson J, Watkinson RE, Lau YS, Abdulrazeg O, et al. Effects of BNT162b2 mRNA vaccine on COVID-19 infection and hospitalisation amongst older people: matched case control study for England. BMC Med. 2021;19(1):275.

268. Monge S, Olmedo C, Alejos B, Lapena MF, Sierra MJ, Limia A, et al. Direct and Indirect Effectiveness of mRNA Vaccination against Severe Acute Respiratory Syndrome Coronavirus 2 in Long-Term Care Facilities, Spain. Emerg Infect Dis. 2021;27(10):2595-603.
269. Pritchard E, Matthews PC, Stoesser N, Eyre DW, Gethings O, Vihta KD, et al. Impact of vaccination on new SARS-CoV-2 infections in the United Kingdom. Nat Med. 2021;27(8):1370-8.
270. Regev-Yochay G, Amit S, Bergwerk M, Lipsitch M, Leshem E, Kahn R, et al. Decreased infectivity following BNT162b2 vaccination: A prospective cohort study in Israel. Lancet Reg Health Eur. 2021;7:100150.
271. Shrotri M, Krutikov M, Palmer T, Giddings R, Azmi B, Subbarao S, et al. Vaccine effectiveness of the first dose of ChAdOx1 nCoV-19 and BNT162b2 against SARS-CoV-2 infection in residents of long-term care facilities in England (VIVALDI): a prospective cohort study. Lancet Infect Dis. 2021;21(11):1529-38.
272. Swift MD, Breeher LE, Tande AJ, Tommaso CP, Hainy CM, Chu H, et al. Effectiveness of Messenger RNA Coronavirus Disease 2019 (COVID-19) Vaccines Against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in a Cohort of Healthcare Personnel. Clin Infect Dis. 2021;73(6):e1376-e9.
273. Thompson MG, Burgess JL, Naleway AL, Tyner H, Yoon SK, Meece J, et al. Prevention and Attenuation of Covid-19 with the BNT162b2 and mRNA-1273 Vaccines. N Engl J Med. 2021;385(4):320-9.
274. Frenck RW, Jr., Klein NP, Kitchin N, Gurtman A, Absalon J, Lockhart S, et al. Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents. N Engl J Med. 2021;385(3):239-50.
275. June Choe Y, Yi S, Hwang I, Kim J, Park YJ, Cho E, et al. Safety and effectiveness of BNT162b2 mRNA Covid-19 vaccine in adolescents. Vaccine. 2021.
276. Lutrick K, Rivers P, Yoo YM, Grant L, Hollister J, Jovel K, et al. Interim Estimate of Vaccine Effectiveness of BNT162b2 (Pfizer-BioNTech) Vaccine in Preventing SARS-CoV-2 Infection Among Adolescents Aged 12-17 Years - Arizona, July-December 2021. MMWR Morb Mortal Wkly Rep. 2021;70(5152):1761-5.
277. Glatman-Freedman A, Bromberg M, Dichtiar R, Hershkovitz Y, Keinan-Boker L. The BNT162b2 vaccine effectiveness against new COVID-19 cases and complications of breakthrough cases: A nation-wide retrospective longitudinal multiple cohort analysis using individualised data. EBioMedicine. 2021;72:103574.
278. Pilishvili T, Fleming-Dutra KE, Farrar JL, Gierke R, Mohr NM, Talan DA, et al. Interim Estimates of Vaccine Effectiveness of Pfizer-BioNTech and Moderna COVID-19 Vaccines Among Health Care Personnel - 33 U.S. Sites, January-March 2021. MMWR Morb Mortal Wkly Rep. 2021;70(20):753-8.
279. Martinez-Baz I, Miqueleiz A, Casado I, Navascues A, Trobajo-Sanmartin C, Burgui C, et al. Effectiveness of COVID-19 vaccines in preventing SARS-CoV-2 infection and hospitalisation, Navarre, Spain, January to April 2021. Euro Surveill. 2021;26(21).
280. Vasileiou E, Simpson CR, Shi T, Kerr S, Agrawal U, Akbari A, et al. Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study. Lancet. 2021;397(10285):1646-57.
281. ecdc.europa.eu [Internet]. Interim analysis of COVID-19 vaccine effectiveness against Severe Acute Respiratory Infection due to laboratory-confirmed SARS-CoV-2 among individuals aged 50 years and older, ECDC multi-country study – first update. European Centre for Disease Prevention and Control. [20 January 2022; cited 24 January 2022]. Available from:

https://www.ecdc.europa.eu/en/publications-data/interim-analysis-covid-19-vaccine-effectiveness-against-severe-acute-respiratory

282. Rosenberg ES, Dorabawila V, Easton D, Bauer UE, Kumar J, Hoen R, et al. Covid-19 Vaccine Effectiveness in New York State. N Engl J Med. 2022;386(2):116-27.
283. Olson SM, Newhams MM, Halasa NB, Price AM, Boom JA, Sahni LC, et al. Effectiveness of BNT162b2 Vaccine against Critical Covid-19 in Adolescents. N Engl J Med. 2022.
284. Zambrano LD, Newhams MM, Olson SM, Halasa NB, Price AM, Boom JA, et al. Effectiveness of BNT162b2 (Pfizer-BioNTech) mRNA Vaccination Against Multisystem Inflammatory Syndrome in Children Among Persons Aged 12-18 Years - United States, July-December 2021. MMWR Morb Mortal Wkly Rep. 2022;71(2):52-8.
285. Emary KRW, Golubchik T, Aley PK, Ariani CV, Angus B, Bibi S, et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B.1.1.7): an exploratory analysis of a randomised controlled trial. Lancet. 2021;397(10282):1351-62.
286. astrazeneca.com [Internet]. AZD1222 US Phase III trial met primary efficacy endpoint in preventing COVID-19 at interim analysis. AstraZeneca. [22 March 2021; cited 15 October 2021]. Available from: https://www.astrazeneca.com/media-centre/press-releases/2021/astrazeneca-us-vaccine-trial-met-primary-endpoint.html
287. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet. 2021;397(10269):99-111.
288. Madhi SA, Baillie V, Cutland CL, Voysey M, Koen AL, Fairlie L, et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant. N Engl J Med. 2021;384(20):1885-98.
289. Pramod S, Govindan D, Ramasubramani P, Kar SS, Aggarwal R, Manoharan N, et al. Effectiveness of Covishield vaccine in preventing Covid-19 – A test-negative case control study. MedRxiv [Preprint]. 2021.
290. Falsey AR, Sobieszczyk ME, Hirsch I, Sproule S, Robb ML, Corey L, et al. Phase 3 Safety and Efficacy of AZD1222 (ChAdOx1 nCoV-19) Covid-19 Vaccine. N Engl J Med. 2021;385(25):2348-60.
291. Clemens SAC, Folegatti PM, Emary KRW, Weckx LY, Ratcliff J, Bibi S, et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 lineages circulating in Brazil. Nat Commun. 2021;12(1):5861.
292. Voysey M, Costa Clemens SA, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. Lancet. 2021;397(10277):881-91.
293. Bhattacharya A, Ranjan P, Ghosh T, Agarwal H, Seth S, Maher GT, et al. Evaluation of the dose-effect association between the number of doses and duration since the last dose of COVID-19 vaccine, and its efficacy in preventing the disease and reducing disease severity: A single centre, cross-sectional analytical study from India. Diabetes Metab Syndr. 2021;15(5):102238.
294. Malathi Murugesan, Prasad Mathews, Hema Paul, Rajiv Karthik, Joy John Mammen, Rupali. P. Protective Effect Conferred by Prior Infection and Vaccination on COVID-19 in a Healthcare Worker Cohort in South India. SSRN [Preprint]. 2021.
295. Alencar CH, Cavalcanti LPG, Almeida MM, Barbosa PPL, Cavalcante KKS, Melo DN, et al. High Effectiveness of SARS-CoV-2 Vaccines in Reducing COVID-19-Related Deaths in over 75-Year-Olds, Ceara State, Brazil. Trop Med Infect Dis. 2021;6(3).

296. Cerqueira-Silva T, Oliveira VdA, Pescarini J, Bertoldo Júnior J, Machado TM, Flores-Ortiz R, et al. The effectiveness of Vaxzevria and CoronaVac vaccines: A nationwide longitudinal retrospective study of 61 million Brazilians (VigiVac-COVID19). . MedRxiv [Preprint]. 2021.
297. Otavio T Ranzani, Rogério dos Santos Leite, Larissa Domingues Castilho, Crhistinne Cavalheiro Maymone Gonçalves, Geraldo Resende, Rosana Leite de Melo, et al. Vaccine effectiveness of Ad26.COV2.S against symptomatic COVID-19 and clinical outcomes in Brazil: a test-negative study design. MedRxiv [Preprint]. 2021.
298. Corchado-Garcia J, Puyraimond-Zemmour D, Hughes T, Cristea-Platon T, Lenehan P, Pawlowski C, et al. Real-world effectiveness of Ad26.COV2.S adenoviral vector vaccine for COVID-19. MedRxiv [Preprint]. 2021.
299. Barlow RS, Jian K, Larson L. Effectiveness of COVID-19 Vaccines Against SARS-CoV-2 Infection During a Delta Variant Epidemic Surge in Multnomah County, Oregon, July 2021. MedRxiv [Preprint]. 2021.
300. Polinski JM, Weckstein AR, Batech M, Kabelac C, Kamath T, Harvey R, et al. Effectiveness of the Single-Dose Ad26.COV2.S COVID Vaccine. MedRxiv [Preprint]. 2021.
301. Corchado-Garcia J, Zemmour D, Hughes T, Bandi H, Cristea-Platon T, Lenehan P, et al. Analysis of the Effectiveness of the Ad26.COV2.S Adenoviral Vector Vaccine for Preventing COVID-19. JAMA Netw Open. 2021;4(11):e2132540.
302. Chin ET, Leidner D, Zhang Y, Long E, Prince L, Li Y, et al. Effectiveness of the mRNA-1273 Vaccine during a SARS-CoV-2 Delta Outbreak in a Prison. N Engl J Med. 2021;385(24):2300-1.
303. Gupta K, O'Brien WJ, Bellino P, Linsenmeyer K, Doshi SJ, Sprague RS, et al. Incidence of SARS-CoV-2 Infection in Health Care Workers After a Single Dose of mRNA-1273 Vaccine. JAMA Netw Open. 2021;4(6):e2116416.
304. Chemaitelly H, Yassine HM, Benslimane FM, Al Khatib HA, Tang P, Hasan MR, et al. mRNA-1273 COVID-19 vaccine effectiveness against the B.1.1.7 and B.1.351 variants and severe COVID-19 disease in Qatar. Nat Med. 2021;27(9):1614-21.
305. Herlihy R, Bamberg W, Burakoff A, Alden N, Severson R, Bush E, et al. Rapid Increase in Circulation of the SARS-CoV-2 B.1.617.2 (Delta) Variant - Mesa County, Colorado, April-June 2021. MMWR Morb Mortal Wkly Rep. 2021;70(32):1084-7.
306. Bruxvoort KJ, Sy LS, Qian L, Ackerson BK, Luo Y, Lee GS, et al. Real-world effectiveness of the mRNA-1273 vaccine against COVID-19: Interim results from a prospective observational cohort study. Lancet Reg Health Am. 2021:100134.
307. Bruxvoort KJ, Sy LS, Qian L, Ackerson BK, Luo Y, Lee GS, et al. Effectiveness of mRNA-1273 against delta, mu, and other emerging variants of SARS-CoV-2: test negative case-control study. BMJ. 2021;375:e068848.
308. El Sahly HM, Baden LR, Essink B, Doblecki-Lewis S, Martin JM, Anderson EJ, et al. Efficacy of the mRNA-1273 SARS-CoV-2 Vaccine at Completion of Blinded Phase. N Engl J Med. 2021;385(19):1774-85.
309. Li XN, Huang Y, Wang W, Jing QL, Zhang CH, Qin PZ, et al. Effectiveness of inactivated SARS-CoV-2 vaccines against the Delta variant infection in Guangzhou: a test-negative case-control real-world study. Emerg Microbes Infect. 2021;10(1):1751-9.
310. Min Kang, Yao Yi, Yan Li, Limei Sun, Aiping Deng, Ting Hu, et al. Effectiveness of Inactivated COVID-19 Vaccines Against COVID-19 Pneumonia and Severe Illness Caused by the B.1.617.2 (Delta) Variant: Evidence from an Outbreak in Guangdong, China. SSRN [Preprint]. 2021.

311. Silva-Valencia Javier, Soto-Becerra Percy, Escobar-Agreda Stefan, Fernández-Navarro Manuel, Moscoso-Porras Miguel, Solari Lely, et al. Effectiveness of the BBIPB-CorV Vaccine in Preventing Infection and Death in Health Care Workers in Peru 2021. SSRN [Preprint]. 2021.
312. Al Kaabi N, Zhang Y, Xia S, Yang Y, Al Qahtani MM, Abdulrazzaq N, et al. Effect of 2 Inactivated SARS-CoV-2 Vaccines on Symptomatic COVID-19 Infection in Adults: A Randomized Clinical Trial. JAMA. 2021;326(1):35-45.
313. Farida Ismail AlHosani, Anderson Eduardo Stanciole, Bashir Aden, Andrey Timoshkin, Omar Najim, Walid Abbas Zaher, et al. Sinopharm's BBIBP-CorV vaccine effectiveness on preventing hospital admission and deaths: results from a retrospective study in the Emirate of Abu Dhabi, United Arab Emirates (UAE). SSRN [Preprint]. 2021.
314. AlQahtani M, Bhattacharyya S, Alawadi A, Mahmeed HA, Sayed JA, Justman J, et al. Morbidity and mortality from COVID-19 postvaccination breakthrough infections in association with vaccines and the emergence of variants in Bahrain. Research Square [Preprint]. 2021.
315. Jara A, Undurraga EA, Gonzalez C, Paredes F, Fontecilla T, Jara G, et al. Effectiveness of an Inactivated SARS-CoV-2 Vaccine in Chile. N Engl J Med. 2021;385(10):875-84.
316. Ranzani OT, Hitchings MDT, Dorion M, D'Agostini TL, de Paula RC, de Paula OFP, et al. Effectiveness of the CoronaVac vaccine in older adults during a gamma variant associated epidemic of covid-19 in Brazil: test negative case-control study. BMJ. 2021;374:n2015.
317. Hitchings MDT, Ranzani OT, Torres MSS, de Oliveira SB, Almiron M, Said R, et al. Effectiveness of CoronaVac among healthcare workers in the setting of high SARS-CoV-2 Gamma variant transmission in Manaus, Brazil: A test-negative case-control study. Lancet Reg Health Am. 2021;1:100025.
318. Enny S. Paixao, Kerry LM Wong, Flavia Jôse Oliveira Alves, Vinicius de Araújo Oliveira, Thiago Cerqueira-Silva, Juracy Bertoldo Júnior, et al. Effectiveness of the CoronaVac vaccine in prevention of symptomatic and progression to severe Covid-19 in pregnant women in Brazil. SSRN [Preprint]. 2021.
319. Hitchings MDT, Ranzani OT, Scaramuzzini Torres MS, de Oliveira SB, Almiron M, Said R, et al. Effectiveness of CoronaVac in the setting of high SARS-CoV-2 P.1 variant transmission in Brazil: A test-negative case-control study. MedRxiv [Preprint]. 2021.
320. Tanriover MD, Doganay HL, Akova M, Guner HR, Azap A, Akhan S, et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. Lancet. 2021;398(10296):213-22.
321. Palacios R, Batista AP, Albuquerque CSN, Patiño EG, Santos JdP, Tilli Reis Pessoa Conde M, et al. Efficacy and Safety of a COVID-19 Inactivated Vaccine in Healthcare Professionals in Brazil: The PROFISCOV Study. SSRN [Preprint]. 2021.
322. Ella R, Reddy S, Blackwelder W, Potdar V, Yadav P, Sarangi V, et al. Efficacy, safety, and lot-to-lot immunogenicity of an inactivated SARS-CoV-2 vaccine (BBV152): interim results of a randomised, double-blind, controlled, phase 3 trial. Lancet. 2021;398(10317):2173-84.
323. Desai D, Khan AR, Soneja M, Mittal A, Naik S, Kodan P, et al. Effectiveness of an inactivated virus-based SARS-CoV-2 vaccine, BBV152, in India: a test-negative, case-control study. Lancet Infect Dis. 2021.
324. Malhotra S, Mani K, Lodha R, Bakhshi S, Mathur VP, Gupta P, et al. SARS-CoV-2 Reinfection Rate and Estimated Effectiveness of the Inactivated Whole Virion Vaccine BBV152 Against Reinfection Among Health Care Workers in New Delhi, India. JAMA Netw Open. 2022;5(1):e2142210.

325. Heath PT, Galiza EP, Baxter DN, Boffito M, Browne D, Burns F, et al. Safety and Efficacy of NVX-CoV2373 Covid-19 Vaccine. N Engl J Med. 2021;385(13):1172-83.
326. Dunkle LM, Kotloff KL, Gay CL, Anez G, Adelglass JM, Barrat Hernandez AQ, et al. Efficacy and Safety of NVX-CoV2373 in Adults in the United States and Mexico. N Engl J Med. 2021.
327. Toback S, Galiza E, Cosgrove C, Galloway J, Goodman AL, Swift PA, et al. Safety, immunogenicity, and efficacy of a COVID-19 vaccine (NVX-CoV2373) co-administered with seasonal influenza vaccines: an exploratory substudy of a randomised, observer-blinded, placebo-controlled, phase 3 trial. Lancet Respir Med. 2021.
328. Shinde V, Bhikha S, Hoosain Z, Archary M, Bhorat Q, Fairlie L, et al. Efficacy of NVX-CoV2373 Covid-19 Vaccine against the B.1.351 Variant. N Engl J Med. 2021;384(20):1899-909.

Response to Reviewers - COVID-19: Virology, variants, and vaccines

We would like to thank the editor and reviewers for their insightful and useful comments on our review. We have addressed the comments within the article and outlined the changes we have made below. We believe these alterations and changes have significantly improved the review as a result. The reviewer's comments are preceded by "**Comment**" and our response is preceded by "**Response**". Where possible, we have included the in-text amendments after each response in italics. Any changes or additions to the text are also highlighted in the manuscript.

Editors' comments:

Comment

1. Please provide a **document labelled 'response to reviewers'** which gives a point-by-point response to both the referees comments and those of the editors.

Response

Thank you. This document provides a point-by-point response of both the editors and reviewers comments.

Comment

2. Abstract: as the review is not a systematic review and therefore not classed as original Research, please remove the structured headings. The abstract should just summarise what the review is about in 2-300 words (ie the same as your BMJ review).

Response

Thank you for the suggestion. We have updated the abstract and removed the structed headings. It now reads as following:

*"**Abstract***

As of 25th January 2022, there have been over 349 million confirmed cases of COVID-19, with over 5.59 million confirmed deaths associated with the SARS-CoV-2 virus. The COVID-19 pandemic has prompted an extensive, global effort to study the molecular evolution of the virus and develop vaccines to combat its spread. Although rigorous determination of SARS-CoV-2 infectivity remains elusive, due to the continuous evolution of the virus, steps have been made to understand its genome, structure, and emerging genetic mutations. The SARS-CoV-2 genome is composed of a number of open reading frames (ORFs) and structural proteins, including the spike protein, which is essential for entry into host cells. As of the 25th January 2022, the WHO reports five variants of concern (VOC) two variants of interest (VOI) and three variants under monitoring (VUM). The mutations harboured in these variants confer an increased transmissibility, severity of disease, and escape from neutralising antibodies compared to the primary strain. The current vaccine strategy, including booster doses, provides protection from severe disease. As of 24th January 2022, there are 33 approved vaccines in use in 197 countries. In this review, we discuss the genetics, structure and transmission methods of SARS-CoV-2 and its variants, highlighting how mutations provide enhanced abilities to spread and inflict disease. We also outline the vaccines currently in use around the world, providing evidence for the immunogenicity and effectiveness of each."

Comment

3. Methods: please include the dates you searched from and to. Due to the additions requested below the end search date will be more current. Please provide more detail about the exclusion criteria (study design etc).

Response

We have updated the dates we searched to and from.
Due to the restrictions on the word count, we have provided some more information on selection criteria within the methods section, however, we have also provided a supplementary file describing the specific search terms and the inclusion/exclusion criteria that we used.

The methods section now reads as:

"We searched PubMed and Embase databases for COVID-19-related articles published between 1st January 2020 and 25th January 2022 and for general coronavirus-related articles published from 1st January 2000 onwards. Our search terms included SARS-CoV-2, COVID-19, and specific terms including virology, genome, variants, and vaccine. Additional, specific search terms are outlined in supplementary file 1. We performed further manual searching for additional articles and data using relevant databases, including who.int, gov.uk, and ecdc.europa.eu/en. Due to the rapidly evolving nature of the literature involving SARS-CoV-2, we also searched preprint databases including MedRxiv and BioRxiv. Due to the various topics addressed here, studies were selected through different criteria, details of which can be found in supplementary file 1. Overall, studies were selected based on quality and journal reputation, with real-world studies with large sample sizes of greatest interest."

Comment

4. **OMICRON**: Please can you include in relevant sections throughout the review what is known about the new OMICRON variant, and any other variants of interest.

Response

We have included a section dedicated to the Omicron variant in the variants of concern section, while relevant omicron studies have been included and discussed elsewhere, e.g. in the waning immunity and boosters section.

This section now reads as:

"5.1.5 Omicron

The Omicron variant is of the B.1.1.529 lineage and was first discovered in November 2021 in South Africa and Botswana before being detected in multiple countries and classified as a VOC on 26th November 2021(3). This variant contains over 30 S protein mutations(100), 23 of which have been previously identified, including K417N, T478K, E484A, D614G, H655Y, P681H, and N501Y(131). 15 Omicron mutations are contained within the RBD(17) providing the variant with a significantly enhanced binding affinity to the ACE2 receptor(131, 132). In addition, various single mutations harboured with the RBD of the Omicron variant impair the effectiveness of neutralising antibodies, including K417N, N440K, G446S, E484A, Q493K, G496S, G339D, S371L, and S375F(17).

The emergence of Omicron has been followed by a tidal wave of infections worldwide. Early data from South Africa demonstrated that the proportion of COVID-19 cases caused by the Omicron variant rose from 3% in early October, to 98% by early December(133). In late December 2021, meanwhile, the doubling time for number of positive Omicron cases was between two and three in the UK, US, and much of Europe(134, 135), highlighting the transmissibility of this variant. The mutations harboured by Omicron that enhance its binding affinity(131, 132) and ability to escape neutralising antibodies(17) likely drove its rapid spread, as did its fast replication rate, which is around 70 times faster than the Delta and wild-type strains(136). The reinfection rate of Omicron has also been found to be significantly higher than that of previous variants in studies from Scotland(137) and South Africa(138).

The Omicron variant has extensive but incomplete escape from naturally acquired and vaccine-induced immunity(139, 140). Compared to the Delta variant, Omicron requires around a ten-fold

increased antibody titre to be neutralised, following vaccination with either Oxford-AstraZeneca or Pfizer/BioNtech vaccines(141). Indeed, blood sera from individuals who had received two doses of the Pfizer/BioNtech vaccine exhibited more than a 25-fold reduction in neutralising antibody titres against the Omicron variant compared to the wild-type strain(142). T-cell responses to Omicron may remain intact, however. One preprint study demonstrated that 70-80% of the T-cell response targeting the S protein was maintained in those vaccinated or with prior infection, while the magnitude of Omicron cross-reactive T-cells was similar to that of both Delta and Beta variants(143). Furthermore, data from Pfizer/BioNtech revealed that 80% of the epitopes in the Omicron variant S protein that are recognised by CD8+ T-cells were not affected by this variant's mutations, following two-doses of the vaccine(142). T-cell responses induced from vaccine administration or prior infection may, therefore, provide some protection from severe disease.

Recent real-world evidence has implied that Omicron infection is milder in severity than previous variants. In an early South African analysis, the risk of hospitalisation (aOR=0.2) was lower for Omicron infections compared to non-Omicron SARS-CoV-2 infections(133) while, compared to earlier infections associated with the Delta variant, Omicron-infected individuals had a lower risk of severe disease (aOR=0.3)(133). In December 2021 in England, Omicron cases were found to induce a significantly reduced risk of hospitalisation or presentation for emergency care in comparison to Delta cases(144, 145). The decreased disease severity inflicted by Omicron may be due to its reduced capacity for replication in lung tissue, which was found to be more than ten times less in lung tissue compared to Delta(136). Concordantly, the S protein of the Omicron variant is less efficient at cleaving the ACE2 receptor and entering cells of lung organoids(141), while is also less able to cause fusion between lung cells compared to Delta(141), which is often observed in cases of severe COVID-19. The reduction in replication within the lungs, and the preservation of T-cell responses likely contribute to the milder disease exerted by the Omicron variant.

Although the Omicron variant appears to manifest in mild disease, high case numbers may still result in a large number of hospitalisations and deaths in those vulnerable to the virus. Omicron case numbers may be beginning to peak, however. In South Africa, a 29.7% decrease in weekly COVID-19 cases were reported in the week ending 25th December 2021, compared to the previous week, and the Omicron wave is said to have passed(146). Concerningly, global case numbers continue to rise rapidly(147) and many countries will continue to feel the pressure exerted by the wave of Omicron infections."

Comment

5. Vaccination/Waning immunity sections: please update these sections to include any new data on efficacy, and the recent data on the efficacy of the different booster jabs.

Response

We have updated these sections with new data. Table 2 has also been updated to include new data on vaccine effectiveness.

The waning immunity and boosters section now reads as:
"6.11 Waning immunity and boosters
Throughout the COVID-19 pandemic, emerging variants have threatened the effectiveness of vaccines (table 2). Simultaneously, waning immunity following vaccination questions how long vaccines remain effective, and highlights the importance of booster doses. Indeed, protection against SARS-CoV-2 following vaccination decreases over time, both in terms of antibody titres(188-190) and vaccine effectiveness(191-194). Cellular responses, such as T-cell immunity, may persist for longer periods, however(195, 196). With a gradual loss of protection from SARS-CoV-2 following COVID-19 vaccination, many countries are now rolling out booster programmes with the aim of raising levels of immunity.

Since booster programmes began, evidence that a booster vaccine dose enhances antibody and cellular responses has accumulated. Following a third dose of vaccine, neutralising antibody titres increase significantly(197-200) and, in some cases, to higher levels than after the primary two doses(197). Additionally, boosters have also been found to increase neutralising antibody titres against Beta, Gamma, Delta, and Omicron variants(198, 201, 202). T-cell response is also enhanced following a third dose(199, 203, 204). Together, enhancing neutralising antibody and cellular responses with a booster vaccine dose is likely to provide a greater level of protection than relying on immunity built through a primary regimen.

The antibody and cellular responses observed following booster vaccinations have been found to correlate with increased levels of protection against SAR-CoV-2 infetion and severe illness. On 30th July 2021, Israel was the first country to offer a third dose of BNT162b2 to certain groups. Subsequently, several studies have revealed that those who received a third vaccine dose were significantly less likely to be infected or have severe disease with SARS-CoV-2 compared to those who received two-doses(205-208). In those aged 60 or older, an observational study demonstrated that the rate of severe COVID-19 and death was lower in the boosted group by a factor of 17.9 and 14.7, respectively, compared to the non-boosted group(209). Booster doses of COVID-19 vaccine have been shown to be effective against infection with Delta(210, 211) and, to a lesser degree, Omicron variants(141, 142, 145, 211-213) despite the numerous mutations harboured by these variants. Overall, increasing evidence is pointing towards the benefits of booster doses of COVID-19 vaccines, therefore it is expected that booster programmes will continue to roll out across the globe. Based on current evidence, the CDC recommend that the time interval for receiving a booster following the primary regiment is five months for Pfizer/BioNTech BNT162b2 primary regimen, six months for Moderna mRNA-1273 primary regimen, and two months for Johnson & Johnson Ad26.COV2.S primary regimen(214). As the pandemic progresses and new variants emerge, variant-specific vaccines may require development, with pre-clinical studies demonstrating their efficacy(215) and pharmaceutical companies, such as Pfizer, advancing in variant-specific vaccine development(142). Policy makers should also consider when vaccine boosters will be given in the future and who will receive booster doses in the long-term."

Comment

6. Tables: please update the tables to include any new data.

Response

Thank you, the following sentences outline the updates that have been made to each table.

Table 1 has been updated to include the current VOC/VUI/VUM, as listed by WHO.

Table 2 has been updated to include new data on vaccine effectiveness.

Table 3 has been updated to include current vaccines that are approved in at least 1 county, that are not discussed in the main manuscript text.

Comment

7. Please include a section on **EMERGING TREATMENTS**: Please include a brief section on new techniques and advances that are currently being studied, cite the appropriate studies, and say when they will report.

Response

Thank you, we have now included this section with some discussion of recently approved drugs and those in development:

"7. Emerging Treatments

As more is learnt about the virus, the therapeutic strategy against COVID-19 devlops. There are currently over two thousand ongoing trials assessing certain treatment strategies for COVID-19(216). Recently, antivirals including molnupiravir (Lagevrio) and nirmatrelvir/ritonavir (Paxlovid) have been approved in the UK(217, 218), US(219, 220), and Europe(221, 222) for treating COVID-19 in certain risk groups. Similarly, sotrovimab (Xevudy), a monoclonal antibody treatment, has recently been approved for use in treating certain COVID-19 patients in the UK(223), US(224), and Europe(225). These drugs have been shown to be effective at preventing poor clinical outcomes, including death, in those vulnerable to severe COVID-19 infection. Other drug treatments, such as janus kinase inhibitors, corticosteroids, and anti-inflammatories have contrasting evidence to support their use, and therefore, the use of specific drugs is either recommended for or against by certain treatment and management guidelines, which are discussed below."

Comment

8. **GUIDELINES**: Please cite any relevant international guidelines and say how they differ, what their strengths and weaknesses are, and under what circumstances they are most appropriate. Please give preference to the most independent and recently updated guidelines.

Response

Thank you, we have now included this section to outline which treatment guidelines are available for COVID-19.

"8. Guidelines

The treatment and management of COVID-19 is a continually evolving topic, however, health authorities have published and continue to update guidelines and recommendations for treating COVID-19. The WHO living guildeline on COVID-19 and therapeutics is regularly updated, with the latest version, published on 14th January 2022 containing 14 recommendations on COVID-19 treatment(226). In the UK, the National Institute for Health and Care Excellence (NICE)(227) and Medicines and Healthcare products Regulatory Agency (MHRA)(228) provide updated guidelines on COVID-19 treatment, while in Europe, the ECDC regularly publishes several guidelines providing recommendations on a range of COVID-19 related topics(229). In the US, the National Institutes of Health (NIH)(230) and the CDC(231) provide guidance on COVID-19 treatment and management, with the CDC supplying guidelines for specific groups including, employers, schools, health departments, and governments."

Reviewer: 1

Comment

1. In the section "3. Viral transmission, clinical presentation, and genetic susceptibility of COVID-19", there could be a further briefing of the spectrum of the characteristic symptoms (clinical characteristics). It would also benefit by mentioning that the whole of the population would be susceptible to COVID-19 although there exist some subgroups more susceptible to develop poorer clinical outcomes.

Response

Thank you, we have added to this section to mention the broad spectrum of COVID-19 symptoms and have mentioned that although everyone is susceptible to covid-19, some groups are more susceptible to poorer outcomes:

"The clinical presentation of COVID-19 is non-specific, heterogeneous, and infection can result in a wide spectrum of symptoms. Following an incubation period of 4-14 days, symptoms develop ranging

from mild to severe disease and, in some cases, can result in death(12). The most common COVID-19 symptoms include fever, cough, dyspnoea, and fatigue(13, 14), while myalgia, gastrointestinal issues, cognitive deficits, and other symptoms are reported. Asymptomatic individuals can also test positive for COVID-19(15, 16). Although the entire population is susceptible to COVID-19 infection, some subgroups within the general population exist that are more susceptible to developing poorer clinical outcomes."

Comment

2. Also within the same section, the description for the gene loci associated with the risk of severe disease could be streamlined a bit since the contents did not seem to be aligned well in the current form. There could also be the introduction regarding the polygenetic risk score and the comorbidities (e.g., COPD) for predicting the susceptibility to COVID-19.

Response

Thank you for this comment. This section has been shortened in order to keep the focus firmly on the main topics of the article. We have also included a short introduction of polygenetic risk scores and how they may be used along with comorbidities to infer risk of COVID-19:

"The utilisation of polygenetic risk scores (PRS) may be useful in determining an individual's risk for developing severe disease caused by COVID-19(35). A PRS infers a person's risk of susceptibility to or development of a certain disease based on the total number of genomic variations they possess. Determining PRS with the inclusion of comorbidities, such as chronic obstructive pulmonary disease(36), or other aspects, such as coagulation factors(37), may improve the usefulness of PRS in determining a person's risk of severe COVID-19."

Comment

3. In the section "4. Virology of SARS-CoV-2", it would be better to summarize the duration that the SARS-CoV-2 could survive in the environment (e.g., metal surface, etc.).

Response

Towards the end of section "4. Virology of SARS-CoV-2", which now provides a useful description of how long the virus can survive in the environment, which is a contributing factor to its transmission:

"The SARS-CoV-2 virus may survive on surfaces or suspended in air droplets for varying periods of time. Indeed, on plastic, stainless steel, and glass surfaces, the half-life of the virus is around 5.3, 4.4, and 4.2 hours, respectively(7), with no difference seen between SARS-CoV-2 variants(8). Although SARS-CoV-2 can be detected on inanimate surfaces for hours and days, due to the evaporation of water droplets, the viruses' living environment, the concentration of the virus plummets rapidly(9). Protective measures, including using personal protective equipment (PPE), maintaining indoor ventilation, and disinfecting hands and surfaces, can effectively limit the spread of SARS-CoV-2(10)."

Comment

4. Perhaps it would merit if the conformational changes of the S protein that occur after binding with the host cell be described.

Response

Thank you. To address this comment, we have added a short description of the S protein structure and the conformational changes that occur:

"The subunits of the trimeric S complex are either in a closed (pre-fusion stage) or open (post-fusion stage) conformation(62), with one subunit always in an open conformation to allow for ACE2 recognition and binding(63). The RBD itself consists of five anti-parallel β-strands surrounded by several α-helices(64). From closed to open conformation, the RBD undergoes structural rearrangement whereby the globular head region rotates clockwise, which alters is elecropotential surface(64). Once positioned, numerous residues within the RBD form either hydrogen bonds or salt bridges with residues of the ACE2 receptor, allowing for tight binding(65), while the concave structure of the RBD allows for three distinct binding regions(64)."

Comment

5. Not sure why there should be the section "4.1 Other human coronaviruses" which seemed less relevant to the topic.

Response

Thank you, we agree that this section was less relevant and did not add much to the overall manuscript, therefore, this section has been removed.

Comment

6. In the section "5. Variants of SARS-CoV-2" perhaps it would not be necessary to address the abbreviations for VOI and VUM again since this has already been introduced well before.

Response

Thank you, we agree with this comment. As VOC/VOI/VUM have been defined previously in the introduction, it is not needed here. This repetition of definitions has been removed from section 5.

Comment

7. I am afraid that the authors should contemplate on what the focus of the VOC should be. Basic science or clinical themes? Most of the current efforts seemed to focus on the former rather than the latter. However, the impact of the variants on the subsequent waves of outbreaks globally would seem more important to the epidemiologist and clinicians. This is perhaps most relevant to the Delta strain.

Response

This is an important point and we have included the following section to stress the importance of the clinical themes, in addition to the basic science in regard to VOCs:
"The current method of identifying variants relies on the use of genomic testing such as whole genome sequencing, partial S-gene sequencing, or nucleic acid amplification technique (NAAT)-based assays(72). The aspects of different variants that most people experience, however, is the clinical symptoms they inflict. Certain variants induce a greater risk of severe disease and death, such as Alpha and Delta(73), while others are more likely to induce milder symptoms, such as Omicron(74, 75). Moreover, individual symptoms can differ between variants. For example, the Gamma variant is associated inflicting anosmia and dysgeusia(76), which is less commonly seen in Omicron infections. Moving forward, the clinical themes and symptoms associated with emerging variants should be elucidated rapidly in order for the public and healthcare professionals to rapidly identify possible cases of COVID-19."

Comment

8. The section "6. Vaccinations" seemed to be a pile-up of the evidence without a clear focus. I am afraid that not all identical weight should be given to the different vaccines. Moreover, the most

well-proven efficacy, safety, reactogenicity and adverse events should be summarized in a clearer way.

Response

We agree that this section had little focus and certain vaccines should have greater weight than others. We have attempted to address this by giving the major vaccines the majority of the weight and giving each vaccine section a clear structure: i) what the vaccine is ii) immunogenicity iii) reactogenicity iv) safety/adverse events v) mention that effectiveness can be seen in table 2. To save on words, effectiveness has not been fully outlined in the text, instead table 2 outlines studies that give estimations of effectiveness for each vaccine.
This section now reads as:

"6. Vaccinations
The COVID-19 pandemic prompted a rapid international search for safe and effective vaccines against the SARS-CoV-2 virus. In line with previous vaccine development, including for both SARS-CoV and MERS-CoV, the S protein was a key target for COVID-19 vaccine development(154). As of 24th January 2022, 33 approved vaccines are in use in 197 countries, with ten vaccines having gained emergency use listing approval from the WHO(4), (table 2). As of 25th January 2022 there are 194 vaccines in pre-clinical development and 140 in clinical development(155). Numerous studies have explored the effectiveness of approved vaccines, however, large variations in vaccine effectiveness are reported. This variability is likely due to several factors in the studies including, the country, date, and population size of the study, as well as the SARS-CoV-2 variants circulating during the study period. These factors, along with how the effectiveness is reported, mean that it is difficult to compare vaccines and fully understand how effective each vaccine is. Here, we review the COVID-19 vaccines in use around the world.

6.1 Pfizer/BioNtech - BNT162b2

The BNT162b2 vaccine (Comirnaty) is a lipid nanoparticle-formulated, nucleoside-modified mRNA vaccine encoding a modified SARS-CoV-2 S protein which was developed through a collaborative effort between Pfizer (New York, US) and BioNTech (Mainz, Germany)(156, 157). BNT162b2 gained WHO emergency use listing on 31st December 2020(158) and, as of 24th January 2022, has been approved for use in 136 countries(4). Following administration of BNT162b2, a Th1-biased response is observed, with tumour necrosis factor alpha (TNFα), interferon gamma (IFNγ), and interleukin-2 (IL-2) all elevated following vaccination, compared to placebo(159, 160). Highest neutralisation titres are found between seven and fourteen days following the second dose(161), while those previously infected with COVID-19 showed a four-fold increase in antibody binding and a 18-fold increase in neutralisation titres compared to previously uninfected individuals following two-doses(162). The BNT162b vaccine is well tolerated, with limited reactogenicity. Redness and swelling at injection site have been reported, however mild or moderate pain at the injection site is the most commonly reported reaction to vaccination(161). Fatigue, muscle pain, headache and chills are other commonly reported symptoms following BNT162b2 administration(163). The rate of systemic reactions after a second dose of BNT162b has been found to be 1.7 to 2 times higher than after a first dose, possibly suggesting an immunity-boosting effect(164). Many safety reports of this vaccine describe no serious adverse events(161, 164, 165), however, a large study found that BNT162b2 was associated with an increased risk of myocarditis, lymphadenopathy, appendicitis, and herpes zoster

infection(166). Although rare, allergic reaction or anaphylaxis has also been reported following administration of the BNT162b2 vaccine(163). Table 2 outlines clinical trial and real-world data for vaccine effectiveness.

6.2 Oxford-AtraZeneca – AZD1222

The AZD1222 vaccine (Vaxzevria) is a non-replicating vector of the chimpanzee adenovirus ChAdOx1, modified to encode the SARS-CoV-2 S protein(167). Developed through collaboration between the University of Oxford and AstraZeneca (Cambridge, UK), this vaccine was given WHO emergency use listing on 16th February 2021(158) and has been approved for use in 137 countries, as of 24th January 2022(4). The WHO has granted emergency use listing to two versions of this vaccine (AZD1222 and Covishield) in order to utilise Covishield as part of their worldwide COVAX initiate, which is being produced by the Serum Institute of India and AstraZeneca-SKBio (Republic of Korea)(168).

Following administration of AZD1222, significant antibody production, predominantly of IgG1 and IgG3 subclasses, and a Th-1 cell response, with increased expression of IFNγ and TNFα, is seen(122, 169). One dose of AZD1222 has been shown to produce a neutralising antibody response in 91% of participants, while a second dose resulted in 100% of participants producing neutralising antibodies(170). Mild and moderate itch, pain, redness, swelling, tenderness, and warmth are common local reactions, while chills, fatigue, fever, headache, muscle ache, and nausea are commonly reported systemic reactions following AZD1222 administration(170). Rare symptoms, including severe chest pain, nasal bleeding, and allergic reaction have been reported following AZD1222 administration(171). Table 2 outlines clinical trial and real-world data for vaccine effectiveness.

6.3 Johnson & Johnson - Ad26.COV.2.S

The Ad26.COV.2.S vaccine is a non-replicating adenovirus vector, modified to contain the SARS-CoV-2 S protein in a prefusion-stabilised conformation and requires a single dose(172). This vector was developed from the recombinant human adenovirus type 26 by the Janssen pharmaceutical company of Johnson & Johnson (New Brunswick, New Jersey, US)(172) and was listed for WHO emergency use listing on 12th March 2021(158). As of 24th January 2022, Ad26.COV.2.S has been approved for use in 106 countries(4).

The Ad26.COV.2.S vaccine induces the production of a variety of antibody subclasses, such as IgG, IgM and IgA, and promotes several non-neutralising antibody responses, including activation of CD4+ and CD8+ Th1-cells and production if IFNγ, IL-2, and TNFα(173, 174). Although neutralising antibody responses induced by Ad26.COV2.S are reduced against SARS-CoV-2 variants, non-neutralising antibody and T-cell responses have been found to be preserved against VOC(173), while a prior COVID-19 infection significantly increases levels of S protein-binding antibodies, antibody-dependent cellular cytotoxicity, and neutralising antibodies against VOCs including Beta and Delta(175). Ad26.COV.2.S is safe and well tolerated, with a large clinical trial demonstrating that headache, fatigue, and myalgia, are the most common systemic reactions, while injection-site pain is the most common local reaction following administration(172). Like other vaccines, Ad26.COV.2.S has veen associated with serious adverse events, such as allergic reactions and cerebral venous sinus thrombosis, however, these are rare(163, 176). Table 2 outlines clinical trial and real-world data for vaccine effectiveness.

6.4 Moderna – mRNA-1273

The mRNA-1273 vaccine (Spikevax) developed by Moderna (Massachusetts, US) is a lipid-nanoparticle-encapsulated mRNA vaccine expressing the SARS-CoV-2 S protein that has been prefusion-stabilised(177). This vaccine gained WHO emergency use listing on 30th April 2021(158), and as of 24th January 2022, has been approved for use in 85 countries(4).

The mRNA-1273 vaccine elicits a strong CD4+ Th-1 cell response, with TNFα, IFNγ, and IL-2 expression increased following administration(178-180), while neutralising antibody titres have been shown to significantly increase up until around 28 days following the second dose of the vaccine, and afterwards remain consistently high(181). Fatigue, muscle pain, headache, chills, joint pain, and injection-site pain/reaction are common adverse effects caused by the mRNA-1273 vaccine(163, 177), while serious adverse effects are often avoided(177, 181). Serious adverse events, including allergic reaction and anaphylaxis are rare, but not inconceivable following mRNA-1273 administration(163). Table 2 outlines clinical trial and real-world data for vaccine effectiveness.

6.5 Other WHO emergency use listed COVID-19 vaccines

In addition to the five COVID-19 vaccines described previously, five other vaccines have gained emergency use listing by the WHO. First, the Sinopharm BBIBP-CorV COVID-19 vaccine (Covilo) was developed by the Beijing Bio-Institute of Biological Products, a subsidiary of China National Biotec Group, and was given WHO emergency use listing on 7th May 2021(158). This vaccine is a 19nCoV-CDC-Tan-HB02 strain SARS-CoV-2 antigen that is produced in Vero cells, inactivated by β-propiolactone, and then purified and absorbed with aluminium hydroxide(182). Next, the CoronaVac vaccine, developed by Sinovac Biotech (Beijing, China), was listed for WHO emergency use on 1st June 2021(158). Like the BBIBP-CorV vaccine, this vaccine is a Vero cell-based, aluminium hydroxide-adjuvanted, β-propiolactone-inactivated vaccine, however, it is based on the SARS-CoV-2 CZ02 strain(183). Covaxin (BBV152) is a whole virion inactivated SARS-CoV-2 vaccine formula developed by Bharat Biotech International ltd (India)(184) which gained emergency use listing from the WHO On 3rd November 2021(185). Lastly, Covovax and its originator, Nuvaxovid (NVX-CoV2372), were both developed by Novavax (Maryland, United States) and the Coalition for Epidemic Preparedness Innovations (Oslo, Norway), and gained emergency use listing on 17st and 21th December 2021, respectively(186, 187). Both vaccines are manufactured using the same technology, and consist of a recombinant SARS-CoV-2 S protein nanoparticle administered with the adjuvant Matrix-M as a co-formulation(188). These vaccines produce similar immune responses to those already discussed. Studies assessing the efficacy of these vaccines are outlined in table 2.

6.10 Other approved vaccines

In addition to the vaccines that have received emergency use listing from the WHO, around the world, vaccines have been developed, tested and approved to combat COVID-19. As of 24th January 2022, 33 vaccines, including the ten described above, have been approved in at least one country(4). The remaining 23 approved vaccines are outlined in table 3."

Comment

9. Overall, I appreciate the section "6.8 Waning immunity and boosters" but perhaps it would also merit if the interval between the 2nd and 3rd vaccine could be outlined.

Response

Thank you, we have now added the following statement that outlines the recommended time interval between the 2nd and 3rd doses:

"Based on current evidence, the CDC recommend that the time interval for receiving a booster following the primary regiment is five months for Pfizer/BioNTech BNT162b2 primary regimen, six months for Moderna mRNA-1273 primary regimen, and two months for Johnson & Johnson Ad26.COV2.S primary regimen(216)."

Reviewer: 2

Major comments:

Comment

1. Although this is not a systematic review, selecting 227 articles from the enormous covid-19 literature, especially including bioRxiv and medRxiv, must involve many layers of judgment. It'd be important to include more details on this selection than currently-included two sentences.

Response

Thank you for this comment. As mentioned in the editor's comment 3, we have included more detail on the selection criteria that we used in the methods section, and more so in the supplementary file.

Comment

2. Dating: Tables 1 & 2, either in the table or legends need to clearly mark the data and definitions are as of [mm/dd/yyyy], as the authors acknowledged all these variant classification/vaccine data are dynamic.

Response

Thank you, the dynamic nature of this topic does require a time stamp like this. In the legend of table 1, we have now included that "information is correct as of 24th January 2021". While in table 2, we have added the dates which the studies took place to and from in order to give clarity on these data. Similarly we have included the date when information was correct from in table 3.

Comment

3. Large variations in vaccine effectiveness %: could these possibly be explained by the country/study date/variants of the publications that were listed? Table 2 made it evident that there were variable sample sizes and COVID-19 definition of VE against (and in some cases variants), but it remains unclear to the reader why there could be such large variations.

Response

We agree that the large variations in vaccine effectiveness reported by studies are confusing and required clarification. We have explained in section 5 why these variations may occur: *"Numerous studies have explored the effectiveness of approved vaccines, however, large variations in vaccine effectiveness are reported. This variability is likely due to several factors in the studies including, the country, date, and population size of the study, as well as the SARS-CoV-2 variants circulating during the study period. These factors, along with how the effectiveness is reported, mean that it is difficult to compare vaccines and fully understand how effective each vaccine is. Here, we review the COVID-19 vaccines in use around the world."*

Comment

4. Considerations for the future: The reviewer feels this is the weakest part of the review manuscript, making only vague/broad statements, not considering examples where covid-19 was controlled (ex. Taiwan, New Zealand). Even in countries with fluctuations, some key approaches have worked but are not discussed here. Ex. The rollout of rapid-testing and quarantine of positive cases, especially given asymptomatic individuals can also spread infections.) This part needs to be largely improved upon or toned down in the abstract.

Response

Thank you, we agree with this comment and therefore have re-written this section to include two main parts; what went wrong, and what went right when attempting to control COVID-19:

"9. Considerations for the future

Novel infectious diseases and pandemics are an unpredictable but inevitable aspect of nature and it is, therefore, important that we learn from past pandemics to prepare for future ones. Firstly, the COVID-19 pandemic has highlighted and amplified the existing inequalities within society(234), with non-white ethnicity, social disadvantage, and unemployment all risk factors for testing positive for COVID-19(235) and those most economically deprived found to be particularly vulnerable(236). These inequalities require addressing in order to be better prepared for similar situations in the future. Next, to progress through a pandemic we should be racing the pathogen, not each other. This statement becomes apparent when you consider the problems countries faced when seeking out PPE(237), and the vaccine inequity seen around the world(238), with developed countries often better placed to be able to purchase these items. Initiatives such as the WHO's COVAX programme are vital in order to protect those most vulnerable and reduce the global spread of disease. In October 2021, the UK government released a publication outlining where the policies implemented to reduce the impact of the COVID-19 pandemic failed, and the lessons learned from these failures (239). Here, it is clear that there is room for improvement, with the publication presenting conclusions and recommendations on how to enhance pandemic preparedness, lockdown and social distancing measures, testing and contact tracing, social care, and vaccines. In countries such as the UK, US, and much of Europe, where the COVID-19 death rate has been high, steps need to be taken and lessons need to be learnt in order to be better prepared for the next pandemic. The responsibility of improving pandemic response lies with policy makers, the medical/scientific community, and the public, and will ultimately require a collaborative approach.

Certain aspects of the response to the COVID-19 pandemic have been a triumph, however. One of the major victories was the rapid development and rollout of vaccines(240), which continue to be effective. The rollout of rapid testing and quarantine for positive cases was also important to at least disrupt the spread of the virus, especially given that asymptomatic individuals can contribute to the spread. Furthermore, the swift identification and sharing of knowledge of SARS-CoV-2 variants between countries should be applauded. Lessons can be learned from countries where COVID-19 was controlled. In Taiwan, managing the pandemic as directed by pre-COVID-19 pandemic plans prompted an immediate response; screening of all airline passengers arriving from Wuhan and high risk areas, restricting entry for non-Taiwanese citizens, 14-day quarantine period for contacts of confirmed cases or returning travellers, a ban on large gatherings, and widespread mask wearing were some of the quickly implemented management strategies(241). New Zealand implemented similarly effective restrictions, with the addition of a national lockdown(241). Many of the pandemic control components that kept case and death numbers low in Taiwan and New Zealand could be adopted by other countries in the future and may lead to greater outcomes in terms of protecting both health of individuals and the health and wellbeing of the country. Overall, there is much to be

learnt from the COVID-19 pandemic and, as we emerge from it, inspection of which policies failed, and which succeeded are imperative."

Minor comments:

Comment

1. Table 1 is a great summary of variants, if journal format allows, color-coding the mutations could allow people to quickly digest which variants share which mutations.

Response

Thank you, we agree that colour coding the mutations shared by different variants make it clearer to quickly digest the information, so have colour coded the mutations accordingly.

Comment

2. Figure 1, the texts in the figures (ex. D614G, ORF6, variant designations) could be enlarged

Response

Thank you, the text in figure 1 has been enlarged to make for easier reading.

Reviewer: 3

Comment

1. This review was not written in the systematic review format, which authors can use the statistical method to measurement the significant different between virology variant and vaccine aspects.

Response

Thank you for this comment. As this is not a systematic review in the strictest sense, we believe that this is difficult. We have aimed to explore the relationships between vaccines and circulating variants where possible, for example, where vaccine effectiveness against certain variants is stated in articles, we include it in table 2, while the dates that studies took place from and to are included and can be correlated with circulating variants.

Comment

2. The criteria of choosing and exclude scientific data / paper need to be explained to eliminated the potential bias.

Response

Thank you, as mentioned in previous responses, we have updated the methods section and included a supplementary file to explain our search and inclusion criteria.

Comment

3. Since, the severity of diseases did not depend on only viral genetic, host, and immune status, as well as significant risk factors, but also depend on medical treatment and duration of onset in each data set which are important confounding factors.

Response

Indeed, duration of disease and the treatment patients receive are important factors in determining the severity of disease patients endure, we have included the following statement to cover this:

"The duration of symptoms endured by COVID-19 patients, as well as the treatment they receive will also have profound influences on the severity of disease they experience and both the acute and long-term outcomes following recovery."

Comment

4. Most of review data are not suitable for publication in the modern scientific format but can be re-written with additional level of evidence based medicine.

Response

We believe that the review is written in a concise and methodical manner with all comments supported by published evidence and suitable data.

Comment

5. The basic knowledge and 3D structure of spike RBD and NTD molecule in each mutation and vaccine sequence antibody (MRNA)/ (VIRAL VECTORS) should be reviewed if authors want to determine the correlation of vaccine efficacy and variant of SARS-CoV-2. The authors can use the essential real world data of vaccine effectiveness to determine the response of vaccine across the variant in different time and place of epidemic.

Response

Thank you. Due to the limited word count available, it was not possible to explain the spike protein 3D structure changes caused by each mutation, however we have detailed the structure of the spike protein and where the mutations are located within the spike. We have indicated that mutations within the spike alter its 3D structure and influence immune escape:

Section 4:

"The subunits of the trimeric S complex are either in a closed (pre-fusion stage) or open (post-fusion stage) conformation(62), with one subunit always in an open conformation to allow for ACE2 recognition and binding(63). The RBD itself consists of five anti-parallel β-strands surrounded by several α-helices(64). From closed to open conformation, the RBD undergoes structural rearrangement whereby the globular head region rotates clockwise, which alters is elecropotential surface(64). Once positioned, numerous residues within the RBD form either hydrogen bonds or salt bridges with residues of the ACE2 receptor, allowing for tight binding(65), while the concave structure of the RBD allows for three distinct binding regions(64).

Section 5:

"Many of the mutations observed in SARS-CoV-2 variants are found within the RBD or the N-terminal domain of the S protein, which alters the three-dimensional structure of the S protein. Not only can these changes affect the transmission abilities of the virus, but can also allow it to better escape the immune response, including from neutralising antibodies either elicited through vaccine administration or natural infection."

Comment

6. The booster dose data should be reviewed in term of antibody response and T cell response.

Response

Thank you, we agree with this and we have now included some discussion of antibody and T-cell responses following booster dose:

"Since booster programmes began, evidence that a booster vaccine dose enhances antibody and cellular responses has accumulated. Following a third dose of vaccine, neutralising antibody titres increase significantly(199-202) and, in some cases, to higher levels than after the primary two doses(199). Additionally, boosters have also been found to increase neutralising antibody titres against Beta, Gamma, Delta, and Omicron variants(200, 203, 204). T-cell response is also enhanced following a third dose(201, 205, 206). Together, enhancing neutralising antibody and cellular responses with a booster vaccine dose is likely to provide a greater level of protection than relying on immunity built through a primary regimen."

Reviewer: 4

Comment

1) Introduction

- Line 22 - can you include the difference between VOI and VUM? e.g. in VUM evidence of phenotypic or epidemiological effect is currently unclear, and a name has not yet been assigned.

Response

Thank you, we agree that the differences between VOC, VUI and VUM should have been defined more clearly to include the difference between each. We have updated this as follows:

"The World Health Organisation (WHO) classify SARS-CoV-2 variants that increase transmissibility, disease severity or virulence, or decrease the effectiveness of public health measures, diagnostics, therapeutics or vaccines as variants of concern (VOC). Variants with genetic changes that are predicted to enhance the virulence and transmissibility of the virus which have been identified to cause community transmission in multiple countries posing a possible risk to global public health are defined as variants of interest (VOI). Lastly, the WHO defines variants with genetic changes that are suspected to affect virus characteristics and have currently unclear phenotypic or epidemiological effects as variants under monitoring (VUM). VUM are not typically assigned a name until they are upgraded to VOI or VOC. The full working definitions of VOC, VOI and VUM can be found on the WHO 'tracking SARS-CoV-2 variants' website: www.who.int/en/activities/tracking-SARS-CoV-2-variants/(3)."

Comment

2) Methods

- Including the specifics of how the searches were done would add clarity (maybe as a supplementary file), many of the terms which were searched for are not specific

Response

Thank you, clarity on the search terms and selection criteria was needed. We have included a supplementary file which includes the specific search terms that we used as well as the selection criteria that was implemented for different sections of the review.

Comment

3) Transmission

- Line 32 - maybe use "biological material" instead of "biological samples", presumably the virus doesn't normally spread via the samples themselves

Response

Thank you, this has been changed from "biological samples" to "biological material"

Comment

4) Virology
Page 6
line 8 typo - "interacting WITH host cell organelles"
line 25 - both halves of this sentence are talking about TMPRSS2 but it doesn't sound like it

Response

Thank you, these errors have been corrected:
"with" has now been inserted into "interacting WITH host cell organelles".

The TMPRSS2 sentence has been amended:

"Meanwhile, TMPRSS2, a host cell protease, facilitates fusion of the viral and host cell membranes(68), and may play a role in the spread of the virus in the airways(68)."

Comment

5) VOC
- You frequently refer to an increase in these variants, and state or imply that this is relative to the wild-type. Can you include a section at the start of 5 where you specify what that wild-type is? Is it clear that samples from a particular time period or geographic area are wild-type?

Response

Thank you. We agree that simply using 'wild-type' to discuss a SARS-CoV-2 strain is confusing. Firstly, we have changed this wording to refer to the initial strain that emerged from Wuhan as the 'primary strain, and have described what is meant by that at the end of section 5:
"Herein, we report studies that compare SARS-CoV-2 variants to the 'primary' virus strain. 'Primary strain' refers to the strain of the virus that first emerged in Wuhan, China at the end of 2019 and spread around the world in the first wave of infections, which is often also referred to as the Wuhan-Hu-1, B.1, or wild-type strain."

Comment

6) VOC - Alpha
line 22 typo "probable" not "probably"
line 48 typo "de-escalated"

Response

Thank you for highlighting these errors.
Due to re-wording of this section, "probably" has now been removed, while "de-escalated" has been amended.

Comment

7) 5.1.4 VOC – Delta
- p10 48 Transmissibility of Delta is 97% greater, or three times Alpha, Beta and Gamma?
- p10 54 Isn't replication rate a factor in transmissibility rather than an addition to it?
- p11 line 27 - when you talk about younger people, can you specify which age cutoff you are talking about?

Response

Thank you for identifying this.

The transmissibility sentence was worded poorly in the original manuscript, this has been amended to explain exactly what is meant:
"It was estimated that the reproduction number of the Delta variant is 97% greater than non-VOC/VOI and approximately three times that of the Alpha, Beta, and Gamma variants(110),"

We agree that replication rate is a factor in transmissibility, therefore we have amended this sentence:
"The fast replication rate of Delta likely contributes to its increased transmissibility compared to Alpha, Beta, and Gamma."

We also agree that it was unclear what "younger people" meant, we have amended the statement as follows:
"Lastly, a study in India found that the risk of death was around 1.8 times higher for Delta infections, while Delta also infected and induced symptoms in a greater proportion of younger people (0-19 years old), compared to the primary strain(131)."

Comment

8) Vaccination 6.1 Pfizer
line 15 - typo repeating "elicit a strong"

6.3 Johnson and Johnson
- Line 9 a bit unclear, is the point that there is a time lag of around 28 days before peak effectiveness? After second dose? And compared with how many days?

6.6 Sinovac
Line 6 - typo "alike" should be "like"

6.8 Boosters
Line 56 typo "On 30th July 2021" appears twice

Response

Thank you.
Repetition of "elicit a strong" has been corrected.
Due to re-wording of the manuscript, the statement commenting on the time lag of around 28 days before peak effectiveness has been removed.
"like" now replaces "alike" within the Sinovac section.
The second appearance of "On 30th July 2021" has been removed.

Comment

8 Conclusions

- Line 23 "Yet to be eradicated" - this is absolutely true; but this is unlikely to happen for decades if ever, and there are other more immediate unmet goals it might be better to mention, such as attaining high vaccination coverage globally, ensuring all health systems have the capacity to cope with seasonal waves.

Response

Thank you, we agree that "yet to be eradicated" is possibly a misleading statement. We have amended this part of the conclusion as follows:

"Although rollout of vaccines has been successful, we must aim to address unmet goals, such as attaining a high global vaccination coverage and ensuring that all healthcare systems have the capacity to cope with seasonal waves."

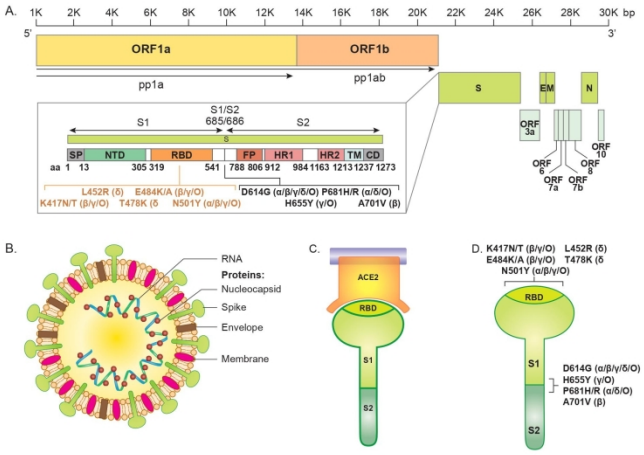

Figure 1: Genome and structure of SARS-CoV-2.

210x297mm (300 x 300 DPI)

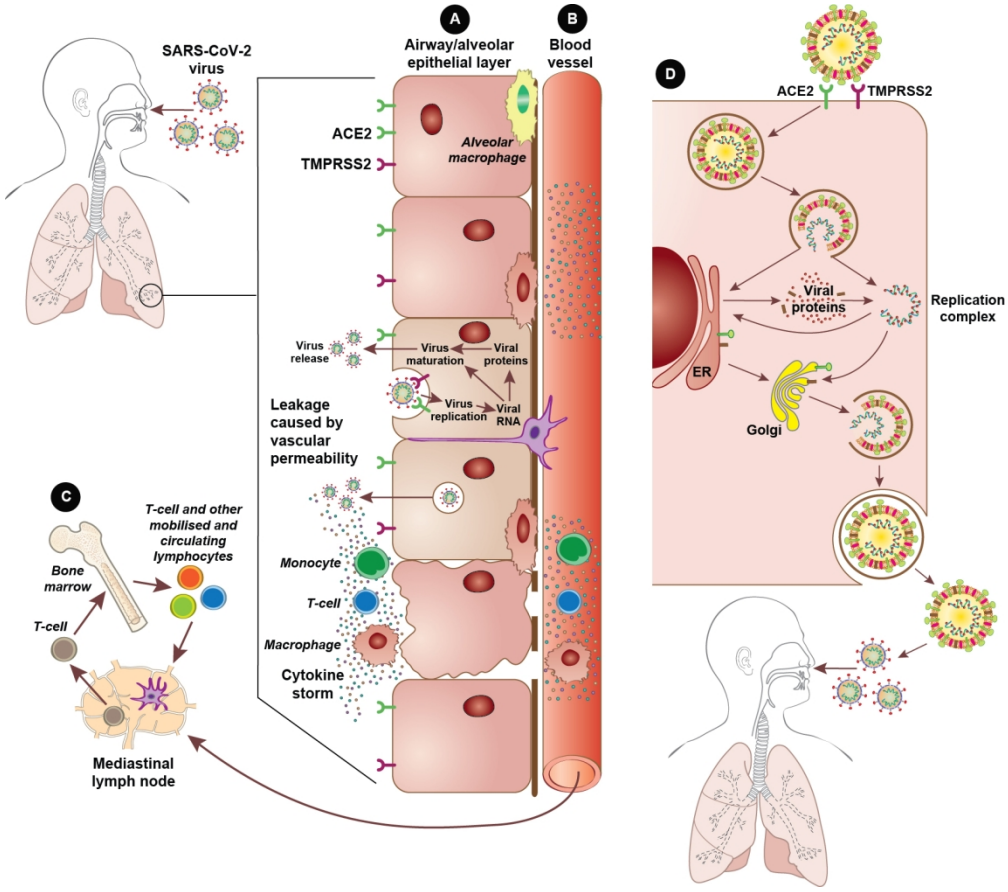

Figure 2: Viral entry and host response.

153x135mm (300 x 300 DPI)

Variants of concern			
WHO nomenclature or designation	**Pango Lineage**	**S protein mutations of interest**	**First detected samples ***
Alpha	B.1.1.7	N501Y D614G P681H	UK, Sept 2020
Beta	B.1.351	N501Y D614G E484K K417N A701V	South Africa, May 2020
Gamma	P.1	N501Y D614G E484K K417T H655Y	Brazil, Nov 2020
Delta	B.1.617.2	L452R D614G P681R T478K	India, Oct 2020
Omicron	B.1.1.529	N501Y D614G E484A P681H K417N H655Y A67V Δ69-70 T95I G142D Δ143-145 N211I Δ212 ins215EPE G339D S371L S373P S375F N440K G446S S477N T478K Q493R G496S Q498R Y505H T547K N679K N764K D796Y N856K Q954H N969K L981F	South Africa and Botswana, Nov 2021
Variants of Interest			
WHO nomenclature or designation	**Pango Lineage**	**S protein mutations of interest**	**First detected samples ***
Lambda	C.37	L452Q D614G F490S	Peru, Dec 2020
Mu	B.1.621	N501Y D614G P681H R346K E484K	Columbia, Jan 2021
Variants under monitoring			
Pango Lineage		**S protein mutations of interest**	**First detected samples ***
B.1.1.318		D614G P681H E484K	Multiple countries, Jan 2021
C.1.2		N501Y D614G E484K H655Y N679K Y449H	South Africa, May 2021
B.1.640		N501Y D614G P681H F490R N394S R346S Y449N 137–145del	Multiple countries, Sep 2021

Vaccine and vaccine type	Recommended dose and administration	Study ref.	Study type	Study date and location(s)	N	Vaccine effectiveness % (95% confidence interval) *		
						Against	One dose	Two doses
Pfizer/BioNtech (BNT162b2) – mRNA.	Two doses (30µg, 0.3ml each) intramuscularly (deltoid) with a recommended interval of 21-28 days between doses.	(156)	Randomised controlled trial	27/7/2020 to 14/11/2020 US, Argentina, Brazil, South Africa, Germany, and Turkey.	37,706	Symptomatic infection		95% (90.3–97.6%)
		(241)	Observational	20/12/2020 to 1/2/2021 Israel.	1,193,236	Documented infection	46% (40-51%)	92% (88-95%)
						Symptomatic infection	57% (50-63%)	94% (87-98%)
						Hospitalisation	74% (56-86%)	87% (55-100%)
						Severe disease	62% (39-80%)	92% (75-100%)
		(242)	Test-negative case-control	26/10/2020 to 16/5/2021 UK.	19,109	Infection with Alpha	47.5% (41.6–52.8%)	93.7% (91.6–95.3%)
						Infection with Delta	35.6% (22.7–46.4%)	88.0% (85.3–90.1%)
		(243)	Test-negative case-control	1/2/2021 to 31/3/2021 Qatar.	213,758	Infection with Beta		75.0% (70.5-78.9%)
						Infection with Alpha or Beta		97.4% (92.2-99.5%)
		(244)	Test-negative case-control	14/12/2020 to 19/4/2021 Canada.	324,033	Symptomatic infection	14-20 days: 48% (41-54%)	≥7 days: 91% (89-93%)
							≥14 days: 60% (57-64%)	
							35-41 days: 71% (63-78%)	
						Hospital admission or death	14-20 days: 62% (44-75%)	≥7 days: 98% (88-100%)
							≥14 days: 70% (60-77%)	
							≥35 days: 91% (73-97%)	
						[NOTE: Participants in this study received an mRNA vaccine (either BNT162b2 or mRNA-1273)]		
		(245)	Test-negative case-control	14/12/2020 to 3/8/2021 Canada.	682,071	Symptomatic infection - Alpha	≥14 days: 66% (95% CI: 64-68%)	≥7 days: 89% (86–91%)
						Symptomatic infection - Beta or Gamma variants	≥14 days: 60% (52-67%)	≥7 days: 84% (69–92%)
						Symptomatic infection - Delta	≥14 days: 56% (45-64%)	≥7 days: 87% (64–95%)
						Against hospitalisation or death - Alpha	≥14 days: 80% (78-82%)	≥7 days: 95% (92-97%)
						Against hospitalisation or death - Beta or Gamma	≥14 days: 77% (69-83%)	≥7 days: 95% (81-99%)
						Against hospitalisation or death - Delta	≥14 days: 78% (65-86%)	
		(246)	Retrospective case-control	January to July 2021 US.	119,463	Infection		≥14 days: 86% (81-90.6%)
						Hospitalisation		≥14 days: 85% (73-93%)
						Admission to an ICU		≥14 days: 87% (46-98.6%)
		(133)	Test-negative observational	1/4/2021 to 6/6/2021 Scotland.	400,827	Infection - Alpha		92% (90–93%)
						Infection - Delta		79% (75-82%)
		(247)			14,019	Hospitalisation - Alpha	83% (62-93%)	95% (78-99%)

			Test-negative case-control	12/4/2021 to 4/6/2021 England.		Hospitalisation - Delta	94% (46-99%)	96% (86-99%)
		(248)	Test-negative case-control	8/12/2020 to 19/2/2021. England.	156,930	Infection		10-13 days: 70% (59-78%)
								≥14 days: 89% (85-93%)
								28-34 days: 61% (51-69%)
		(249)	Test-negative case-control	4/4/2021 to 1/5/2021 Canada.	16,993	Infection	0-13 days: 14% (0-26%)	
							14-20 days: 43% (30-53%)	
							35-41 days: 75% (63-83%)	
						Infection		≥21 days: 65% (58-71%)
						Infection - non-VOC		72% (58-81%)
						Infection - Alpha		67% (57-75%)
						Infection - Gamma		61% (45-72%)
		(250)	Test-negative case-control	17/1/2021 to 5/6/2021 Canada.	5,8476	Infection	≥14 days: 70.3% (68.1-72.4%)	≥7 days: 85.5% (80.4-89.3%)
		(251)	Case-control	14/2/2021 to 3/5/2021 France.	67,760	Infection		≥7 days: 88% (81-92%)
						Infection - Alpha		≥7 days: 86% (81-90%)
						Infection - Beta/Gamma		≥7 days: 77% (63-86%)
		(252)	Test-negative case-control	23/3/2021 to 7/9/2021 Qatar.	1 dose: 906,078 2 doses: 877,354	Infection – Delta	65.5% (40.9-79.9%)	≥14 days: 59.6% (50.7-66.9%)
						Severe disease or death - Delta		97.3% (84.4-99.5%)
		(192)	Test-negative case-control	1/1/2021 to 5/9/2021 Qatar.	1 dose: 947,035 2 doses: 907,763	Symptomatic infection	0-13 days: -5.5% (-12.9-1.4%)	
							≥14 days: 47.9% (43.6-51.9%)	
							1 month: 81.5% (79.9-83.0%)	
							2 months: 72.5% (69.6-75.1%)	
							3 months: 70.6% (66.4-74.3%)	
							4 months: 57.0% (48.6-64.0%)	
							5 months: 12.0% (-6.1-27.1%)	
							6 months: 12.8% (-9.1-30.3%)	
							≥7 months: 27.8% (-1.4-48.7%)	
						Hospitalisation and death	0-13 days: 7.5% (−11.9-23.6%)	
							≥14 days: 65.0% (55.0-72.8%)	
							1 month: 95.9% (93.6-97.3%)	
							2 months: 96.3% (92.9-98.0%)	
							3 months: 93.4% (87.5-96.5%)	
							4 months: 80.8% (56.9-91.4%)	
							6 months: 81.8% (18.5-95.9%)	
							≥7 months: 44.1% (-86.5-83.3%)	
		(253)	Prospective cohort	7/12/2020 to 5/2/2021	23,324	Infection	≥21 days: 70% (55-85%)	≥7 days: 85% (74-96%)

				UK.				
		(254)	Observational	24/1/2021 to 3/4/2021 Israel.	186,109	Infection		≥7 days: 95.3% (94.9-95.7%)
						Asymptomatic infection		≥7 days: 91.5% (90.7-92.2%)
						Symptomatic infection		≥7 days: 97.0% (96.7-97.2%)
						Hospitalisation		≥7 days: 97.2% (96.8-97.5%)
						Severe or critical infection		≥7 days: 97.5% (97.1-97.8%)
						Death		≥7 days: 96.7% (96.0-97.3%)
		(255)	Observational	1/3/2021 to 1/8/2021 US.	10,428,783	Infection – Pre-Delta period		≥14 days: 74.2% (68.9-78.7%)
						Infection – Intermediate period		≥14 days: 66.5% (58.3-73.1%)
						Infection – Delta		≥14 days: 52.4% (48.0-56.4%)
		(256)	Observational	14/12/2020 to 14/8/2021 US.	Delta: 2,840 Pre-Delta: 7,012	Infection – Delta		14–119 days: 85% (68-93%)
								120–149 days: 81% (34-95%)
								≥150 days: 73% (49-86%)
						Infection – Pre-Delta		91% (81-96%)
					[NOTE only 65% of participants in this study received BNT162b2 (33% received mRNA-1273, and 2% received Ad26.COV2.S]			
		(257)	Observational	15/1/2021 to 16/4/2021 France.	378	Infection – Beta		≥7 days: 49% (14-69%)
						Severe disease		≥7 days: 86% (67-94%)
		(258)	Observational	1/12/2020 to 1/8/2021 UK.	384,543	Infection – Alpha	≥21 days: 59% (52-65%)	
						Infection – Delta	≥21 days: 57% (50-63%)	
						Infection – Alpha		0-13 days: 77% (66-84%)
								≥14 days: 78% (68-84%)
						Infection – Delta		0-13 days: 82% (75-87%)
								≥14 days: 80% (77-83%)
		(259)	Observational	April to May 2021. Canada	224	Infection		66.2% (2.3-88.3%)
						Symptomatic infection		25.6% (-157.8-78.5%)
		(260)	Retrospective cohort	27/12/2020 to 24/3/2021 Italy.	6,423	Infection	0-14 days: 47.3% (24.7-63.1%)	≥7 days: 95.1% (62.4-99.4%)
							14-21 days: 84.1% (39.7-95.8%)	
							≥21 days: 85.4% (-35.3-98.4%)	
						Symptomatic infection	0-14 days: 39.9% (9.1-60.3%)	≥7 days: 93.7% (50.8-99.2%)
							14-21 days: 83.3% (14.8-96.7%)	
							≥21 days: 65.9% (-171-95.7%)	
		(261)	Randomised controlled trial	27//7/2020 to 29/10/2020 US, Argentina, Brazil, South Africa, Germany, Turkey	44,165	Infection (without evidence of prior infection)		≥7 days: 91.3% (89-93.2%)
						Infection (with evidence of previous infection)		≥7 days: 91.1% (88.8-93.0%)
						Infection	<11 days: 18.2% (−26.1-47.3%)	<7 days: 91.5% (72.9-98.3%)
							≥11 days to second dose: 91.7% (79.6-97.4%)	≥7 days: 91.2% (88.9-93.0%)

								≥7 days to <2 months: 96.2% (93.3-98.1%)
								≥2 months to <4 months: 90.1% (86.6-92.9%)
								≥4 months: 83.7% (74.7-89.9%)
		(262)	Retrospective cohort	20/12/2020 to 25/2/2021 Israel.	6,710	Symptomatic Infection	7-21 days: 89% (83-94%)	≥7 days: 97% (94-99%)
								≥21 days: 98% (94-100%)
						Asymptomatic Infection	7-21 days: 36% (-51-69%)	≥7 days: 86% (69-93%)
								≥21 days: 94% (78-98%)
		(263)	Cohort	27/12/2020 to 28/2/2021 Sweden.	805,741	Infection	≥14 days: 42% (14-63%)	<7 days: 60% (27-81%)
								≥7 days: 86% (72-94%)
		(264)	Prospective cohort	27/12/2020 to 26/5/2021 Spain.	28,594	Infection – Nursing home residents	12 days: 20% (19.76-20.3%)	90.89% (90.84-90.95%
							40.28% (40.17-40.39)	
					26,238	Infection – Nursing home staff	12 days: 20.27% (19.8-20.73%)	85.02% (84.86-85.17%)
							26.49% (26.25-26.74%)	
					61,951	Infection – Healthcare workers	12 days: 15.44% (15.19-15.68%)	94% (93.92-94.1%)
							33.8% (33.66-33.92%)	
					28,594	Hospital admission - Nursing home residents	12 days: 67.59% (65.29-69.75%)	95.06% (94.73-95.38%)
							46.24% (45.62-46.86%)	
						Death - Nursing home residents	12 days: 43.95% (37.87-49.44%)	96.73% (96.43-96.99)
							51.71% (51.17-52.23%)	
		(265)	Cohort	27/12/2020 to 11/4/2021 Denmark.	864,096	Infection - Prioritised risk groups	0-14 days: -72% (-80- -64%)	0-7 days: 42% (33-50%)
							>14 days to second dose: 7% (-1-15%)	> 7 days: 82% (79-84%)
						COVID-19-related hospitalisation - Prioritised risk groups	0-14 days: 54% (44-62%)	0-7 days: 90% (80-95%)
							>14 days to second dose: 35% (18-49%)	>7 days: 93% (89-96%)
						COVID-19-related death - Prioritised risk groups	0-14 days: 76% (68-82%)	>7 days: 94% (90-96%)
							>14 to second dose days: 7% (-15-25%)	
		(266)	Case-control	27.1.2021 to 7/2/2021 Spain.	268	Infection	52.6% (95%CI: 1.1-77.3)	
		(267)	Observational	15/12/2020 to 3/2/2021 England.	170,226	Infection	21-27 days: 55.2% (40.8-66.8%)	
						Emergency hospital attendance	21-27 days: 57.8% (30.8-74.5%)	
						Hospitalisation	21-27 days: 50.1% (19.9-69.5%)	
		(268)	Cohort	27/12/2020 to 10/3/2021 Spain.	299,209	Infection (without evidence of prior infection)	0-14 days: 28.9% (26.9-31%)	
							15-21 days: 51.9% (50.7-53.1%)	
							22-28 days: 62.9% (61.9-64%)	
							≥29 days: 81.8% (81.0-82.7%)	
							0-14 days: 9.6% (-6.9-26.8%)	

						Infection (with evidence of prior infection)	15-21 days: 25.5% (15.1-36.6%)	
							22-28 days: 34.6% (25.7-44.1%)	
							≥29 days: 56.8% (47.1-67.7%)	
		(269)	Observational	1/12/2020 to 8/5/2021 UK.	383,812	Infection	8-20 days after either dose: 56% (51-61%)	
							≥21 days: 64% (59-68%)	≥21 days: 80% (74-84%)
					[NOTE: Both BNT162b2 and AZD1222 vaccines were included in this study]			
		(270)	Cohort	19/12/2020 to 14/3/2021 Israel.	9,347	Infection	4-10 days: 28% (-18-57%)	≥11 days: 65% (45-79%)
							≥11 days after first, ≤10 days after second: 55% (32-70%)	
						Symptomatic infection	4-10 days: 21% (-32-41%)	≥11 days: 90% (84-94%)
							≥11 days after first, ≤10 days after second: 80% (69-87%)	
		(271)	Prospective cohort	8/12/2020 to 15/3/2021 England.	10,412	Infection	0-6 days: 36% (-6-62%)	
							7-13 days: 17% (-28-46%)	
							14-20 days: 4% (-60-43%)	
							21-27 days: 8% (-59-47%)	
							28-34 days: 56% (19-76%)	
							35-48 days: 62% (23-81%)	
							≥49 days: 51% (-17-80%)	
					[NOTE: Both BNT162b2 and AZD1222 vaccines were included in this study]			
		(272)	Retrospective cohort	1/1/2021 to 31/3/2021 US.	44,498	Infection	>14 days after first, ≤14 days after second: 78.1% (71.1-82%)	
								>14 days: 96.8% (95.3-97.8%)
		(273)	Prospective cohort	14/12/2020 to 10/4/2021 US.	3,975	Infection	≥14 days after first, <14 days after second: 80% (60-90%)	
								≥14 days: 93% (78-98%)
		(274)	Randomised controlled trial	15/10/2020 to 12/1/2021 US.	2,260	Infection - Adolescents (12-15 years of age) - (without evidence of prior infection)		≥7 days: 100% (75.3-100%)
						Infection - Adolescents (12-15 years of age) - (with or without evidence of prior infection)		≥7 days: 100% (78.1-100%)
		(275)	Retrospective cohort	19/7/2021 to 13/11/2021 South Korea.	444,313	Infection – Adolescents (16-18 years of age)	≥14 days: 91.1% (89.6-92.5%)	≥14 days: 99.1% (98.5-99.5%)
		(276)	Prospective cohort	25/7/2021 to 4/12/2021 US.	243	Infection - Adolescents (12-17 years of age)		≥14 days: 92% (79-97%)
		(277)	Retrospective longitudinal cohort	21/12/2020 to 6/2/2021 Israel.	5,439,734 first dose, 5,112,516 second dose	Infection	14-20 days: 54.3% (50.6-57.8%)	8-14 days: 89.9% (88.6-91.1%)
						Symptomatic infection	14-20 days: 58.3% (54.7-61.6%)	8-14 days: 93.6% (92.7-94.3%)
						Hospitalisation	14-20 days: 74.5% (69.1-79%)	8-14 days: 93.8% (91.9-95.2%)
						Severe/Critical disease	14-20 days: 77.3% (71.2-82.1%)	8-14 days: 94.4% (92.6-95.8%)
						Death	14-20 days: 71.7% (64.1-77.7%)	8-14 days: 91.3% (87.4-94.0%)
						Infection		15-21 days: 96.8% (96.1-97.4%)

						Symptomatic infection		15-21 days: 98.1% (97.7-98.5%)
						Hospitalisation		15-21 days: 98% (97.1-98.6%)
						Severe/Critical disease		15-21 days: 98.6% (97.8-99.1%)
						Death		15-21 days: 97.7% (95.9-98.7%)
						Infection		22-28 days: 97.3% (96.7-97.8%)
						Symptomatic infection		22-28 days: 97.9% (97.4-98.3%)
						Hospitalisation		22-28 days: 99% (98.4-99.3%)
						Severe/Critical disease		22-28 days: 99.2% (98.6-99.5%)
						Death		22-28 days: 98.6% (97-99.3%)
		(278)	Test-negative case-control	January to March 2021 US.	1,843	Infection	≥14 days: 81.7% (74.3-86.9%)	≤2 days: 81.7% (74.3-86.9%)
								3-6 days: 81.7% (74.3-86.9%)
								≥7 days: 93.5% (86.5-96.9%)
					[NOTE: 76% of case-patients and 78% of controls received BNT162b2, remainder received mRNA-1273]			
		(279)	Prospective cohort	January to April 2021 Spain.	20,961	Infection	21% (3-36%)	65% (56-73%)
						Symptomatic infection	30% (10-45%)	82% (73-88%)
						Symptomatic infection – 18-59 years old	50% (12-72%)	85% (74-91%)
						Symptomatic infection - ≥60 years old	20% (−7-40%)	76% (55-87%)
						Hospitalisation	65% (25-83%)	94% (60-99%)
		(280)	Prospective cohort	8/10/2020 to 22/2/2021 Scotland.	409,588	Hospitalisation	0-6 days: 86% (81-90%)	
							7-13 days: 53% (45-59%)	
							14-20 days: 69% (62-75%)	
							21-27 days: 78% (71-83%)	
							28-34 days: 91% (85-94%)	
							35-41 days: 78% (69-85%)	
							≥42 days: 77% (68-83%)	
		(281)	Test-negative case-control	27/12/2020 to 30/6/2021 Belgium, Croatia, Czechia, France, Greece, Ireland, Luxembourg, Malta, Portugal, Spain.	1,893	Infection	≥14 days: 76% (61-86%)	≥14 days: 94% (88-97%)
		(282)	Prospective cohort	1/5/2021 to 3/9/2021 US.	8,690,825	Infection - 18-49 years old		≥14 days: 93.3% (92.2-94.4%)
						Infection - 50-64 years old		≥14 days: 95.0% (94.0-96.0%)
						Infection - ≤65 years old		≥14 days: 91.4% (90.0-92.8%)
						Hospitalisation - 18-49 years old		≥14 days: 96.1% (94.1-97.6%)
						Hospitalisation - 50-64 years old		≥14 days: 95.6% (94.2-96.7%)
						Hospitalisation - ≤65 years old		≥14 days: 94.8% (94.0-95.5%)
		(283)			1,222	Hospitalisation 12-18 years old	97% (86-100%)	≥14 days: 94% (90-96%)

			Test-negative case-control	1/7/2021 to 25/10/2021 US.		ICU admission – 12-18 years old		≥14 days: 98% (93-99%)
						Life support – 12-18 years old		≥14 days: 98% (92-100%)
		(284)	Test-negative case-control	1/7/2021 to 9/12/2021 US.	283	COVID-19 multisystem inflammatory syndrome – 12-18 years old		≥14 days: 92% (77-97%)
Oxford University/ AstraZeneca (AZD1222) - Non-replicating adenovirus viral vector (ChAdOx1).	Two doses (0.5ml each) intramuscularly (deltoid) with a recommended interval window of 8 to 12 weeks.	(242)	Test-negative case-control	26/10/2020 to 16/5/2021 UK.	19,109	Infection - Alpha	48.7% (45.2–51.9%)	74.5% (68.4–79.4%)
						Infection - Delta	30.0% (24.3–35.3%)	67.0% (61.3–71.8%)
		(245)	Test-negative case-control	14/12/2020 to 3/8/2021 Canada.	682,071	Symptomatic infection - Alpha	64% (60-68%)	
						Symptomatic infection – Beta or Gamma	48% (28-63%)	
						Symptomatic infection - Delta	67% (44-80%)	
						Hospitalisation or death - Alpha	85% (81-88%)	
						Hospitalisation or death – Bet or Gamma	83% (66-92%)	
						Hospitalisation or death - Delta	88% (60-96%)	
		(133)	Test-negative observational	1/4/2021 to 6/6/2021 Scotland.	462,755	Infection with Alpha variant		73% (66-78%)
						Infection with Delta variant		60% (53-66%)
		(285)	Randomised controlled trial	1/10/2020 to 14/1/2021 UK.	8,534	Symptomatic infection – Alpha		70.4% (43.6-84%%)
						Symptomatic infection – non-Alpha		81.5% (67.9-89.4%)
		(286)	Randomised controlled trial	28/8/2020 to 5/3/2021 US.	32,449	Symptomatic infection		79%
						Severe disease or hospitalisation		100%
		(247)	Test-negative case-control	12/4/2021 to 4/6/2021 England.	14,019	Hospitalisation – Alpha	76% (61-85%)	86% (53-96%)
						Hospitalisation – Delta	71% (51-83%)	92% (75-97%)
		(287)	Randomised controlled trial	23/4/2020 to 4/11/2020 UK, Brazil.	11,636	Infection		62.1% (41.0-75.7%)
		(288)	Randomised controlled trial	24/6/2020 to 9/11/2020 South Africa.	2,026	Symptomatic infection		21.9% (-49.9-59.8%)
						Symptomatic infection - Beta		10.4% (-76.8-54.8%)
		(248)	Test-negative case-control	8/12/2020 to 19/2/2021. England.	156,930	Symptomatic infection		28-34 days: 60% (41-73%)
								≥35 days: 73% (27-90%)
		(258)	Observational	1/12/2020 to 1/8/2021 UK.	384,543	Infection - Alpha	≥21 days: 63% (55–69%)	0-13 days: 72% (50-84%)
								≥14 days: 79% (56–90%)
						Infection Delta	≥21 days: 46% (35–55%)	0-13 days: 71% (64–77%)
								≥14 days: 67% (62–71%)
		(289)	Test-negative case-control	1/3/2021 to 31/5/2021 India	720	Infection	49% (17-68%)	54% (27-71%)
						Symptomatic infection	58% (28-75%)	64% (38-78%)
						Moderately severe disease	Any dosage >3 weeks ago: 95% (44-100%)	

		(269)	Observational	1/12/2020 to 8/5/2021 UK.	383,812	Infection	8-20 days after either dose: 56% (51-61%)	
							≥21 days: 64% (59-68%)	≥21 days: 80% (74-84%)
					[NOTE: Both BNT162b2 and AZD1222 vaccines were included in this study]			
		(290)	Randomised controlled trial	28/8/2020 to 15/1/2021 US, Chile, Peru.	32,451	Symptomatic infection		≥15 days: 74.0% (65.3-80.5%)
						Severe or critical infection		≥15 days: 100.0% (71.6-NE%)
						Emergency department visit		≥15 days: 94.8% (59.0-99.3%)
						Hospitalisation		≥15 days: 94.2% (53.3-99.3%)
						ICU admission		≥15 days: 100.0 (−1781.6-NE%)
		(291)	Clinical trial	23/6/2020 to 1/12/2020 Brazil.	9433	Infection – B.1.1.33		88.2 (5.4, 98.5)
						Infection – B.1.1.28		72.6% (46.4-86.0%)
						Infection – Zeta		68.7% (54.9-78.3%)
						Infection – Gamma		63.6% (−2.1-87.0%)
						Infection – Undetermined variant		56.6% (28.2-73.8%)
						Hospitalisation – Any variant		95% (61-99%)
		(292)	Meta-analysis	23/4/2020 to 6/12/2020 UK, Brazil, South Africa.	17,178	Asymptomatic infection		≥14 days: 22.2% (–9·9-45%)
						Symptomatic infection		≥14 days: 66.7% (57.4-74%)
						Asymptomatic infection - <6 weeks prime-boost interval (standard doses)		≥14 days: –11.8% (–189.5-56.8%)
						Asymptomatic infection - 6-8 weeks prime-boost interval (standard doses)		≥14 days: –74.2% (–330.3-29.5%)
						Asymptomatic infection – 9-11 weeks prime-boost interval (standard doses)		≥14 days: 39.9% (–62.3-77.8%)
						Asymptomatic infection - ≥12 weeks prime-boost interval (standard doses)		≥14 days: 22.8% (–63.3-63.5%)
						Symptomatic infection - <6 weeks prime-boost interval (standard doses)		≥14 days: 55.1% (33-69.9%)
						Symptomatic infection - 6-8 weeks prime-boost interval (standard doses)		≥14 days: 59.9% (32-76.4%)
						Symptomatic infection – 9-11 weeks prime-boost interval (standard doses)		≥14 days: 63.7% (28-81.7%)
						Symptomatic infection - ≥12 weeks prime-boost interval (standard doses)		≥14 days: 81.3% (60.3-91.2%)
		(293)	Cross-sectional observational	1/5/2021 to 31/5/2021 India.	583	Infection	<14 days: 15% (-68-57%)	<14 days: 66% (34-81%)
							≥14 days: 44% (7-66%)	≥14 days: 83% (73-89%)
						Hospitalisation	<14 days: 43% (-68-81%)	<14 days: 83% (17-96%)
							≥14 days: 76% (21-92%)	≥14 days: 88% (55-97%)
						ICU admission or death	<14 days: 62% (-27-89%)	<14 days: 93% (35-99%)
							≥14 days: 53% 9-29-83%)	≥14 days: 93% (64-99%)
					[NOTE: Participants either received Covaxin or Covishield (AZD1222)]			
		(279)	Prospective cohort	January to April 2021 Spain.	20,961	Infection	44% (31-54%)	
						Symptomatic infection	50% (37-61%)	
						Symptomatic infection – 18-59 years old	50% (34-62%)	

						Symptomatic infection - ≥60 years old	53% (19-72%)	
						Hospitalisation	92% (46-99%)	
		(294)	Retrospective cohort	1/6/2020 to 31/5/2021 India.	11,405	Infection (with evidence of prior infection)		≥14 days: 91.1% (84.1-94.9%)
						Infection (without evidence of prior infection)		≥14 days: 31.8% (23.5-39.1%)
					[NOTE: 5.77% of participants received Covaxin, 94.23% received Covishield (AZD1222)]			
		(280)	Prospective cohort	8/10/2020 to 22/2/2021 Scotland	409,588	Hospitalisation	0-6 days: 72% (66-77%)	
							7-13 days: 68% (61-73%)	
							14-20 days: 73% (66-79%)	
							21-27 days: 81% (72-87%)	
							28-34 days: 88% (75-94%)	
							35-41 days: 97% (63-100%)	
							≥42 days: 59% (–296-96%)	
		(295)	Cohort	17/1/2021 to 11/5/2021 Brazil.	313,328	Death	≥21 days: 94.4% (93.9-94.8%)	≥21 days: 99.8 (99.6-99.9%)
						Death – 75-79 years old	≥21 days: 88% (85.8-90%)	
						Death – 80-89 years old	≥21 days: 96.8% (96.5-97.2%)	
						Death - ≥90 years old	≥21 days: 99.2% (99.1-99.4%)	
		(296)	Retrospective cohort	18/1/2021 to 30/6/2021 Brazil.	60,577, 870	Infection	≥14 days: 34% (33.2-34.7%)	0-13 days: 56.9% (55.3-58.5%)
								≥14 days: 70% (68.6-71.3%)
						Hospitalisation	≥14 days: 52.2% (50.9-53.4%)	0-13 days: 69.6% (67.2-71.8%)
								≥14 days: 86.8% (85.2-88.2%)
						ICU admission	≥14 days: 54% (51.8-56%)	0-13 days: 69.2% (65-72.8%)
								≥14 days: 88.1% (85.4-90.3%)
						Death	≥14 days: 49.3% (47-51.5%)	0-13 days: 72.1% (69.1-74.9%)
								≥14 days: 90.2% (88.3-91.8%)
Johnson & Johnson (Ad26.COV2.S) - Recombinant, replication-incompetent adenovirus serotype 26 (Ad26) vector.	One dose (0.5ml) intramuscularly (deltoid).	(172)	Randomised controlled trial	21/9/2020 to 22/1/2021 Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, US.	39,321	Moderate to severe-critical infection	≥14 days: 66.9% (59.0-73.4%)	
							≥28 days: 66.1% (55.0-74.8%)	
						Severe-critical infection	≥14 days: 76.7% (54.6-89.1%)	
							≥28 days: 85.4% (54.2-96.9%)	
		(297)	Test-negative case-control	25/6/2021 to 30/9/2021 Brazil.	11,817	Symptomatic infection	14-27 days: 27.4% (8.7-42.7%)	
							≥28 days: 50.9% (35.5-63.0%)	
						Hospitalisation	14-27 days: 33.5% (-29.1-69.8%)	
							≥28 days: 72.9% (35.1-91.1%)	
						Admission to an ICU	14-27 days: 56.0% (-52.8-93.1%)	
							≥28 days: 92.5% (54.9-99.6%)	
							14-27 days: 65.2% (-74.7-98.1%)	

						Mechanical ventilation	≥28 days: 88.7% (17.9-99.5%)	
						Death	14-27 days: 48.9% (-92.3-92.5%)	
							≥28 days: 90.5% (31.5-99.6%)	
		(298)	Retrospective case-control	27/2/2021 to 14/4/2021 US.	126,572	Symptomatic infection	≥1 day: 50.6% (14.0-74.0%)	
							≥8 days: 65.5% (23.3-87.5%)	
							≥15 days: 76.7% (30.3-95.3%)	
		(299)	Test-negative case-control	1/7/2021 to 31/7/2021 US.	1,000	Symptomatic infection	51% (95% CI: -2-76%)	
		(256)	Observational	14/12/2020 to 14/8/2021 US.	Delta: 2,840 Pre-Delta: 7,012	Infection – Delta	14–119 days: 85% (68-93%)	
							120–149 days: 81% (34-95%)	
							≥150 days: 73% (49-86%)	
						Infection – Pre-Delta	91% (81-96%)	
					[NOTE: 2% of study participants received Ad26.COV2.S (65% received BNT162b2, and 33% received mRNA-1273)]			
		(300)	Cohort	March to July 2021 US.	1,914,670	Infection	79% (77-80%)	
						Hospitalisation	81% (79-84%)	
		(301)	Retrospective cohort	27/2/2021 to 22/7/2021 US.	97,787	Infection	≥1 day: 73.6% (65.9-79.9%)	
							≥8 days: 72.9% (64.2-79.9%)	
							≥15 days: 74.2% (64.9-81.6%)	
		(282)	Prospective cohort	1/5/2021 to 3/9/2021 US.	8,690,825	Infection - 18-49 years old		≥14 days: 89% (86.5-91.5%)
						Infection - 50-64 years old		≥14 days: 86.1% (82.5-89.6%)
						Infection - ≤65 years old		≥14 days: 80.8% (75.2-86.5%)
						Hospitalisation - 18-49 years old		≥14 days: 95.7% (91.1-98.3%)
						Hospitalisation - 50-64 years old		≥14 days: 87.5% (82.4-91.4%)
						Hospitalisation - ≤65 years old		≥14 days: 85.2% (81.1-88.6%)
Moderna (mRNA-1273) - mRNA	Two doses (100µg, 0.5ml each) intramuscularly (deltoid) with a recommended interval of 28 days between doses.	(245)	Test-negative case-control	14/12/2020 to 3/8/2021 Canada.	682,071	Symptomatic infection – Alpha	≥14 days: 83% (80-86%)	≥7 days: 92% (86-96%)
						Symptomatic infection – Beta or Gamma	≥14 days: 77% (63-86%)	
						Symptomatic infection – Delta	≥14 days: 72% (57-82%)	
						Hospitalisation - Alpha	≥14 days: 79% (74-83%)	≥7 days: 94% (89-97%)
						Hospitalisation – Beta or Gamma	≥14 days: 89% (73-95%)	
						Hospitalisation - Delta	≥14 days: 96% (72-99%)	
		(246)	Retrospective case-control	January to July 2021 US.	60,083	Infection		≥14 days: 86% (81-90.6%)
						Hospitalisation		≥14 days: 91.6% (81-97%)
						Admission to an ICU		≥14 days: 93.3% (57-99.8%)
		(250)	Test-negative case-control	17/1/2021 to 5/6/2021 Canada.	5,8476	Infection	≥14 days: 68.7% (59.5-75.9%)	≥7 days: 84.1% (34.9-96.1%)
		(252)	Test-negative case-control	23/3/2021 to 7/9/2021	1 dose: 490,828	Infection - Delta	≥14 days: 79.7% (60.8-89.5%)	≥14 days: 86.1% (78.0-91.3%)

				Qatar.	2 doses: 409,041			
		(255)	Observational	1/3/2021 to 1/8/2021 US.	10,428,783	Infection – Pre-Delta period		≥14 days: 74.7% (66.2-81.1%)
						Infection – Intermediate period		≥14 days: 70.4% (60.1-78.0%)
						Infection – Delta		≥14 days: 50.6% (45.0-55.7%)
		(256)	Observational	14/12/2020 to 14/8/2021 US.	Delta: 2,840 Pre-Delta: 7,012	Infection – Delta		14–119 days: 85% (68-93%)
								120–149 days: 81% (34-95%)
								≥150 days: 73% (49-86%)
						Infection – Pre-Delta		91% (81-96%)
					[NOTE: 33% of study participants received mRNA-1273 (2% received Ad26.COV2.S, and 65% received BNT162b2)]			
		(258)	Observational	1/12/2020 to 1/8/2021 UK.	384,543	Infection - Delta	75% (64-83%)	
		(259)	Observational	April to May 2021. Canada	124	Infection		52.5% (26.9-69.1%)
						Symptomatic infection		65.6% (33.8-82.1%)
						Severe infection		78.6% (47.9-91.2%)
		(272)	Retrospective cohort	1/1/2021 to 31/3/2021 US.	4,722	Infection	>14 days after first, ≤14 days after second: 91.2% (80.6-96.1%)	
								>14 days: 98.6% (90.1-99.8%)
		(273)	Prospective cohort	14/12/2020 to 10/4/2021 US.	3,975	Infection	≥14 days after first, <14 days after second: 83% (40-95%)	
								≥14 days: 82% (20-96%)
		(177)	Randomised controlled trial	27/7/2020 to 23/10/2020 US.	30,420	Infection		≥14 days: 94.1% (89.3-96.8%)
						Infection - ≥18 to <65 years of age		≥14 days: 95.6% (90.6-97.9%)
						Infection - ≥65 years of age		≥14 days: 86.4% (61.4-95.2%)
		(302)	Retrospective cohort	16/7/2021 to 15/8/2021 US.	827	Infection		≥14 days: 56.6% (42.0-67.5%)
						Symptomatic infection		≥14 days: 84.2% (56.4-94.3%)
		(303)	Retrospective cohort	22/12/2020 to 2/2/2021 US.	4,028	Infection	8-42 days: 77.5% (61.2-87%)	
							15-42 days: 95% (86-98.2%)	
		(304)	Test negative case-control	28/10/2020 to 10/5/2021 Qatar.	256,037	Infection – Alpha	0-6 days: 2.4% (0-21.7%)	0-6 days: 98.0% (94.7-99.5%)
							7-13 days: 0.0% (0.0-11.9%)	7-13 days: 99.2% (95.3-100.0%)
							14-20 days: 81.6% (73.1-87.8%)	
							21-27 days: 94.4% (89.1-97.5%)	
						Infection - Beta	0-6 days: 4.2% (0-15.1%)	0-6 days: 94.2% (92.1-95.9%)
							7-13 days: 0.0% (0.0-0.0%)	7-13 days: 96.4% (94.3-97.9%)
							14-20 days: 47.9% (39.5-55.2%)	
							21-27 days: 73.7% (67.6-78.8%)	
						Any severe, critical, or fatal infection	0-6 days: 18.7% (0-44.7%)	0-6 days: 100.0% (93.9-100.0%)
							7-13 days: 0.0% (0.0-10.1%)	7-13 days: 100.0% (86.9-100.0%)

							14-20 days: 70.3% (48.9-83.5%)	
							21-27 days: 92.1% (78.4-97.9%)	
		(305)	Retrospective cohort	27/4/2021 to 6/6/2021 US.	1,945	Symptomatic infection - Mesa County, US	(36% fully vaccinated) Crude vaccine effectiveness 78% (71-84%)	
						Symptomatic infection - Other Colorado counties, US	(44% fully vaccinated) Crude vaccine effectiveness 89% (88-91%)	
		(306)	Prospective cohort	18/12/2020 to 31/03/2021 US.	705,756	Infection		87.4% (85.6-89.1%
						Hospitalisation		95.8% (92.5-97.6%)
						Hospital death		97.9% (84.5-99.7%
		(307)	Test-negative case control	1/3/2021 to 27/7/2021 US.	8153 cases and matched controls.	Infection - Alpha	≥14 days: 90.1 (82.9 to 94.2)	≥14 days: 98.4 (96.9 to 99.1)
						Infection – Delta	≥14 days: 77.0% (60.7-86.5%)	≥14 days: 86.7% (84.3-88.7%)
						Infection – Epsilon	≥14 days: 76.3% (48.1-89.1%)	≥14 days: 97.6% (90.2-99.4%)
						Infection – Gamma	≥14 days: 74.2% (43.8-88.1%)	≥14 days: 95.5% (90.9-97.8%)
						Infection – Iota	≥14 days: 88.8% (0.7-98.7%)	≥14 days: 95.7% (81.7-99.0%)
						Infection – Mu	≥14 days: 45.8% (0.0-88.9%)	≥14 days: 90.4% (73.9-96.5%)
						Infection – Other	≥14 days: 84.3% (65.9-92.7%)	≥14 days: 96.4% (91.2-98.5%)
						Infection - Unidentified	≥14 days: 67.6% (57.1-75.6%)	≥14 days: 79.9% (76.9-82.5%)
		(278)	Test-negative case-control	January to March 2021 US.	1,843	Infection	≥14 days: 81.7% (74.3-86.9%)	≤2 days: 81.7% (74.3-86.9%)
								3-6 days: 81.7% (74.3-86.9%)
								≥7 days: 93.5% (86.5-96.9%)
					[NOTE: 24% of case-patients and 22% of controls received mRNA-1273, remainder received BNT162b2]			
		(282)	Prospective cohort	1/5/2021 to 3/9/2021 US.	8,690,825	Infection - 18-49 years old		≥14 days: 96.3% (95.4-97.2%)
						Infection - 50-64 years old		≥14 days: 97.3% (96.4-98.1%)
						Infection - ≤65 years old		≥14 days: 96.0% (95.1-96.9%)
						Hospitalisation - 18-49 years old		≥14 days: 96.6% (94.3-98.1%)
						Hospitalisation - 50-64 years old		≥14 days: 97.3% (95.9-98.2%)
						Hospitalisation - ≤65 years old		≥14 days: 97.1% (96.5-97.6%)
		(308)	Randomised controlled trial	27/7/2020 to 23/10/2020 US.	30,415	Asymptomatic infection		63.0% (56.6-68.5%)
						Symptomatic infection		93.2% (91.0-94.8%)
						Severe infection		98.2% (92.8-99.6%)
						Death		100.0% (NE-100.0%)
Sinopharm BBIBP-CorV - Aluminium-hydroxide-adjuvanted, inactivated whole virus vaccine	Two doses (0.5ml) intramuscularly (deltoid) with a recommended interval of 3 weeks between doses.	(309)	Test-negative case-control	18/5/2021 to 20/6/2021 China.	366	Infection	13.8% (-60.2-54.8%)	59.0% (16.0-81.6%)
						Moderately severe infection		70.2% (29.6-89.3%)
					[NOTE: 27.5% of study participants were vaccinated with Sinopharm BIBP (61.3% received CoronaVac)]			
		(310)	Retrospective cohort	May to June 2021 China.	10,813	Infection with Pneumonia – Delta	8.4% (-47.6-64.4%)	69.5% (42.8-96.3%)
						Severe/critical disease -Delta	100% (NA)	100% (NA)
		(311)	Retrospective cohort	9/2/2021 to 30/6/2021	606,772	Infection	≥14 days: 15·3 (12·7 to 17·8	≥14 days: 49·2 (47·9 to 50·4)
						COVID-19 mortality	≥14 days: 45.2% (28.8-57.8%)	≥14 days: 93.9% (90.9-95.9%)

				Peru.		Infection - ≥60 years old	≥14 days: 14.1% (5.2-22.2%)	≥14 days: 54.7% (50.7-58.3%)
						COVID-19 mortality - ≥60 years old	≥14 days: 25.5% (-10.2-49.7%)	≥14 days: 90.6% (83.8-94.5%)
		(312)	Randomised controlled trial	16/7/2020 to 20/12/2020 UAE, Bahrain.	40,382	Infection		≥14 days: 73.5% (60.6-82.2%)
						Symptomatic infection		≥14 days: 78.1% (64.8-86.3%)
						Severe infection		≥14 days: 100% (NA)
		(313)	Retrospective cohort	1/9/2020 to 1/5/2021 UAE.	176,640	Hospitalisation	-20% (-28.6-11.8%)	79.8% (78-81.4%)
						Critical care admission	3.7% (-12.8-18.1%)	92.2% (89.7-94.1%)
						Death	27.9% (-61-72.6%)	97.1% (83-99.9%)
		(314)	Observational	9/12/2020 to 17/7/2021 Bahrain.	569,054	Symptomatic infection		45.5%
						Hospitalisation		44.5%
						Hospitalisation - >50 years old		72%
						Death		63%
Sinovac-CoronaVac - Aluminium-hydroxide-adjuvanted, inactivated whole virus vaccine	Two doses (0.5ml) intramuscularly (deltoid) with a recommended interval window of 2 to 4 weeks.	(309)	Test-negative case-control	18/5/2021 to 20/6/2021 China.	366	Infection	13.8% (-60.2-54.8%)	59.0% (16.0-81.6%)
						Moderately severe infection		70.2% (29.6-89.3%)
					[NOTE: 61.3% of study participants were vaccinated with CoronaVac (27.5% recieved Sinopharm BIBP)]			
		(315)	Observational	2/2/2021 to 1/5/2021 Chile.	10,187, 720	Infection	17.2% (15.8–18.6%)	63.7% (62.8–64.6%)
						Hospitalisation	40.3% (37.6–42.8%)	86.5% (85.6–87.4%)
						Admission to an ICU	45.3% (41.2–49.2%)	90.2% (88.9–91.4%)
						Death	46.0% (40.7–50.8%)	86.7% (84.9–88.3%)
		(316)	Test-negative case-control	17/1/2021 to 29/4/2021 Brazil.	43,774	Symptomatic infection - Gamma	0-13 days: −0.8% (−9.4 to 7.2%)	0-13 days: 24.7% (14.7 to 33.4%)
							≥14 days: 12.5% (3.7 to 20.6%)	≥14 days: 46.8% (38.7 to 53.8%)
						Hospitalisation - Gamma	0-13 days: 6.6% (−4.3 to 16.3%)	0-13 days: 39.1% (28.0 to 48.5%)
							≥14 days: 16.9% (5.7 to 26.8%)	≥14 days: 55.5% (46.5 to 62.9%)
						Death - Gamma	0-13 days: 13.1% (−1.5 to 25.6%)	0-13 days: 48.9% (34.4 to 60.1%)
							≥14 days: 31.2% (17.6 to 42.5%)	≥14 days: 61.2% (48.9 to 70.5%)
		(317)	Test-negative case-control	19/1/2021 to 13/4/2021 Brazil.	53,153	Infection – Gamma	≥14 days: 49.4% 13.2-71.9%)	≥14 days: 37.1% (-53.3-74.2%)
						Infection	≥14 days: 35.1% (-6.6-60.5%)	37.9% (-46.4-73.6%)
		(115)	Prospective cohort	February to March 2021 Brazil.	20,187	Infection		≥14 days: 50.7% (33.3-62.5%)
								≥21 days: 51.8% (30-66.0%)
								≥28 days: 68.4% (51-80.8%)
								≥35 days: 73.8% (57-84.8%)
		(318)	Test-negative case-control	15/3/2021 to 3/10/2021 Brazil.	19,838	Symptomatic infection – Pregnant women	≥14 days: 5.02% (-18.22-23.69%)	≥14 days: 40.97% (27.07-52.22%)
						Severe infection – Pregnant women	≥14 days: 67.74% (20-87%)	≥14 days: 85.39% (59.44-94.80%)
		(319)			2,656	Symptomatic infection – Gamma	≥14 days: 49.6% (11.3-71.4%)	

			Test-negative case-control	19/1/2021 to 25/3/2021 Brazil.		Symptomatic infection	≥14 days: 35.1% (-6.6-60.5%)	
		(320)	Randomised controlled trial	14/9/2020 to 5/1/2021 Turkey.	10,029	Symptomatic infection	14-27 days: 46.4% (0.4-71.2%)	≥14 days: 83.5% (65.4-92.1%)
						Hospitalisation		≥14 days: 100% (20.4-100%)
		(321)	Randomised controlled trial	21/7/2020 to 16/12/2020 Brazil.	9,823	Infection	≤14 days: -3.3% (-4.8- -1.9%)	≥14 days: 50.7% (35.9-62%)
							14-28 days: 94.0% (55.1-99.2%)	
							≤28 days: 42.5% (32.9-50.7%)	
							≤42 days: 56.5% (49.6-62.5%)	
							≤56 days: 60.4% (56.5-63.9%)	
							≤70 days: 54.7% (53.2-56.1%)	
							≤84 days: 53.7% (52.7-54.7%)	
							≤98 days: 52.5% (51.9-53.1%)	
						Infection requiring medical assistance (hospitalisation)		≥14 days: 83.7% (58.0-93.7%)
						Moderate infection		≥14 days: 100% (56.4-100%)
						Severe infection or death		≥14 days: 100% (16.9-100%)
						Infection - <21 days between 2 doses		≥14 days: 49.1% (33-61.4%)
						Infection - ≥21 days between 2 doses		≥14 days: 62.3% (13.9-83.5%)
		(295)	Cohort	17/1/2021 to 11/5/2021 Brazil.	313,328	Death	≥21 days: 95.1% (94.7-95.5%)	≥21 days: 99.1% (98.9-99.3%)
						Death – 75-79 years old	≥21 days: 86.3% (84.7-87.7%)	
						Death – 80-89 years old	≥21 days: 97.6% (97.2-97.9%)	
						Death - ≥90 years old	≥21 days: 99.3% (99.1-99.5%)	
		(296)	Retrospective cohort	18/1/2021 to 30/6/2021 Brazil	60,577, 870	Infection	≥14 days: 16.4% (15.2-17.5%)	0-13 days: 40.3% (39.4-41.2%)
								≥14 days: 54.2% (53.4-55.0%)
						Hospitalisation	≥14 days: 26.6% (24.6-28.4%)	0-13 days: 57.3% (56.0-58.6%)
								≥14 days: 72.6% (71.6-73.6%)
						ICU admission	≥14 days: 28.1% (24.9-31.1%)	0-13 days: 58.1% (55.9-60.1%)
								≥14 days: 74.2% (72.6-75.7%)
						Death	≥14 days: 29.4% (26.7-32.0%)	0-13 days: 58.7% (56.9-60.4%)
								≥14 days: 74% (72.6-75.3%)
Bharat Biotech – Covaxin – whole virion inactivated virus vaccine	Two doses (0.5ml) intramuscularly (deltoid) with a recommended interval window of 28 days.	(322)	Randomised controlled trial	16/11/2020 to 7/1/2021 India.	25 798	Symptomatic infection		≥14 days: 77.8% (65.2-86.4%)
						Severe disease		≥14 days: 93.4% (57.1-99.8%)
						Symptomatic infection – 18-59 years old		≥14 days: 79.4% (66.0-88.2%)
						Symptomatic infection - ≥60 years old		≥14 days: 67.8% (8.0-90.0%)
						Symptomatic infection – participants with pre-existing chronic medical condition		≥14 days: 66.2% (33.8-84.0%)
						Asymptomatic infection		≥14 days: 63.6% (29.0-82.4%)

						Symptomatic or asymptomatic infection		≥14 days: 68.8% (46.7-82.5%)
		(323)	Test-negative case-control	15/4/2021 to 15/5/2021 India.	3,732	Symptomatic infection	<7 days: 40% (-21-71%)	<14 days: 27% (-35-61%)
							≥7 days: 1% (-30-25%)	≥14 days: 50% (33-62%)
							≥21 days: –1% (-51-33%)	≥28 days: 46% (22-62%)
								≥42 days: 57% (21-76%)
		(293)	Cross-sectional observational	1/5/2021 to 31/5/2021 India.	583	Infection	<14 days: 15% (-68-57%)	<14 days: 66% (34-81%)
							≥14 days: 44% (7-66%)	≥14 days: 83% (73-89%)
						Hospitalisation	<14 days: 43% (-68-81%)	<14 days: 83% (17-96%)
							≥14 days: 76% (21-92%)	≥14 days: 88% (55-97%)
						ICU admission or death	<14 days: 62% (-27-89%)	<14 days: 93% (35-99%)
							≥14 days: 53% 9-29-83%)	≥14 days: 93% (64-99%)
					[NOTE: Participants either received Covaxin or Covishield (AZD1222)]			
		(294)	Retrospective cohort	1/6/2020 to 31/5/2021 India.	11,405	Infection (with evidence of prior infection)		≥14 days: 91.1% (84.1-94.9%)
						Infection (without evidence of prior infection)		≥14 days: 31.8% (23.5-39.1%)
					[NOTE: 5.77% of participants received Covaxin, 94.23% received Covishield (AZD1222)]			
		(324)	Retrospective cohort	3/3/2020 to 18/6/2021 India.	15,244	Reinfection		86% (77-92%)
						Symptomatic reinfection		87% (76-93%)
						Asymptomatic reinfection		84% (47-95%)
Novavax – NVX-CoV2373 (Nuvaxovid) or Serum Institute of India – COVOVAX (Novavax formulation - recombinant SARS-CoV-2 S protein nanoparticle as a coformulation with the adjuvant Matrix-M	Two doses (0.5 ml) intramuscularly (deltoid) with a recommended interval of 3-4 weeks.	(325)	Randomised controlled trial	28/9/2020 to 28/10/2020 UK.	14,039	Infection		89.7% (80.2-94.6%)
						Infection – 18 to 64 years old		89.8% (79.7-95.5%)
						Infection – 65 to 84 years old		88.9% (20.2-99.7%)
						Infection – Alpha		86.3% (71.3-93.5%)
						Infection – Non-Alpha		96.4% (73.8-99.5%)
		(326)	Randomised controlled trial	27/12.2020 to 18/2/2021 US, Mexico.	29,949	Infection		≥7 days: 89.3% (81.6-93.8%)
						Infection – COVID-19 high risk group		≥7 days: 91.0% (83.6-95.0%)
		(327)	Randomised controlled trial	28/9/2020 to 28/10/2020 UK.	15,139	Infection		89.8% (79.7-95.5%)
						Infection – 18-64 years old		87.5% (–0.2-98.4%)
		(328)	Randomised controlled trial	17/7/2020 to 25/11/2020 South Africa.	2,684	Symptomatic infection		≥7 days: 49.4% (6.1-72.8%)
						Symptomatic infection – Beta		≥7 days: 51.0% (-0.6-76.2%)

Vaccine type	Vaccine	Company	Countries approved for use in	Clinical trials
Inactivated virus	**KoviVac**	Chumakov Center (Moscow, Russia)	***3 countries:*** Belarus, Cambodia, Russian Federation	Phase 1: 502 (Russian Federation). Phase 2: 502 (Russian Federation). 622 (Russian Federation).
	QazVac	Kazakhstan Research Institute for Biological Safety Problems (RIBSP) (Kazakhstan)	***2 countries:*** Kazakhstan, Kyrgyzstan	Phase 1: NCT04530357 (Kazakhstan). Phase 2: NCT04530357 (Kazakhstan). Phase 3: NCT04691908 (Kazakhstan).
	KCONVAC	Minhai Biotechnology Co. (Beijing, China)	***2 countries:*** China, Indonesia	Phase 1: NCT05003479 (China). ChiCTR2000038804, NCT04758273 (China). Phase 2: ChiCTR2000039462, NCT04756323 (China). NCT05003466 (China). Phase 3: NCT04852705
	COVIran Barekat	Shifa Pharmed Industrial Co. (Tehran, Iran)	***1 country:*** Iran	Phase 1: IRCT20201202049567N1 (Iran). IRCT20201202049567N2 (Iran). IRCT20171122037571N3 (Iran). Phase 2: IRCT20201202049567N3 (Iran). IRCT20171122037571N3 (Iran). Phase 3: IRCT20201202049567N3 (Iran).
	Inactivated (Vero Cells)	Sinopharm (Wuhan, China)	***2 countries:*** China, Philippines	Phase 1: ChiCTR2000031809 (China) Phase 2: NCT04885764 (Egypt). ChiCTR2000031809 (China). Phase 3: NCT04885764 (Egypt). ChiCTR2000034780 (United Arab Emirates). NCT04612972 (Peru). NCT04510207 (Bahrain, Egypt, Jordan, United Arab Emirates). ChiCTR2000039000 (Morocco).
	Turkovac	Health Institutes of Turkey (Istanbul, Turkey)	***1 country:*** Turkey	Phase 1: NCT04691947 (Turkey). Phase 2: NCT04824391 (Turkey). NCT04979949 (Turkey). NCT05035238 (Turkey). Phase 3: NCT04942405 (Turkey). NCT05077176 (Turkey).
	FAKHRAVAC (MIVAC)	Organization of Defensive Innovation and Research (Tehran, Iran)	***1 country:*** Iran	Phase 1: IRCT20210206050259N1 (Iran). Phase 2: IRCT20210206050259N2 (Iran). Phase 3: IRCT20210206050259N3 (Iran).
Non-replicating viral vector	**Convidecia**	CanSino (Tianjin, China)	***10 countries:*** Argentina, Chile, China, Ecuador, Hungary, Indonesia, Malaysia, Mexico, Pakistan, Republic of Moldova	Phase 1: NCT05043259 (China). ChiCTR2000030906, NCT04313127 (China). NCT04568811 (China). NCT04840992 (China). Phase 2: NCT05043259 (China). NCT05162482 (Pakistan). NCT04840992 (China). ChiCTR2000031781, NCT04341389 (China). NCT04566770 (China). NCT05005156 (Argentina). Phase 3: NCT05169008 (Chile, Mexico). NCT04526990 (Argentina, Chile, Mexico, Pakistan, Russian Federation). NCT04540419 (Russian Federation).
	Sputnik Light	Gamaleya Research Institute of Epidemiology and	***24 countries:*** Angola, Argentina, Armenia, Bahrain, Belarus, Cambodia, Egypt, Iran, Kazakhstan,	Phase 1: NCT04713488 (Russian Federation). Phase 2: NCT04713488 (Russian Federation).

		Microbiology (Moscow, Russia)	Kyrgyzstan, Lao People's Democratic Republic, Mauritius, Mongolia, Nicaragua, Philippines, Republic of the Congo, Russian Federation, San Marino, Tunisia, Turkmenistan, United Arab Emirates, United Republic of Tanzania, Venezuela, West Bank	NCT05027672 (Argentina). Phase 3: NCT04741061 (Russian Federation).
	Sputnik V	Gamaleya Research Institute of Epidemiology and Microbiology (Moscow, Russia)	***74 countries:*** Albania, Algeria, Angola, Antigua and Barbuda, Argentina, Armenia, Azerbaijan, Bahrain, Bangladesh, Belarus, Bolivia, Bosnia and Herzegovina, Brazil, Cambodia, Cameroon, Chile, Djibouti, Ecuador, Egypt, Gabon, Ghana, Guatemala, Guinea, Guyana, Honduras, Hungary, India, Indonesia, Iran, Iraq, Jordan, Kazakhstan, Kenya, Kyrgyzstan, Lao People's Democratic Republic, Lebanon, Libya, Maldives, Mali, Mauritius, Mexico, Mongolia, Montenegro, Morocco, Myanmar, Namibia, Nepal, Nicaragua, Nigeria, North Macedonia, Oman, Pakistan, Panama, Paraguay, Philippines, Republic of Moldova, Republic of the Congo, Russian Federation, Rwanda, Saint Vincent and the Grenadines, San Marino, Serbia, Seychelles, Sri Lanka, Syrian Arab Republic, Tunisia, Turkey, Turkmenistan, United Arab Emirates, Uzbekistan, Venezuela, Vietnam, West Bank, Zimbabwe	Phase 1: NCT04760730 (United Arab Emirates). NCT04684446 (Belarus, Russian Federation). NCT04436471, 241 (Russian Federation). NCT04437875 (Russian Federation). Phase 2: NCT05027672 (Argentina). NCT04988048 (Argentina). NCT04954092 (Russian Federation). NCT04962906 (Argentina). NCT04983537 (Argentina). NCT04760730 (United Arab Emirates). NCT04684446 (Belarus, Russian Federation). NCT04686773 (Azerbaijan). NCT04436471, 241 (Russian Federation). NCT04437875 (Russian Federation). NCT04587219 (Russian Federation). NCT04640233 (India). Phase 3: NCT04564716 (Belarus). NCT04530396 (Russian Federation). NCT04642339 (Venezuela). NCT04656613 (United Arab Emirates). NCT04954092 (Russian Federation). NCT04640233 (India).
RNA	**TAK-919 (Moderna formulation)**	Takeda (Tokyo, Japan)	***1 country:*** Japan	Phase 1: NCT04677660 (Japan). Phase 2: NCT04677660 (Japan).
DNA	**ZyCoV-D**	Zydus Cadila (Ahmedabad, India)	***1 country:*** India	Phase 1: CTRI/2020/07/026352 (India). CTRI/2021/03/032051 (India). Phase 2: CTRI/2020/07/026352 (India). CTRI/2021/03/032051 (India). Phase 3: CTRI/2021/01/030416 (India).
Protein subunit	**ZF2001**	Anhui Zhifei Longcom (Hefei, China)	***3 countries:*** China, Indonesia, Uzbekistan	Phase 1: NCT04445194 (China). NCT04636333 (China). NCT04550351, ChiCTR2000035691 (China). NCT04961359 (China). Phase 2: NCT04466085 (China). NCT05109598 (China). NCT04813562 (China). Phase 3: NCT05091411 (China). NCT05128643 (China). NCT05107375 (China). ChiCTR2000040153, NCT04646590 (China, Ecuador, Indonesia, Pakistan, Uzbekistan). ChiCTR2100050849 (China).
	Abdala	Center for Genetic Engineering and Biotechnology (CIGB) (Havana, Cuba)	***6 countries:*** Cuba, Mexico, Nicaragua, Saint Vincent and the Grenadines, Venezuela, Vietnam	Phase 1: RPCEC00000345 (Cuba). RPCEC00000346 (Cuba). Phase 2: RPCEC00000345 (Cuba) RPCEC00000346 (Cuba).

				Phase 3: RPCEC00000359 (Cuba).
	EpiVacCorona	FBRI (Koltsovo, Russia)	***4 countries:*** Cambodia, Russian Federation, Turkmenistan, Venezuela	Phase 1: NCT04527575 (Russian Federation). Phase 2: NCT04527575 (Russian Federation). Phase 3: NCT04780035 (Russian Federation). NCT05021016 (Russian Federation)
	Aurora-CoV	FBRI (Koltsovo, Russia)	***1 country:*** Russian Federation	Phase 1: 197 (Russian Federation). Phase 2: 197 (Russian Federation).
	MVC-COV1901	Medigen Biotechnology Corp. (Taipei City, Taiwan)	***2 countries:*** Somaliland, Taiwan	Phase 1: NCT05132855 (Taiwan). NCT04487210 (Taiwan). Phase 2: NCT05132855 (Taiwan). NCT04695652 (Taiwan, Vietnam). NCT04822025 (Taiwan). NCT04951388 (Taiwan). NCT05038618 (Taiwan). NCT05048849 (Taiwan). NCT05054621 (Taiwan). Phase 3: NCT05011526 (Paraguay)
	SpikoGen	Vaxine/CinnaGen Co. (Iran)	***1 country:*** Iran	Phase 1: NCT04453852 (Australia). Phase 2: IRCT20150303021315N23 (Iran). NCT04944368, IRCT20150303021315N23 (Iran). NCT05148871 (Australia). Phase 3: NCT05005559, IRCT20150303021315N24 (Iran). NCT05148871 (Australia). NCT05175625, IRCT20150303021315N26 (Iran).
	Corbevax	Biological E Limited (Telangana, India)	***1 country:*** India	Phase 1: CTRI/2020/11/029032 (India). Phase 2: CTRI/2020/11/029032 (India). CTRI/2021/06/034014 (India). CTRI/2021/10/037066 (India). Phase 3: CTRI/2021/06/034014 (India). CTRI/2021/08/036074 (India). CTRI/2021/10/037066 (India).
	Soberana 02	Instituto Finlay de Vacunas Cuba (Havana, Cuba)	***4 countries:*** Cuba, Iran, Nicaragua, Venezuela	Phase 1: IFV/COR/06 (Cuba). Phase 2: IFV/COR/08 (Cuba). Phase 3: IFV/COR/09 (Cuba).
	Soberana Plus	Instituto Finlay de Vacunas Cuba (Havana, Cuba)	***1 country:*** Cuba	Phase 1: IFV/COR/15 (Cuba). IFV/COR/05 (Cuba). Phase 2: IFV/COR/11 (Cuba). IFV/COR/15 (Cuba). Phase 3: IFV/COR/09 (Cuba).
	Razi Cov Pars	Razi Vaccine and Serum Research Institute (Karaj, Iran)	***1 country:*** Iran	Phase 1: IRCT20201214049709N1 (Iran). Phase 2: IRCT20201214049709N2 (Iran). Phase 3: IRCT20201214049709N3 (Iran).
	Recombinant SARS-CoV-2 Vaccine (CHO Cell)	National Vaccine and Serum Institute (Beijing, China)	***1 country:*** United Arab Emirates	Phase 1: NCT04869592 (China). Phase 2: NCT04869592 (China) Phase 3: NCT05069129 (United Arab Emirates)

Supplementary file 1:

1a: Specific database search terms:

"transmission", "host cell entry", "clinical presentation", "symptoms", "risk factors", "genetic risk", "coronavirus", "structure", "genetics", "replication", open reading frame", "structural proteins", "accessory proteins", "spike", "receptor binding domain", "mutation", "variant of concern", "variant of interest", "alpha", "beta", "gamma", "delta", "omicron", "lambda", "mu", "pfizer", "BNT162b2", "oxford-AtraZeneca", "AZD1222", "ChAdOx1", "johnson and johnson", "janssen", "Ad26.COV.2.S", "moderna", "mrna-1273", "sinopharm", "BBIBP-CorV", "sinovac", "CoronaVac", "bharat biotech", "Covaxin", "BBV152", "Novavax", " Coalition for Epidemic Preparedness Innovations", "Covovax", "Nuvaxovid", "NVX-CoV2372", "immunogenicity" "antibody", "neutralisation", "reactogenicity", "safety", "adverse events", "effectiveness", "efficacy", "immunity", "booster", "treatment", "therapy", "guideline", "recommendations".

1b: Selection of studies (inclusion/exclusion criteria):

Virology studies – preference was given to studies directly examining/discussing SARS-CoV-2, however, useful papers that explored the structure, genetics, and virology of coronaviruses in general were considered.

Variant studies – in general, large epidemiological studies that explored the prevalence and risk of certain outcomes (e.g. hospitalisation, death, etc.) with COVID-19 infection for certain variants were included. Authors aimed to include studies from multiple countries.

Vaccine studies – Studies with human derived data (e.g. blood sera, phase 1/2 trials) were of greatest interest when collating information on immunogenicity, reactogenicity, and safety. Large randomised controlled trials, test-negative case-control, and observational studies were of selected when exploring vaccine efficacy. Review articles summarising effectiveness studies were excluded, unless a meta-analysis was performed.

bmjmedicine

COVID-19: Virology, variants, and vaccines

Journal:	*BMJ Medicine*
Manuscript ID	bmjmed-2021-000040.R2
Article Type:	Specialist review
Date Submitted by the Author:	24-Feb-2022
Complete List of Authors:	Young, Megan; Imperial College London, Faculty of Medicine Crook, Harry; Imperial College London, Faculty of Medicine Scott, Janet; University of Glasgow, Centre for Virus Research Edison, Paul; Imperial College London, Faculty of Medicine; Cardiff University, School of Medicine
Keywords:	Covid-19, COVID-19, Virology

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COVID-19: Virology, variants, and vaccinations

Keywords: Covid-19, Coronavirus, Virology, SARS-CoV-2 variants, Vaccines.

Megan Young[1†], Harry Crook[1†], Janet Scott[2], Paul Edison[1,3,*]

[1] Faculty of Medicine, Imperial College London, London, UK.
[2] Medical Research Council-University of Glasgow Centre for Virus Research, University of Glasgow, UK
[3] School of Medicine, Cardiff University, Cardiff, UK.

† Both authors contributed equally to the manuscript

*Corresponding author:
Dr Paul Edison, MD, MRCP, PhD, FRCP, FRCPI,
Clinical Senior Lecturer, Imperial College London and Honorary Professor, Cardiff University, UK
Division of Neurology, Faculty of Medicine, Imperial College London
Level 2, Commonwealth Building,
Hammersmith Campus, Imperial College London,
Du Cane Road, London, W12 0NN, UK

Tel: +442075941081
E-mail: paul.edison@imperial.ac.uk

No authors have any competing interests.

Abstract

As of 25th January 2022, there have been over 349 million confirmed cases of COVID-19, with over 5.59 million confirmed deaths associated with the SARS-CoV-2 virus. The COVID-19 pandemic has prompted an extensive, global effort to study the molecular evolution of the virus and develop vaccines to combat its spread. Although rigorous determination of SARS-CoV-2 infectivity remains elusive, due to the continuous evolution of the virus, steps have been made to understand its genome, structure, and emerging genetic mutations. The SARS-CoV-2 genome is composed of several open reading frames (ORFs) and structural proteins, including the spike protein, which is essential for entry into host cells. As of 25th January 2022, the WHO reports five variants of concern (VOC) two variants of interest (VOI) and three variants under monitoring (VUM). The mutations harboured in these variants confer an increased transmissibility, severity of disease, and escape from neutralising antibodies compared to the primary strain. The current vaccine strategy, including booster doses, provides protection from severe disease. As of 24th January 2022, there are 33 approved vaccines in use in 197 countries. In this review, we discuss the genetics, structure and transmission methods of SARS-CoV-2 and its variants, highlighting how mutations provide enhanced abilities to spread and inflict disease. We also outline the vaccines currently in use around the world, providing evidence for the immunogenicity and effectiveness of each.

Introduction

There are seven coronaviruses that infect humans, all belonging to either alpha- or beta-coronavirus subgroups, including 229E (alpha), NL63 (alpha), OC43 (beta), and HKU1 (beta)(1). Over the last two decades, three notable beta-coronaviruses, severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002, Middle East respiratory syndrome coronavirus (MERS-CoV) in 2011, and most recently, severe acute respiratory syndrome 2 (SARS-CoV-2) in 2019, have emerged and caused severe illness resulting in debilitating disease and worldwide fatalities. SARS-CoV-2 is the pathogen responsible for the current Coronavirus 2019 (COVID-19) pandemic and has caused more than 5.59 million deaths in approximately two years and resulted in multisystem illness in several million people(2).

All viruses change and mutate over time, with most changes having little to no impact. However, some mutations may alter its pathogenic or transmission potential and could, therefore, increase disease severity or hinder the effectiveness of vaccines and therapeutic strategies. The World Health Organisation (WHO) (3) classify SARS-CoV-2 variants that increase transmissibility, disease severity or virulence, or decrease the effectiveness of public health measures, diagnostics, therapeutics, or vaccines as variants of concern (VOC). Variants with genetic changes that are predicted to enhance the virulence and transmissibility of the virus which have been identified to cause community transmission in multiple countries posing a possible risk to global public health are defined as variants of interest (VOI). Lastly, the WHO defines variants with genetic changes that are suspected to affect virus characteristics and have currently unclear phenotypic or epidemiological effects as variants under monitoring (VUM). VUM are not typically assigned a name until they are upgraded to VOI or VOC. The full working definitions of VOC, VOI and VUM can be found on the WHO 'tracking SARS-CoV-2 variants' website: www.who.int/en/activities/tracking-SARS-CoV-2-variants/(3). As of 25th January 2022, the WHO reports five VOC; Alpha, Beta, Gamma, Delta and Omicron, two VOI;

Lambda and Mu, and three VUM(3). Former VOC/VOI/VUM have been reclassified as 'formerly monitored variants' due to them either no longer circulating, having little impact on the epidemiological situation, or having no concerning properties(3). Since the beginning of the COVID-19 pandemic, the rapid development of effective COVID-19 vaccines has taken place around the world. As of 24th January 2022, there are 33 approved vaccines in use in 197 countries, with ten vaccines having gained emergency use listing approval from the WHO(4).

In this review, we provide an overview of the genome and structure of SARS-CoV-2, describing how these elements allow the virus to infect and replicate inside of host cells, before outlining how certain mutations harboured by SARS-CoV-2 variants enhance these abilities. Next, we examine the current state of vaccine development around the world and provide evidence of the effectiveness of booster doses.

Methods

We searched PubMed and Embase databases for COVID-19-related articles published between 1st January 2020 and 25th January 2022 and for general coronavirus-related articles published from 1st January 2000 onwards. Our search terms included SARS-CoV-2, COVID-19, and specific terms including virology, genome, variants, and vaccine. Additional, specific search terms are outlined in supplementary file 1. We performed further manual searching for additional articles and data using relevant databases, including who.int, gov.uk, and ecdc.europa.eu/en. Due to the rapidly evolving nature of the literature involving SARS-CoV-2, we also searched preprint databases including MedRxiv and BioRxiv. Due to the various topics addressed here, studies were selected through different criteria, details of which can be found in supplementary file 1. Overall, studies were selected based on quality and impact factor of publishing journal, with real-world studies with large sample sizes of greatest interest.

Viral transmission, clinical presentation, and genetic susceptibility of COVID-19

SARS-CoV-2 is predominantly spread via respiratory droplet transmission, spreading between people through close contact, coughing, or sneezing. It has been documented that the virus can also spread through airborne transmission, fomite transmission, and via other modes, such as through biological material including urine and faeces, and through (5, 6). The SARS-CoV-2 virus may survive on surfaces or suspended in air droplets for long periods of time. Indeed, on plastic, stainless steel, and glass surfaces, the half-life of the virus is around 5.3, 4.4, and 4.2 hours, respectively(7), with no difference seen between SARS-CoV-2 variants(8). Although SARS-CoV-2 can be detected on inanimate surfaces for hours and days, due to the evaporation of water droplets, the viruses' living environment, the concentration of the virus plummets rapidly(9). Protective measures, including using personal protective equipment (PPE), maintaining indoor ventilation, and disinfecting hands and surfaces, can effectively limit the spread of SARS-CoV-2(10).

Once inside the airways, SARS-CoV-2 can directly or indirectly infect ciliated, mucus-secreting, and club cells of bronchial epithelium, type 1 pneumocytes within the lungs, and the conjunctival mucosa(11). The clinical presentation of COVID-19 is non-specific, heterogeneous, and infection can result in a wide spectrum of symptoms. Following an incubation period of 4-14 days, symptoms develop ranging from mild to severe disease and, in some cases, can result in death(12). The most common COVID-19 symptoms include fever,

cough, dyspnoea, and fatigue(13, 14), while myalgia, gastrointestinal issues, cognitive deficits, and other symptoms are reported. Asymptomatic individuals can also test positive for COVID-19(15, 16). Although the entire population is susceptible to COVID-19 infection, some subgroups within the general population exist that are more susceptible to developing poorer clinical outcomes.

Risk factors associated with increased risk of hospitalisation, severe disease, and fatal outcome with COVID-19 have been identified. Older age(17-19), male sex(20, 21), non-white ethnicity(21, 22), comorbidities including diabetes, hypertension, and lung disease(18, 23-25), malignancy and immunodeficiency(26-28) have all been associated with more severe COVID-19. The duration of symptoms endured by COVID-19 patients, as well as the treatment they receive will also have profound influences on the severity of disease they experience and both the acute and long-term outcomes following recovery. The host genetic background is thought to have an influence on the susceptibility and severity of COVID-19, possibly explaining the broad spectrum of clinical manifestations that can develop in seemingly similar individuals. A study examining individuals with COVID-19 across numerous ancestry groups identified four gene loci associated with susceptibility to COVID-19; SLC6A20, RPL24, ABO, PLEKHA4, and nine associated with increased risk of severe COVID-19; LZTFL1, FOXP4, TMEM65, OAS1, KANSL1, TAC4, DPP9, RAVER1, and IFNAR2(29). Meanwhile, genome-wide association studies spanning across Europe, the United States (US), and the United Kingdom (UK) identified a gene cluster on chromosome three (chr3p21.31) as being strongly linked with susceptibility and severity of COVID-19(30, 31). Polymorphisms in the angiotensin-converting enzyme 2 (ACE2) receptor and transmembrane protease serine 2 (TMPRSS2) have also been shown to enhance SARS-CoV-2 viral entry(32, 33), with differential polymorphisms seen across ethnic populations, which may partly explain why certain ethnic groups are more susceptible to severe COVID-19. Increased ACE2 receptor levels have also been associated with other risk factors of COVID-19 including smoking and increasing age(34). The use of polygenetic risk scores (PRS) may be useful in determining an individual's risk for developing severe disease caused by COVID-19(35). A PRS infers a person's risk of susceptibility to, or development of a certain disease based on the total number of genomic variations they possess. Determining PRS with the inclusion of comorbidities, such as chronic obstructive pulmonary disease(36), or other aspects, such as coagulation factors(37), may improve the usefulness of PRS in determining a person's risk of severe COVID-19.

Virology of SARS-CoV-2

SARS-CoV-2 is a positive-stranded ribonucleic acid (RNA) virus belonging to Coronaviridae family. Coronaviruses, which have crownlike appearances, are the largest known RNA viruses and are thought to primarily infect vertebrates(38, 39). SARS-CoV-2 belongs to the beta genus of the coronaviruses and has a genome varying from 29.8kb to 29.9kb in size(40). Human coronaviruses (HCoV) genomes consist of a variable number of open reading frames (ORFs). Following the typical 5'-3' order, the beginning two-thirds of the SARS-CoV-2 genome contains two ORFs, ORF1a and ORF1b which, inside the host cell, are translated at the rough endoplasmic reticulum into polyprotein 1a (pp1a) and polyprotein 1ab (pp1ab), respectively(40). These polyproteins are cleaved into 16 non-structural proteins (nsp); nsp1-11, from pp1a and nsp12-16, from pp1ab. The proteolytic release of nsp1 occurs rapidly,

which enables it to interfere with translation processes of the host cell by inducing cellular mRNA degradation(41-43). Nsp2-16 contain the viruses' replication and transcription complex (RTC) and encode multiple enzymes with many functions including, proteases, helicase, polymerase, exo- and endo-nuclease, N7- and 2'O-methyltransferases, and de-ubiquitination enzymes(44, 45). The final third of HCoV genomes contain genes that encode structural and accessory proteins. The four major structural proteins encoded here are the nucleocapsid (N), membrane (M), envelope (E), and spike glycoprotein (S) proteins(46, 47). The N protein is associated with the viral RNA genome and is involved in RNA synthesis regulation and interacts with the M protein during viral budding(39, 48). The M protein is important for viral assembly, it contains a short N-terminal domain that projects onto the external surface of the envelope and a long internal C terminus(39). The E protein function is largely unknown; however, along with the N and M proteins, it is required for viral assembly and release(47) . Lastly, the S protein gives coronaviruses their characteristic spikes that compose their crownlike appearance. This protein projects through the viral envelope, is heavily glycosylated, and regulates host cell membrane receptor binding and fusion of the viral and cellular membrane(49). The functions of the eleven accessory proteins encoded within the one-third closest to the 3' end of the SARS-CoV-2 genome are not fully understood. These accessory proteins are encoded by the ORF3a, ORF3b, ORF3c, ORF3d, ORF6, ORF7a, ORF7b, ORF8, ORF9b, ORC9c, and ORF10 genes. Some of these proteins, including ORF3b, ORF6, ORF7a and ORF8 are interferon antagonists which impair the host cell immune response(50-53), while ORF3a may promote virus release(54) and is involved in apoptosis of host cells through caspase-3 activation(55). ORF9b and ORF9c are known to supress the host antiviral response by interacting with host cell organelles(56-58), while a clear understanding of the functions of ORF3c, ORF7b, and ORF10 remains elusive(59). ***Figure 1*** (A and B) depicts the genome and structure of SARS-CoV-2.

The S glycoprotein is composed of two functionally distinct subunits (S1 and S2) and is essential for viral entry into host cells. The N-terminal S1 domain of the protein contains the receptor-binding domain (RBD) that directly interacts with the ACE2 receptor on the host cell, the primary receptor that SARS-Cov-2 utilises for cell entry(60). The C-terminal S2 domain fuses the host and viral membranes to allow for entry of the viral genome into the host cell(61). The subunits of the trimeric S complex are either in a closed (pre-fusion stage) or open (post-fusion stage) conformation(62), with one subunit always in an open conformation to allow for ACE2 recognition and binding(63). The RBD itself consists of five anti-parallel β-strands surrounded by several α-helices(64). From closed to open conformation, the RBD undergoes structural rearrangement whereby the globular head region rotates clockwise, which alters is elecropotential surface(64). Once positioned, numerous residues within the RBD form either hydrogen bonds or salt bridges with residues of the ACE2 receptor, allowing for tight binding(65), while the concave structure of the RBD allows for three distinct binding regions(64). Following binding between the S protein and the host cell receptor, host cell proteases cleave the S protein, causing the release of the S2 domain which allows for fusion and cell entry(66). ***Figure 1*** (C and D) demonstrate the structure and function of the S protein.

The ACE2 receptor is expressed in numerous cell types throughout the human body, including in the lungs, oral and nasal mucosa, heart, gastrointestinal tract, kidneys, liver, spleen, and brain(67), highlighting the widespread infection that SARS-CoV-2 can inflict.

Meanwhile, TMPRSS2, a host cell protease, facilitates fusion of the viral and host cell membranes(68), and may play a role in the spread of the virus in the airways(68). Host cell cathepsin L may also aid in SARS-CoV-2 cell entry by cleaving the S protein(69). Indeed, a clinically approved protease inhibitor has been shown to block SARS-CoV-2 cell entry(70). ***Figure 2*** depicts the mechanism by which SARS-CoV-2 gains entry into and replicates inside host cells, and summarises the host cell immune response.

Variants of SARS-CoV-2

Most viral mutations have a limited impact on the viruses' ability to infect, replicate, escape host immunity, and transmit, however, certain mutations may give a viral strain a competitive advantage and, through natural selection, give it the ability to become dominant. Many of the mutations observed in SARS-CoV-2 variants are found within the RBD or the N-terminal domain of the S protein, which alters the three-dimensional structure of the S protein. Not only can these changes affect the transmission abilities of the virus but can also allow it to better escape the immune response, including from neutralising antibodies either elicited through vaccine administration or natural infection.

The SARS-CoV-2 virus has mutated numerous times, with estimates suggesting that circulating lineages acquire nucleotide mutations at rates of around one to two mutations per month(71). The current method of identifying variants relies on the use of genomic testing such as whole genome sequencing, partial S-gene sequencing, or nucleic acid amplification technique (NAAT)-based assays(72). The aspects of different variants that most people experience, however, is the clinical symptoms they inflict. Certain variants induce a greater risk of severe disease and death, such as Alpha and Delta(73), while others are more likely to induce milder symptoms, such as Omicron(74, 75). Moreover, individual symptoms can differ between variants. For example, the Gamma variant is associated inflicting anosmia and dysgeusia(76), which is less commonly seen in Omicron infections. Moving forward, the clinical themes and symptoms associated with emerging variants should be elucidated rapidly so that the public and healthcare professionals can rapidly identify possible cases of COVID-19.

The WHO have tracked and monitored SARS-CoV-2 variants since the COVID-19 pandemic began to identify VOCs. As of 25th January 2022, the WHO reports five VOC, two VOI, and three VUM(3) (***Table 1***). Herein, we report studies that compare SARS-CoV-2 variants to the 'primary' virus strain. 'Primary strain' refers to the strain of the virus that first emerged in Wuhan, China at the end of 2019 and spread around the world in the first wave of infections, which is often also referred to as the Wuhan-Hu-1, B.1, or wild-type strain.

Variants of concern

Alpha

The Alpha SARS-CoV-2 variant, of the B.1.1.7 lineage, was first documented in the UK in September 2020 and classified as a VOC on 18th December 2020(3, 77). This variant contains S protein mutations which have potential biological effects. Firstly, the S protein residue 501, a key contact residue within the RBD, forms a portion of the binding loop in the contact region of the ACE2 receptor, forms a hydrogen bond with the Y41 residue of the ACE2 receptor, and stabilises the ACE2 K353 residue(65, 78, 79). Alpha harbours an N501Y

mutation which increases the binding affinity of the RBD to the ACE2 receptor(80). Next, the P681H mutation contained within the Alpha variant is located immediately adjacent to the 682-685 furin cleavage site, at the interface of the S1 and S2 domains(81). The S1/S2 furin cleavage site prompts entry into respiratory epithelial cells and partly determines the transmissibility of the virus(82-84), while the P681H mutation makes the furin cleavage site less acidic, meaning it is more effectively recognised and cleaved(85, 86). Alpha also contains a D614G mutation, located within the S1/S2 furin cleavage site, which increases SARS-CoV-2 binding affinity to the ACE2 receptor and increases infectivity(87). Other mutations harboured within the Alpha variant enhance the ability of the virus to escape antibody detection, such as the two amino acid deletion at the sites 69-70 in the N-terminal domain of the S protein(88, 89), while other mutations demonstrate limited or no effects(90). In February 2021, viruses of the B.1.1.7 lineage with the added S protein mutation E484K were identified, which may have threatened vaccine effectiveness due to the mutation conferring an increased resistance to neutralising vaccine-elicited and monoclonal antibodies(91). This mutation had limited effects, however, and variants containing it failed to dominate.

Epidemiological studies explored the Alpha variant, with a case-control study of 27,633 respiratory samples originating from 20 primary care centres in Madrid, Spain, finding that the probability of admission to an intensive care unit (ICU) was twice as high in patients infected with the Alpha variant compared to those infected with the primary strain(92). Furthermore, this variant became the dominant strain within four months, and led to an increase in disease burden as a result(92).

Meanwhile in Cannes, France, infection with the Alpha variant was associated with a 3.8-fold higher risk of transfer to an ICU or death compared to the primary strain, as determined through a retrospective cohort study of 158 COVID-19 patients(93). A large retrospective cohort study found that, during the third COVID-19 wave in Canada, where 91% of infections were caused by the Alpha variant, the risk of both hospitalisation (adjusted odds ratio (aOR)=1.57) and death (aOR=1.52) was higher compared to primary strain infections(94). Overall, the Alpha variant was approximately 50-70% more transmissible and was associated with a 30-60% increased risk of hospitalisation and death compared to the primary strain(95-100).

The Alpha variant was found to have a minimal impact on the effectiveness of current vaccines(101, 102), while the risk of reinfection remained similar for this variant as with previous ones(103). On 3rd September 2021, the European Centre for Disease Prevention and Control (ECDC) reclassified the Alpha, and the Alpha+E484K mutation variants from a VOC to a ‘de-escalated variant’ (104).

Beta

The Beta SARS-CoV-2 variant, of the B.1.351 lineage, was first documented in South Africa in May 2020(3). This variant contains five S protein mutations of interest: N501Y, E484K, D614G, K417N, and A701V. Like the Alpha variant, Beta contains the mutations N501Y, E484K, and D614G, which increase ACE2 receptor binding affinity(80, 87), increase virulence(105), and enhance resistance to neutralising antibodies(91, 106). The K417 residue of the SARS-CoV-2 S protein interacts with the D30 residue of the ACE2 receptor, forming a salt bridge across the central contact region(65, 78), however, the K417N mutation appears to

have a limited impact on ACE2 receptor binding(80). The A701V mutation is located close to the furin cleavage site but has a minimal impact on transmissibility or antibody resistance(101).

In a genomic and epidemiological study, it was concluded that the Beta SARS-CoV-2 variant had a selective advantage over previous variants from its increased transmissibility and immune escape abilities(107, 108), while the E484K/N501K mutations significantly enhanced the binding affinity of Beta and, hence, increased its transmissibility(109). A retrospective cohort study of 22,068 participants found that infection with the Beta variant was associated with an increased hospitalisation risk compared to an infection with a non-VOC (hazard ratio (HR)=2.30)(100). Overall, Beta is approximately 25-50% more transmissible, is associated with a possible increase in risk of hospital mortality, and has enhanced resistance to antibody neutralisation compared to previous variants(107, 108, 110).

Gamma

The Gamma variant is of the P.1 lineage and was first reported in November 2020 from travellers returning to Japan from Brazil, and was later discovered in Brazil(3, 111). This variant contains the S protein mutations of interest; K417T, E484K, N501Y, D614G, and H655Y(104). As mentioned, the N501Y and D614G mutations increase ACE2 receptor binding affinity and increase infectivity of the virus(80, 87). The N501Y, K417N/T, and E484K mutation trinity, meanwhile, is shared by both Gamma and Beta variants, and is associated with enhanced infectivity and lethality compared to the N501Y mutation alone, possibly due to tighter binding of the S protein to the ACE2 receptor due to increased electrostatic contribution(112). Gamma also possesses the H655Y mutation which was found to provide enhanced viral escape abilities from multiple human monoclonal antibodies *in vitro*(113).

The Gamma variant is associated with heightened transmissibility(109, 110, 114), with one study concluding that it possesses a 1.7- to 2.4-fold increased transmissibility compared to previous variants(115). Additionally, the wave of infections caused by the Gamma variant in Brazil was associated with a 13% increase in death rate compared to the previous wave, suggesting the greater virulence held by Gamma compared to previous viral strains(116).

A surveillance study from seven European countries concluded that the Gamma variant was associated with a higher risk of hospitalisation (aOR=2.6) and admission to an ICU (aOR=2.2) when compared to non-VOC cases(117). In Manaus, Brazil the resurgence of COVID-19, despite high seroprevalence, suggested that the Gamma variant had a moderate resistance to neutralising antibodies(118), however, Gamma has been shown to be significantly less resistant to neutralising antibodies, compared to other variants, including Beta(119).

4 Delta

The Delta variant, from the B.1.617.2 lineage, was first documented in India in October 2020 and was classified as a VOC on 11th May 2021(3). Of the S protein mutations of interest, the aforementioned P681H and D614G are also harboured by the Delta variant(104) and similarly impacts its ACE2 receptor binding affinity and transmissibility(106, 120, 121). Unlike the E484K mutation seen in previous variants, Delta contains the E484Q mutation which, along with a L452R mutation also located within the RBD, causes significantly higher affinity for the ACE2 receptor than the primary strain or the E484K mutation alone(122). The L452R mutation alone results in greater RBD-ACE2 receptor binding affinity and enhanced

escape from neutralising antibodies(123, 124). Lastly, the Delta variant contains the T478K mutation, located on the interface between the S protein and the ACE2 receptor when bound, which increases the electrostatic potential of the S protein and enhances binding affinity(125).

The Delta variant quickly became the dominant variant in the UK(126), US(127), Europe, and around the world(128). The mutations present in the Delta variant, enhanced the transmissibility of the virus as a result of increased binding affinity to the ACE2 receptor(109). It was estimated that the reproduction number of the Delta variant is 97% greater than non-VOC/VOI and approximately three times that of the Alpha, Beta, and Gamma variants(110), which highlights the competitive advantage that this variant had over earlier ones and how it rapidly became the dominant strain globally. The fast replication rate of Delta likely contributes to its increased transmissibility compared to Alpha, Beta, and Gamma. From infected individuals, the Delta variant has been able to be detected by polymerase chain reaction (PCR) within the first four days from exposure, while non-Delta infections could only be detected after six days(129). Furthermore, viral loads of people infected with the Delta variant were found to be significantly higher than people infected with other strains(129), including Beta(130). Delta is also thought to better escape neutralisation, with the frequency of post-vaccination infections much higher for the Delta variant than infections with the primary strain in India(131) and blood sera samples from individuals who had received one dose of a COVID-19 vaccine showing minimal neutralisation of the Delta variant(132).

The Delta variant is also associated with an increased disease severity. In Scotland, infection with the Delta variant was associated with an increased risk of hospitalisation (HR=1.85) compared to infection with the Alpha variant(133). Compared to non-VOC infections, North American retrospective cohort studies demonstrated that infection with Delta was associated with a 108%(134) or HR=2.3(100) increased risk of hospitalisation, a 234% increased risk for admission to an ICU, and a 132% increased risk of death(134). Lastly, a cross-sectional study of 6238 Delta and 3262 primary strain cases in India found that the risk of death was around 1.8 times higher for Delta infections, while Delta also infected and induced symptoms in a greater proportion of younger people (0-19 years old), compared to the primary strain(131).

Omicron

The Omicron variant is of the B.1.1.529 lineage and was first discovered in November 2021 in South Africa and Botswana before being detected in multiple countries and classified as a VOC on 26th November 2021(3). This variant contains over 30 S protein mutations(104), 23 of which have been previously identified, including K417N, T478K, E484A, D614G, H655Y, P681H, and N501Y(135). 15 Omicron mutations are contained within the RBD(17) providing the variant with a significantly enhanced binding affinity to the ACE2 receptor(135, 136). In addition, various single mutations harboured with the RBD of the Omicron variant impair the effectiveness of neutralising antibodies, including K417N, N440K, G446S, E484A, Q493K, G496S, G339D, S371L, and S375F(17).

The emergence of Omicron has been followed by a tidal wave of infections worldwide. Early data from South Africa demonstrated that the proportion of COVID-19 cases caused by the Omicron variant rose from 3% in early October, to 98% by early December(137). In late

December 2021, meanwhile, the doubling time for number of positive Omicron cases was between two and three in the UK, US, and much of Europe(138, 139), highlighting the transmissibility of this variant. The mutations harboured by Omicron that enhance its binding affinity(135, 136) and ability to escape neutralising antibodies(17) likely drove its rapid spread, as did its fast replication rate, which is around 70 times faster than the Delta and primary strains(140). The reinfection rate of Omicron has also been found to be significantly higher than that of previous variants in studies from Scotland(141) and South Africa(142).

The Omicron variant has extensive but incomplete escape from naturally acquired and vaccine-induced immunity(143, 144). Compared to the Delta variant, Omicron requires around a ten-fold increased antibody titre to be neutralised, following vaccination with either Oxford-AstraZeneca or Pfizer/BioNtech vaccines(145). Indeed, blood sera from individuals who had received two doses of the Pfizer/BioNtech vaccine exhibited more than a 25-fold reduction in neutralising antibody titres against the Omicron variant compared to the primary strain(146). T-cell responses to Omicron may remain intact, however. One preprint study demonstrated that 70-80% of the T-cell response targeting the S protein was maintained in those vaccinated or with prior infection, while the magnitude of Omicron cross-reactive T-cells was like that of both Delta and Beta variants(147). Furthermore, data from Pfizer/BioNtech revealed that 80% of the epitopes in the Omicron variant S protein that are recognised by CD8+ T-cells were not affected by this variant's mutations, following two-doses of the vaccine(146). T-cell responses induced from vaccine administration or prior infection may, therefore, provide some protection from severe disease.

Recent real-world evidence has implied that Omicron infection is milder in severity than previous variants. In an early South African analysis, the risk of hospitalisation (aOR=0.2) was lower for Omicron infections compared to non-Omicron SARS-CoV-2 infections(137) while, compared to earlier infections associated with the Delta variant, Omicron-infected individuals had a lower risk of severe disease (aOR=0.3)(137). In December 2021 in England, Omicron cases were found to induce a significantly reduced risk of hospitalisation or presentation for emergency care in comparison to Delta cases(74, 75). The decreased disease severity inflicted by Omicron may be due to its reduced capacity for replication in lung tissue, which was found to be more than ten times less in lung tissue compared to Delta(140). Concordantly, the S protein of the Omicron variant is less efficient at cleaving the ACE2 receptor and entering cells of lung organoids(145), while is also less able to cause fusion between lung cells compared to Delta(145), which is often observed in cases of severe COVID-19. The reduction in replication within the lungs, and the preservation of T-cell responses likely contribute to the milder disease exerted by the Omicron variant.

Although the Omicron variant appears to manifest in mild disease, high case numbers may still result in many hospitalisations and deaths in those vulnerable to the virus. Omicron case numbers may be beginning to peak, however. In South Africa, a 29.7% decrease in weekly COVID-19 cases were reported in the week ending 25th December 2021, compared to the previous week, and the Omicron wave is said to have passed(148). Concerningly, global case numbers continue to rise rapidly(149) and many countries will continue to feel the pressure exerted by the wave of Omicron infections.

Variants of interest

Lambda

The Lambda variant, of the C.37 lineage, was first documented in Peru in December 2020 and was designated as a VOI on 14th June 2021(3). This variant contains the S protein mutations; D614G, L452Q, and F490S(104). The L452Q mutation, located within the RBD, enhances binding affinity to the ACE2 receptor and increases the infectivity of Lambda(150), while, together L452Q and F490S increase the resistance of this variant to vaccine-elicited antibody neutralisation(150). Furthermore, F490S was identified as being a high-risk mutation for enhancing abilities to escape neutralisation(150).

Infectivity of the Lambda variant may be higher than that of Alpha, Gamma, and other D614G containing variants(151), suggesting that Lambda could potentially spread more rapidly and effectively. Additionally, compared to the primary SARS-CoV-2 virus, antibody neutralisation was found to be decreased by 3.05-fold for the Lambda variant, higher than that for Gamma (2.33-fold) and Alpha (2.03-fold) variants(151). However, findings suggest that the Lambda variant can be neutralised by monoclonal antibodies and current vaccines are protective against this variant(150).

Mu

The Mu variant, from the B.1.621 lineage, was first documented in Columbia in January 2021 before receiving designation as a VOI on 30th August 2021(3). This variant contains the aforementioned S protein mutations E484K, N501Y, D614G, and P681H(104). Mu also contains the S protein mutation R346K, located within the RBD(104, 152), which may induce large binding free energy changes that disrupt the binding of antibodies to the S protein and enhance the ability of the variant to escape neutralisation(153). As discussed, the E484K, N501Y, D614G, and P681H mutations have been shown to increase transmissibility(80, 85, 87, 105, 109, 112, 120, 121) and neutralisation escape(91, 106) suggesting that the Mu SARS-CoV-2 variant is likely to be more infectious than the primary strain.

Although the Lambda and Mu variants have been outcompeted by Delta and now Omicron, the development and spread of VOIs will need to be closely monitored and studied to appreciate their pathogenicity, transmissibility, and virulence.

VUM

As of 25th January 2022, there are three VUM listed by the WHO(3) ***(table 1)***.

Vaccinations

The COVID-19 pandemic prompted a rapid international search for safe and effective vaccines against the SARS-CoV-2 virus. In line with previous vaccine development, including for both SARS-CoV and MERS-CoV, the S protein was a key target for COVID-19 vaccine development(154). As of 24th January 2022, 33 approved vaccines are in use in 197 countries, with ten vaccines having gained emergency use listing approval from the WHO(4), (***table 2***). As of 25th January 2022 there are 194 vaccines in pre-clinical development and 140 in clinical development(155). Numerous studies have explored the effectiveness of approved vaccines, however, large variations in vaccine effectiveness are reported. This variability is likely due to several factors in the studies including, the country, date, and population size of the study, as

well as the SARS-CoV-2 variants circulating during the study period. These factors, along with how the effectiveness is reported, mean that it is difficult to compare vaccines and fully understand how effective each vaccine is. Here, we review the COVID-19 vaccines in use around the world.

Pfizer/BioNtech - BNT162b2

The BNT162b2 vaccine (Comirnaty) is a lipid nanoparticle-formulated, nucleoside-modified mRNA vaccine encoding a modified SARS-CoV-2 S protein which was developed through a collaborative effort between Pfizer (New York, US) and BioNTech (Mainz, Germany)(156, 157). BNT162b2 gained WHO emergency use listing on 31st December 2020(158) and, as of 24th January 2022, has been approved for use in 136 countries(4).

Following administration of BNT162b2, a Th1-biased response is observed, with tumour necrosis factor alpha (TNFα), interferon gamma (IFNγ), and interleukin-2 (IL-2) all elevated following vaccination, compared to placebo(159, 160). Highest neutralisation titres are found between seven and fourteen days following the second dose(161), while those previously infected with COVID-19 showed a four-fold increase in antibody binding and a 18-fold increase in neutralisation titres compared to previously uninfected individuals following two-doses(162). The BNT162b vaccine is well tolerated, with limited reactogenicity. Redness and swelling at injection site have been reported, however mild or moderate pain at the injection site is the most commonly reported reaction to vaccination(161). Fatigue, muscle pain, headache and chills are other commonly reported symptoms following BNT162b2 administration(163). The rate of systemic reactions after a second dose of BNT162b has been found to be 1.7 to 2 times higher than after a first dose, possibly suggesting an immunity-boosting effect(164). Many safety reports of this vaccine describe no serious adverse events(161, 164, 165), however, a large study found that BNT162b2 was associated with an increased risk of myocarditis, lymphadenopathy, appendicitis, and herpes zoster infection(166). Although rare, allergic reaction or anaphylaxis has also been reported following administration of the BNT162b2 vaccine(163). ***Table 2*** outlines clinical trial and real-world data for vaccine effectiveness.

Oxford-AstraZeneca – AZD1222

The AZD1222 vaccine (Vaxzevria) is a non-replicating vector of the chimpanzee adenovirus ChAdOx1, modified to encode the SARS-CoV-2 S protein(167). Developed through collaboration between the University of Oxford and AstraZeneca (Cambridge, UK), this vaccine was given WHO emergency use listing on 16th February 2021(158) and has been approved for use in 137 countries, as of 24th January 2022(4). The WHO has granted emergency use listing to two versions of this vaccine (AZD1222 and Covishield) in order to utilise Covishield as part of their worldwide COVAX initiate, which is being produced by the Serum Institute of India and AstraZeneca-SKBio (Republic of Korea)(168).

Following administration of AZD1222, significant antibody production, predominantly of IgG1 and IgG3 subclasses, and a Th-1 cell response, with increased expression of IFNγ and TNFα, is seen(122, 169). One dose of AZD1222 has been shown to produce a neutralising antibody response in 91% of participants, while a second dose resulted in 100% of participants producing neutralising antibodies(170). Mild and moderate itch, pain, redness, swelling,

tenderness, and warmth are common local reactions, while chills, fatigue, fever, headache, muscle ache, and nausea are commonly reported systemic reactions following AZD1222 administration(170). Rare symptoms, including severe chest pain, nasal bleeding, and allergic reaction have been reported following AZD1222 administration(171). ***Table 2*** outlines clinical trial and real-world data for vaccine effectiveness.

Johnson & Johnson - Ad26.COV.2.S

The Ad26.COV.2.S vaccine is a non-replicating adenovirus vector, modified to contain the SARS-CoV-2 S protein in a prefusion-stabilised conformation and requires a single dose(172). This vector was developed from the recombinant human adenovirus type 26 by the Janssen pharmaceutical company of Johnson & Johnson (New Brunswick, New Jersey, US)(172) and was listed for WHO emergency use listing on 12th March 2021(158). As of 24th January 2022, Ad26.COV.2.S has been approved for use in 106 countries(4).

The Ad26.COV.2.S vaccine induces the production of a variety of antibody subclasses, such as IgG, IgM, and IgA, and promotes several non-neutralising antibody responses, including activation of CD4+ and CD8+ Th1-cells and production if IFNγ, IL-2, and TNFα(173, 174). Although neutralising antibody responses induced by Ad26.COV2.S are reduced against SARS-CoV-2 variants, non-neutralising antibody and T-cell responses have been found to be preserved against VOC(173), while a prior COVID-19 infection significantly increases levels of S protein-binding antibodies, antibody-dependent cellular cytotoxicity, and neutralising antibodies against VOCs including Beta and Delta(175). Ad26.COV.2.S is safe and well tolerated, with a large clinical trial demonstrating that headache, fatigue, and myalgia, are the most common systemic reactions, while injection-site pain is the most common local reaction following administration(172). Like other vaccines, Ad26.COV.2.S has been associated with serious adverse events, such as allergic reactions and cerebral venous sinus thrombosis, however, these are rare(163, 176). ***Table 2*** outlines clinical trial and real-world data for vaccine effectiveness.

Moderna – mRNA-1273

The mRNA-1273 vaccine (Spikevax) developed by Moderna (Massachusetts, US) is a lipid-nanoparticle-encapsulated mRNA vaccine expressing the SARS-CoV-2 S protein that has been prefusion-stabilised(177). This vaccine gained WHO emergency use listing on 30th April 2021(158), and as of 24th January 2022, has been approved for use in 85 countries(4).

The mRNA-1273 vaccine elicits a strong CD4+ Th-1 cell response, with TNFα, IFNγ, and IL-2 expression increased following administration(178-180), while neutralising antibody titres have been shown to significantly increase up until around 28 days following the second dose of the vaccine, and afterwards remain consistently high(181). Fatigue, muscle pain, headache, chills, joint pain, and injection-site pain/reaction are common adverse effects caused by the mRNA-1273 vaccine(163, 177), while serious adverse effects are often avoided(177, 181). Serious adverse events, including allergic reaction and anaphylaxis are rare, but not inconceivable following mRNA-1273 administration(163). ***Table 2*** outlines clinical trial and real-world data for vaccine effectiveness.

Other WHO emergency use listed COVID-19 vaccines

In addition to the five COVID-19 vaccines described previously, five other vaccines have gained emergency use listing by the WHO. First, the Sinopharm BBIBP-CorV COVID-19 vaccine (Covilo) was developed by the Beijing Bio-Institute of Biological Products, a subsidiary of China National Biotec Group, and was given WHO emergency use listing on 7th May 2021(158). This vaccine is a 19nCoV-CDC-Tan-HB02 strain SARS-CoV-2 antigen that is produced in Vero cells, inactivated by β-propiolactone, and then purified and absorbed with aluminium hydroxide(182). Next, the CoronaVac vaccine, developed by Sinovac Biotech (Beijing, China), was listed for WHO emergency use on 1st June 2021(158). Like the BBIBP-CorV vaccine, this vaccine is a Vero cell-based, aluminium hydroxide-adjuvanted, β-propiolactone-inactivated vaccine, however, it is based on the SARS-CoV-2 CZ02 strain(183). Covaxin (BBV152) is a whole virion inactivated SARS-CoV-2 vaccine formula developed by Bharat Biotech International ltd (India)(184) which gained emergency use listing from the WHO On 3rd November 2021(185). Lastly, Covovax and its originator, Nuvaxovid (NVX-CoV2372), were both developed by Novavax (Maryland, United States) and the Coalition for Epidemic Preparedness Innovations (Oslo, Norway), and gained emergency use listing on 17st and 21th December 2021, respectively(186, 187). Both vaccines are manufactured using the same technology, and consist of a recombinant SARS-CoV-2 S protein nanoparticle administered with the adjuvant Matrix-M as a co-formulation(188). These vaccines produce similar immune responses to those already discussed. Studies assessing the efficacy of these vaccines are outlined in ***table 2***.

Other approved vaccines

In addition to the vaccines that have received emergency use listing from the WHO, around the world, vaccines have been developed, tested, and approved to combat COVID-19. As of 24th January 2022, 33 vaccines, including the ten described above, have been approved in at least one country(4). The remaining 23 approved vaccines are outlined in ***table 3***.

Waning immunity and boosters

Throughout the COVID-19 pandemic, emerging variants have threatened the effectiveness of vaccines (***table 2***). Simultaneously, waning immunity following vaccination questions how long vaccines remain effective and highlights the importance of booster doses. Indeed, protection against SARS-CoV-2 following vaccination decreases over time, both in terms of antibody titres(189-191) and vaccine effectiveness(192-195). However, cellular responses, such as T-cell immunity, may persist for longer periods (196, 197). With a gradual loss of protection from SARS-CoV-2 following COVID-19 vaccination, many countries are now rolling out booster programmes with the aim of raising levels of immunity.

Since booster programmes began, evidence that a booster vaccine dose enhances antibody and cellular responses has accumulated. Following a third dose of vaccine, neutralising antibody titres increase significantly(198-201) and, in some cases, to higher levels than after the primary two doses(198). Additionally, boosters have also been found to increase neutralising antibody titres against Beta, Gamma, Delta, and Omicron variants(199, 202, 203). T-cell response is also enhanced following a third dose(200, 204, 205). Together, enhancing neutralising antibody and cellular responses with a booster vaccine dose is likely to provide a greater level of protection than relying on immunity built through a primary regimen.

The antibody and cellular responses observed following booster vaccinations have been found to correlate with increased levels of protection against SAR-CoV-2 infection and severe illness. On 30th July 2021, Israel was the first country to offer a third dose of BNT162b2 to certain groups. Subsequently, several studies have revealed that those who received a third vaccine dose were significantly less likely to be infected or have severe disease with SARS-CoV-2 compared to those who received two-doses(206-209). In those aged 60 or older, an observational study demonstrated that the rate of severe COVID-19 and death was lower in the boosted group by a factor of 17.9 and 14.7, respectively, compared to the non-boosted group(210). Booster doses of COVID-19 vaccine have been shown to be effective against infection with Delta(211, 212) and, to a lesser degree, Omicron variants(75, 145, 146, 212-214) despite the numerous mutations harboured by these variants. Overall, increasing evidence is pointing towards the benefits of booster doses of COVID-19 vaccines, therefore it is expected that booster programmes will continue to roll out across the globe. Based on current evidence, the CDC recommend that the time interval for receiving a booster following the primary regiment is five months for Pfizer/BioNTech BNT162b2 primary regimen, six months for Moderna mRNA-1273 primary regimen, and two months for Johnson & Johnson Ad26.COV2.S primary regimen(215). As the pandemic progresses and new variants emerge, variant-specific vaccines may require development, with pre-clinical studies demonstrating their efficacy(216) and pharmaceutical companies, such as Pfizer, advancing in variant-specific vaccine development(146). Policy makers should also consider when vaccine boosters will be given in the future and who will receive booster doses in the long-term.

Emerging Treatments

As more is learnt about the virus, the therapeutic strategy against COVID-19 develops. There are currently over two thousand ongoing trials assessing certain treatment strategies for COVID-19(217). Recently, antivirals including molnupiravir (Lagevrio) and nirmatrelvir/ritonavir (Paxlovid) have been approved in the UK(218, 219), US(220, 221), and Europe(222, 223) for treating COVID-19 in certain risk groups. Similarly, sotrovimab (Xevudy), a monoclonal antibody treatment, has recently been approved for use in treating certain COVID-19 patients in the UK(224), US(225), and Europe(226). These drugs have been shown to be effective at preventing poor clinical outcomes, including death, in those vulnerable to severe COVID-19 infection. Other drug treatments, such as janus kinase inhibitors, corticosteroids, and anti-inflammatories have contrasting evidence to support their use, and therefore, the use of specific drugs is either recommended for or against by certain treatment and management guidelines, which are discussed below.

Guidelines

The treatment and management of COVID-19 is a continually evolving topic, however, health authorities have published and continue to update guidelines and recommendations for treating COVID-19. The WHO living guideline on COVID-19 and therapeutics is regularly updated, with the latest version, published on 14th January 2022 containing 14 recommendations on COVID-19 treatment(227). In the UK, the National Institute for Health and Care Excellence (NICE)(228) and Medicines and Healthcare products Regulatory Agency (MHRA)(229) provide updated guidelines on COVID-19 treatment, while in Europe, the

ECDC regularly publishes several guidelines providing recommendations on a range of COVID-19 related topics(230). In the US, the National Institutes of Health (NIH)(231) and the CDC(232) provide guidance on COVID-19 treatment and management, with the CDC supplying guidelines for specific groups including, employers, schools, health departments, and governments.

Considerations for the future

Novel infectious diseases and pandemics are an unpredictable but inevitable aspect of nature and it is, therefore, important that we learn from past pandemics to prepare for future ones. Firstly, the COVID-19 pandemic has highlighted and amplified the existing inequalities within society(233), with non-white ethnicity, social disadvantage, and unemployment all risk factors for testing positive for COVID-19(234) and those most economically deprived found to be particularly vulnerable(235). These inequalities require addressing to be better prepared for similar situations in the future.

Next, to progress through a pandemic we should be racing the pathogen, not each other. This statement becomes apparent when you consider the problems countries faced when seeking out PPE(236), and the vaccine inequity seen around the world(237), with developed countries often better placed to be able to purchase these items. Initiatives such as the WHO's COVAX programme are vital to protect those most vulnerable and reduce the global spread of disease. In October 2021, the UK government released a publication outlining where the policies implemented to reduce the impact of the COVID-19 pandemic failed, and the lessons learned from these failures (238). Here, there is room for improvement, with the publication presenting conclusions and recommendations on how to enhance pandemic preparedness, lockdown and social distancing measures, testing and contact tracing, social care, and vaccines. In countries such as the UK, US, and much of Europe, where the COVID-19 death rate has been high, steps need to be taken and lessons need to be learnt in order to be better prepared for the next pandemic. The responsibility of improving pandemic response lies with policy makers, the medical/scientific community, and the public, and will ultimately require a collaborative approach.

However, certain aspects of the response to the COVID-19 pandemic have been a triumph. One of the major victories was the rapid development and rollout of vaccines(239), which continue to be effective. The rollout of rapid testing and quarantine for positive cases was also important to at least disrupt the spread of the virus, especially given that asymptomatic individuals can contribute to the spread. Furthermore, the swift identification and sharing of knowledge of SARS-CoV-2 variants between countries should be applauded. Lessons can be learned from countries where COVID-19 was controlled. In Taiwan, managing the pandemic as directed by pre-COVID-19 pandemic plans prompted an immediate response; screening of all airline passengers arriving from Wuhan and high risk areas, restricting entry for non-Taiwanese citizens, 14-day quarantine period for contacts of confirmed cases or returning travellers, a ban on large gatherings, and widespread mask wearing were some of the quickly implemented management strategies(240). New Zealand implemented similarly effective restrictions, with the addition of a national lockdown(240). Many of the pandemic control components that kept case and death numbers low in Taiwan and New Zealand could be adopted by other countries in the future and may lead to greater outcomes in terms of protecting

both health of individuals and the health and wellbeing of the country. Overall, there is much to be learnt from the COVID-19 pandemic and, as we emerge from it, inspection of which policies failed, and which succeeded are imperative.

Conclusion

COVID-19 remains prevalent and life-threatening. Although rollout of vaccines has been successful as attaining a high global vaccination coverage and ensuring that all healthcare systems have the capacity to cope with seasonal waves are essential. With Omicron highly prevalent, we must continue to learn, develop therapeutics, and remain vigilant to new VOCs. Here, we have provided an overview of the virology of SARS-CoV-2, including the mutations harboured by variants of the virus and how these mutations effect its transmissibility and virulence. Lastly, we discussed the vaccines that have been developed and administered around the world and provided evidence supporting the rollout of booster doses. Future priorities should focus on continuing vaccination programmes and developing variant-specific vaccines as new mutations emerge. This, along with the expansion of our knowledge of SARS-CoV-2 and which therapies are most successful to treat infections with it will ultimately lead to favourable outcomes moving forward.

Research Questions

1) How will the SARS-CoV-2 virus mutate in the future, and which mutations will give a competitive advantage that will allow the virus to inflict disease to many people?
2) How do we keep up with the rapidly changing SARS-CoV-2 environment and ensure that vaccines remain effective?
3) How do we manage the booster programme and when will future booster vaccinations be required in order to maintain high levels of immunity?
4) How can we learn from the current and past pandemics so that we are better prepared for the next one?

Patient Involvement: Patients who had been infected with covid-19 were contacted and requested to review the initial drafts of this manuscript. The received feedback was mostly positive and assisted in developing and focusing our review. Final drafts were also reviewed by patients who had had covid-19 and similar positive feedback was received.

Contributorship statement and guarantor: MY and HC performed the literature search and drafted the manuscript. HC revised and finalised the manuscript. JS reviewed and revised the manuscript. PE was responsible for the concept and design of the work. PE reviewed, revised, and finalised the manuscript. PE is the guarantor.

Competing interests: We have read and understood the BMJ policy on declaration of interests and declare the following interests: PE was funded by the Medical Research Council and now by Higher Education Funding Council for England (HEFCE). He has also received grants from Alzheimer's Research, UK, Alzheimer's Drug Discovery Foundation, Alzheimer's Society, UK, Medical Research Council, Alzheimer's Association US, Van-Geest foundation, and European Union grants. PE is a consultant to Roche, Pfizer, and Novo Nordisk. He has received

educational and research grants from GE Healthcare, Novo Nordisk, Piramal Life Science/Life Molecular Imaging, Avid Radiopharmaceuticals and Eli Lilly. He is a member of the Scientific Advisory Board at Novo Nordisk. None of these were related to COVID-19

Figure Legends:

Figure 1: Genome and structure of SARS-CoV-2. A) SARS-CoV-2 genome and S protein amino acid composition. The SARS-CoV-2 genome is approximately 30,000 base pairs (bp) long and consists of open reading frames (ORF) and elements that are essential for the virus' structure. The spike S protein is responsible for binding and entry into host cells. SARS-CoV-2 variants of concern (VOC) contain various S protein non-synonymous mutations that result in amino acid changes in the receptor binding domain (orange text) and the S1/S2 subunit interface (black text) which have been demonstrated to enhance transmissibility of the virus. VOC include Alpha (α), Beta (β), Gamma (γ), and Delta (δ). **B) SARS-CoV-2 structure.** SARS-CoV-2 is a RNA virus that has a crown-like appearance and contains four major structural proteins: nucleocapsid (N), spike (S), envelope (E), and membrane (M). **C) S and ACE2 interaction.** The SARS-CoV-2 S protein directly interacts with human angiotensin-converting enzyme 2 (ACE2) receptors in order to gain entry into host cells. The receptor binding domain (RBD) of the S protein tightly binds to ACE2. **D) Spike protein structure.** The S protein protrudes out from the main SARS-CoV-2 bulk and is comprised of two subunits: S1 and S2. S1 contains the RBD which directly interacts with the human ACE2 receptor, while the S1/S2 interface contains a furin cleavage site which is cleaved to allow S2 to fuse with the host cell membrane. Both the RBD and the S1/S2 interface contain transmissibility increasing mutations that are harboured in variants of concern.

Figure 2: Viral entry and host response. A) At the alveolar epithelial cell layer. Epithelial cells in the lungs express both angiotensin-converting enzyme 2 (ACE2) receptors and transmembrane protease serine 2 (TMPRSS2), allowing for infection by SARS-CoV-2. Replication of the virus within these cells induces an intense immune response that attracts monocytes, T-cells and macrophages and, in some cases, can result in a cytokine storm. **B) Within nearby blood vessels.** Cytokines produced by the epithelial cell layer are released into blood vessels supplying the infected tissue, which causes the recruitment of further immune cells to the area, driving the damaging inflammatory response further. Circulating cytokines also create a systemic inflammatory environment. **C) Adaptive immune response.** Circulating lymphocytes carry viral antigens to lymph nodes and bone marrow to begin the adaptive immune system processes whereby B-cells, and later antibodies, are activated. **D) SARS-CoV2 host replication.** The SARS-CoV-2 virus utilises the ACE2 receptor and TMPRSS2 to gain entry into human cells. Following release of the viral RNA within the host cell, the virus utilises the host endoplasmic reticulum (ER) and Golgi apparatus to produce

and manufacture new viral particles, which are released out of the cell to infect other cells and new hosts.

Table 1: SARS-CoV-2 variants and their S protein mutations. *first detection worldwide. Information correct as of 24th January 2022.

Table 2: Vaccine effectiveness of vaccines that have gained WHO emergency use listing. *Adjusted for covariates when reported by study, dates are reported in dd/mm/yyyy format. Vaccine effectiveness days/months refers to days/months since vaccination dose. Information correct as of reported conclusion date of each study.

Table 3: COVID-19 vaccines approved in at least one country. Information correct as of 24th January 2022.

References

1. CDC.org [Internet]. Human Coronavirus Types. Centres for Disease Control and Prevention. [15 February 2020; cited 12 October 2021]. Available from: https://www.cdc.gov/coronavirus/types.html
2. Who.int [Internet]. Weekly operational update on COVID-19 - 25 January 2022. World Health Organisation. [25 January 2022; cited 26 January 2022]. Available from: https://www.who.int/publications/m/item/weekly-operational-update-on-covid-19---25-january-2022
3. Who.int [Internet]. Tracking SARS-CoV-2 variants. World Health Organisation. [25 January 2022; cited 26 January 2022]. Available from: https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/
4. covid19.trackvaccines.org [Internet]. COVID-19 Vaccine Tracker. [24 January 2022; cited 26 January 2022]. Available from: https://covid19.trackvaccines.org/
5. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet. 2020;395(10223):514-23.
6. Who.int [Internet]. Transmission of SARS-CoV-2: implications for infection prevention precautions - Scientific Brief. World Health Organisation. [9 July 2020; cited 28 October 2021]. Available from: https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions
7. Gidari A, Sabbatini S, Bastianelli S, Pierucci S, Busti C, Bartolini D, et al. SARS-CoV-2 Survival on Surfaces and the Effect of UV-C Light. Viruses. 2021;13(3).
8. Pottage T, Garratt I, Onianwa O, Spencer A, Paton S, Verlander NQ, et al. A comparison of persistence of SARS-CoV-2 variants on stainless steel. J Hosp Infect. 2021;114:163-6.
9. Guo L, Wang M, Zhang L, Mao N, An C, Xu L, et al. Transmission risk of viruses in large mucosalivary droplets on the surface of objects: A time-based analysis. Infect Dis Now. 2021;51(3):219-27.
10. Carraturo F, Del Giudice C, Morelli M, Cerullo V, Libralato G, Galdiero E, et al. Persistence of SARS-CoV-2 in the environment and COVID-19 transmission risk from environmental matrices and surfaces. Environ Pollut. 2020;265(Pt B):115010.

11. Hui KP, Cheung M-C, Perera RA, Ng K-C, Bui CH, Ho JC, et al. Tropism, replication competence, and innate immune responses of the coronavirus SARS-CoV-2 in human respiratory tract and conjunctiva: an analysis in ex-vivo and in-vitro cultures. The Lancet Respiratory Medicine. 2020;8(7):687-95.
12. McAloon C, Collins A, Hunt K, Barber A, Byrne AW, Butler F, et al. Incubation period of COVID-19: a rapid systematic review and meta-analysis of observational research. BMJ Open. 2020;10(8):e039652.
13. Bliddal S, Banasik K, Pedersen OB, Nissen J, Cantwell L, Schwinn M, et al. Acute and persistent symptoms in non-hospitalized PCR-confirmed COVID-19 patients. Sci Rep. 2021;11(1):13153.
14. Grant MC, Geoghegan L, Arbyn M, Mohammed Z, McGuinness L, Clarke EL, et al. The prevalence of symptoms in 24,410 adults infected by the novel coronavirus (SARS-CoV-2; COVID-19): A systematic review and meta-analysis of 148 studies from 9 countries. PLoS One. 2020;15(6):e0234765.
15. Kronbichler A, Kresse D, Yoon S, Lee KH, Effenberger M, Shin JI. Asymptomatic patients as a source of COVID-19 infections: A systematic review and meta-analysis. Int J Infect Dis. 2020;98:180-6.
16. Arons MM, Hatfield KM, Reddy SC, Kimball A, James A, Jacobs JR, et al. Presymptomatic SARS-CoV-2 Infections and Transmission in a Skilled Nursing Facility. N Engl J Med. 2020;382(22):2081-90.
17. Cao Y, Wang J, Jian F, Xiao T, Song W, Yisimayi A, et al. B.1.1.529 escapes the majority of SARS-CoV-2 neutralizing antibodies of diverse epitopes. BioRxiv [Preprint]. 2021.
18. Wolff D, Nee S, Hickey NS, Marschollek M. Risk factors for Covid-19 severity and fatality: a structured literature review. Infection. 2021;49(1):15-28.
19. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62.
20. Zhang J, Wang X, Jia X, Li J, Hu K, Chen G, et al. Risk factors for disease severity, unimprovement, and mortality in COVID-19 patients in Wuhan, China. Clin Microbiol Infect. 2020;26(6):767-72.
21. Ebinger JE, Achamallah N, Ji H, Claggett BL, Sun N, Botting P, et al. Pre-existing traits associated with Covid-19 illness severity. PLoS One. 2020;15(7):e0236240.
22. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;584(7821):430-6.
23. Li R, Tian J, Yang F, Lv L, Yu J, Sun G, et al. Clinical characteristics of 225 patients with COVID-19 in a tertiary Hospital near Wuhan, China. J Clin Virol. 2020;127:104363.
24. Guo L, Shi Z, Zhang Y, Wang C, Do Vale Moreira NC, Zuo H, et al. Comorbid diabetes and the risk of disease severity or death among 8807 COVID-19 patients in China: A meta-analysis. Diabetes Res Clin Pract. 2020;166:108346.
25. Feng Y, Ling Y, Bai T, Xie Y, Huang J, Li J, et al. COVID-19 with Different Severities: A Multicenter Study of Clinical Features. Am J Respir Crit Care Med. 2020;201(11):1380-8.

26. Tian J, Yuan X, Xiao J, Zhong Q, Yang C, Liu B, et al. Clinical characteristics and risk factors associated with COVID-19 disease severity in patients with cancer in Wuhan, China: a multicentre, retrospective, cohort study. Lancet Oncol. 2020;21(7):893-903.
27. Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020;21(3):335-7.
28. Vizcarra P, Perez-Elias MJ, Quereda C, Moreno A, Vivancos MJ, Dronda F, et al. Description of COVID-19 in HIV-infected individuals: a single-centre, prospective cohort. Lancet HIV. 2020;7(8):e554-e64.
29. Baillie JK, Wilson JF, Bulteel N, Hayward C, Klaric L, Porteous DJ, et al. Mapping the human genetic architecture of COVID-19. Nature. 2021.
30. Shelton JF, Shastri AJ, Ye C, Weldon CH, Filshtein-Somnez T, Coker D, et al. Trans-ethnic analysis reveals genetic and non-genetic associations with COVID-19 susceptibility and severity. MedRxiv [Preprint]. 2020.
31. Ellinghaus D, Degenhardt F, Bujanda L, Buti M, Albillos A, Invernizzi P, et al. Genomewide association study of severe covid-19 with respiratory failure/[...]. New England Journal of Medicine Boston: Massachusetts Medical Society, 2020, vol 383, no 16. 2020.
32. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. cell. 2020;181(2):271-80. e8.
33. Hou Y, Zhao J, Martin W, Kallianpur A, Chung MK, Jehi L, et al. New insights into genetic susceptibility of COVID-19: an ACE2 and TMPRSS2 polymorphism analysis. BMC medicine. 2020;18(1):1-8.
34. Barbry P, Muus C, Luecken M, Eraslan G, Waghray A, Heimberg G, et al. Integrated analyses of single-cell atlases reveal age, gender, and smoking status associations with cell type-specific expression of mediators of SARS-CoV-2 viral entry and highlights inflammatory programs in putative target cells. BioRxiv [Preprint]. 2020.
35. Prakrithi P, Lakra P, Sundar D, Kapoor M, Mukerji M, Gupta I, et al. Genetic Risk Prediction of COVID-19 Susceptibility and Severity in the Indian Population. Front Genet. 2021;12:714185.
36. Huang QM, Zhang PD, Li ZH, Zhou JM, Liu D, Zhang XR, et al. Genetic Risk and Chronic Obstructive Pulmonary Disease Independently Predict the Risk of Incident Severe COVID-19. Ann Am Thorac Soc. 2022;19(1):58-65.
37. Zhou Y, Qian X, Liu Z, Yang H, Liu T, Chen K, et al. Coagulation factors and the incidence of COVID-19 severity: Mendelian randomization analyses and supporting evidence. Signal Transduct Target Ther. 2021;6(1):222.
38. Payne S. Family Coronaviridae. Viruses 2017. p. 149-58.
39. Masters PS, Kuo L, Ye R, Hurst KR, Koetzner CA, Hsue B. Genetic and molecular biological analysis of protein-protein interactions in coronavirus assembly. Adv Exp Med Biol. 2006;581:163-73.
40. Khailany RA, Safdar M, Ozaslan M. Genomic characterization of a novel SARS-CoV-2. Gene Rep. 2020;19:100682.
41. Thoms M, Buschauer R, Ameismeier M, Koepke L, Denk T, Hirschenberger M, et al. Structural basis for translational shutdown and immune evasion by the Nsp1 protein of SARS-CoV-2. Science. 2020;369(6508):1249-55.

42. Schubert K, Karousis ED, Jomaa A, Scaiola A, Echeverria B, Gurzeler LA, et al. SARS-CoV-2 Nsp1 binds the ribosomal mRNA channel to inhibit translation. Nat Struct Mol Biol. 2020;27(10):959-66.
43. Huang C, Lokugamage KG, Rozovics JM, Narayanan K, Semler BL, Makino S. SARS coronavirus nsp1 protein induces template-dependent endonucleolytic cleavage of mRNAs: viral mRNAs are resistant to nsp1-induced RNA cleavage. PLoS Pathog. 2011;7(12):e1002433.
44. Snijder EJ, Decroly E, Ziebuhr J. The Nonstructural Proteins Directing Coronavirus RNA Synthesis and Processing. Adv Virus Res. 2016;96:59-126.
45. V'Kovski P, Gerber M, Kelly J, Pfaender S, Ebert N, Braga Lagache S, et al. Determination of host proteins composing the microenvironment of coronavirus replicase complexes by proximity-labeling. Elife. 2019;8.
46. Masters PS. The molecular biology of coronaviruses. Advances in virus research. 2006;66:193-292.
47. Siu Y, Teoh K, Lo J, Chan C, Kien F, Escriou N, et al. The M, E, and N structural proteins of the severe acute respiratory syndrome coronavirus are required for efficient assembly, trafficking, and release of virus-like particles. Journal of virology. 2008;82(22):11318-30.
48. Kuo L, Masters PS. Genetic evidence for a structural interaction between the carboxy termini of the membrane and nucleocapsid proteins of mouse hepatitis virus. J Virol. 2002;76(10):4987-99.
49. Hulswit RJ, de Haan CA, Bosch BJ. Coronavirus Spike Protein and Tropism Changes. Adv Virus Res. 2016;96:29-57.
50. Konno Y, Kimura I, Uriu K, Fukushi M, Irie T, Koyanagi Y, et al. SARS-CoV-2 ORF3b Is a Potent Interferon Antagonist Whose Activity Is Increased by a Naturally Occurring Elongation Variant. Cell Rep. 2020;32(12):108185.
51. Kopecky-Bromberg SA, Martinez-Sobrido L, Frieman M, Baric RA, Palese P. Severe acute respiratory syndrome coronavirus open reading frame (ORF) 3b, ORF 6, and nucleocapsid proteins function as interferon antagonists. J Virol. 2007;81(2):548-57.
52. Xia H, Cao Z, Xie X, Zhang X, Chen JY, Wang H, et al. Evasion of Type I Interferon by SARS-CoV-2. Cell Rep. 2020;33(1):108234.
53. Wong HH, Fung TS, Fang S, Huang M, Le MT, Liu DX. Accessory proteins 8b and 8ab of severe acute respiratory syndrome coronavirus suppress the interferon signaling pathway by mediating ubiquitin-dependent rapid degradation of interferon regulatory factor 3. Virology. 2018;515:165-75.
54. Azad GK, Khan PK. Variations in Orf3a protein of SARS-CoV-2 alter its structure and function. Biochem Biophys Rep. 2021;26:100933.
55. Ren Y, Shu T, Wu D, Mu J, Wang C, Huang M, et al. The ORF3a protein of SARS-CoV-2 induces apoptosis in cells. Cell Mol Immunol. 2020;17(8):881-3.
56. Kreimendahl S, Rassow J. The Mitochondrial Outer Membrane Protein Tom70-Mediator in Protein Traffic, Membrane Contact Sites and Innate Immunity. Int J Mol Sci. 2020;21(19).
57. Gordon DE, Jang GM, Bouhaddou M, Xu J, Obernier K, White KM, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. Nature. 2020;583(7816):459-68.

58. Dominguez Andres A, Feng Y, Campos AR, Yin J, Yang CC, James B, et al. SARS-CoV-2 ORF9c Is a Membrane-Associated Protein that Suppresses Antiviral Responses in Cells. BioRxiv [Preprint]. 2020.
59. Redondo N, Zaldivar-Lopez S, Garrido JJ, Montoya M. SARS-CoV-2 Accessory Proteins in Viral Pathogenesis: Knowns and Unknowns. Front Immunol. 2021;12:708264.
60. Bosch BJ, van der Zee R, de Haan CA, Rottier PJ. The coronavirus spike protein is a class I virus fusion protein: structural and functional characterization of the fusion core complex. J Virol. 2003;77(16):8801-11.
61. Li F. Structure, Function, and Evolution of Coronavirus Spike Proteins. Annu Rev Virol. 2016;3(1):237-61.
62. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020;367(6483):1260-3.
63. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. Cell. 2020;181(2):281-92 e6.
64. Khare S, Azevedo M, Parajuli P, Gokulan K. Conformational Changes of the Receptor Binding Domain of SARS-CoV-2 Spike Protein and Prediction of a B-Cell Antigenic Epitope Using Structural Data. Front Artif Intell. 2021;4:630955.
65. Lan J, Ge J, Yu J, Shan S, Zhou H, Fan S, et al. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. Nature. 2020;581(7807):215-20.
66. Millet JK, Whittaker GR. Host cell proteases: Critical determinants of coronavirus tropism and pathogenesis. Virus Res. 2015;202:120-34.
67. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004;203(2):631-7.
68. Glowacka I, Bertram S, Muller MA, Allen P, Soilleux E, Pfefferle S, et al. Evidence that TMPRSS2 activates the severe acute respiratory syndrome coronavirus spike protein for membrane fusion and reduces viral control by the humoral immune response. J Virol. 2011;85(9):4122-34.
69. Zhao MM, Yang WL, Yang FY, Zhang L, Huang WJ, Hou W, et al. Cathepsin L plays a key role in SARS-CoV-2 infection in humans and humanized mice and is a promising target for new drug development. Signal Transduct Target Ther. 2021;6(1):134.
70. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020;181(2):271-80 e8.
71. Duchene S, Featherstone L, Haritopoulou-Sinanidou M, Rambaut A, Lemey P, Baele G. Temporal signal and the phylodynamic threshold of SARS-CoV-2. Virus Evol. 2020;6(2):veaa061.
72. Ecdc.europa.eu [Internet]. Methods for the detection and characterisation of SARS-CoV-2 variants - first update. European Centre for Disease Prevention and Control. [20 December 2021; cited 7 January 2022]. Available from: https://www.ecdc.europa.eu/en/publications-data/methods-detection-and-characterisation-sars-cov-2-variants-first-update

73. Cdc.gov [Internet]. COVID-19: About Variants. Centers for Disease Control and Prevention. [13 December 2021; cited 7 January 2022]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/variants/about-variants.html
74. Imperial.ac.uk [Internet]. Report 50 - Hospitalisation risk for Omicron cases in England. Imperial College London, MRC Centre for Global Infectious Disease Analysis. [22 December 2021; cited 10 January 2022]. Available from: https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/covid-19/report-50-severity-omicron/
75. Gov.uk [Internet]. SARS-CoV-2 variants of concern and variants under investigation in England - Technical briefing 33. UK Health Security Agency. [23 December 2021; cited 10 January 2022]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1043807/technical-briefing-33.pdf
76. Luna-Muschi A, Borges IC, de Faria E, Barboza AS, Maia FL, Leme MD, et al. Clinical features of COVID-19 by SARS-CoV-2 Gamma variant: A prospective cohort study of vaccinated and unvaccinated healthcare workers. J Infect. 2021.
77. Gov.uk [Internet]. Investigation of novel SARS-CoV-2 variant - Variant of Concern 202012/01 - Technical briefing 5. UK Health Security Agency (formerly Public Health England). [14 January 2021; cited 10 January 2022]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/959426/Variant_of_Concern_VOC_202012_01_Technical_Briefing_5.pdf
78. Wang Y, Liu M, Gao J. Enhanced receptor binding of SARS-CoV-2 through networks of hydrogen-bonding and hydrophobic interactions. Proc Natl Acad Sci U S A. 2020;117(25):13967-74.
79. Yi C, Sun X, Ye J, Ding L, Liu M, Yang Z, et al. Key residues of the receptor binding motif in the spike protein of SARS-CoV-2 that interact with ACE2 and neutralizing antibodies. Cell Mol Immunol. 2020;17(6):621-30.
80. Starr TN, Greaney AJ, Hilton SK, Ellis D, Crawford KHD, Dingens AS, et al. Deep Mutational Scanning of SARS-CoV-2 Receptor Binding Domain Reveals Constraints on Folding and ACE2 Binding. Cell. 2020;182(5):1295-310 e20.
81. Huang Y, Yang C, Xu XF, Xu W, Liu SW. Structural and functional properties of SARS-CoV-2 spike protein: potential antivirus drug development for COVID-19. Acta Pharmacol Sin. 2020;41(9):1141-9.
82. Hoffmann M, Kleine-Weber H, Pohlmann S. A Multibasic Cleavage Site in the Spike Protein of SARS-CoV-2 Is Essential for Infection of Human Lung Cells. Mol Cell. 2020;78(4):779-84 e5.
83. Peacock TP, Goldhill DH, Zhou J, Baillon L, Frise R, Swann OC, et al. The furin cleavage site of SARS-CoV-2 spike protein is a key determinant for transmission due to enhanced replication in airway cells. BioRxiv [Preprint]. 2020.
84. Zhu Y, Feng F, Hu G, Wang Y, Yu Y, Zhu Y, et al. The S1/S2 boundary of SARS-CoV-2 spike protein modulates cell entry pathways and transmission. BioRxiv [Preprint]. 2020.
85. Scudellari M. How the coronavirus infects cells - and why Delta is so dangerous. Nature. 2021;595(7869):640-4.

86. Wang Q, Qiu Y, Li JY, Zhou ZJ, Liao CH, Ge XY. A Unique Protease Cleavage Site Predicted in the Spike Protein of the Novel Pneumonia Coronavirus (2019-nCoV) Potentially Related to Viral Transmissibility. Virol Sin. 2020;35(3):337-9.
87. Yurkovetskiy L, Wang X, Pascal KE, Tomkins-Tinch C, Nyalile TP, Wang Y, et al. Structural and Functional Analysis of the D614G SARS-CoV-2 Spike Protein Variant. Cell. 2020;183(3):739-51 e8.
88. McCarthy KR, Rennick LJ, Nambulli S, Robinson-McCarthy LR, Bain WG, Haidar G, et al. Natural deletions in the SARS-CoV-2 spike glycoprotein drive antibody escape. BioRxiv [Preprint]. 2021.
89. Kemp SA, Collier DA, Datir R, Ferreira I, Gayed S, Jahun A, et al. Neutralising antibodies in Spike mediated SARS-CoV-2 adaptation. MedRxiv [Preprint]. 2020.
90. Gamage AM, Tan KS, Chan WOY, Liu J, Tan CW, Ong YK, et al. Infection of human Nasal Epithelial Cells with SARS-CoV-2 and a 382-nt deletion isolate lacking ORF8 reveals similar viral kinetics and host transcriptional profiles. PLoS Pathog. 2020;16(12):e1009130.
91. Collier DA, De Marco A, Ferreira I, Meng B, Datir RP, Walls AC, et al. Sensitivity of SARS-CoV-2 B.1.1.7 to mRNA vaccine-elicited antibodies. Nature. 2021;593(7857):136-41.
92. Martínez-García L, Espinel MA, Abreu M, González-Alba JM, Gijón D, McGee A, et al. Emergence and Spread of B. 1.1. 7 Lineage in Primary Care and Clinical Impact in the Morbi-Mortality among Hospitalized Patients in Madrid, Spain. Microorganisms. 2021;9(7):1517.
93. Vassallo M, Manni S, Klotz C, Fabre R, Pini P, Blanchouin E, et al. Patients Admitted for Variant Alpha COVID-19 Have Poorer Outcomes than Those Infected with the Old Strain. J Clin Med. 2021;10(16).
94. McAlister FA, Nabipoor M, Chu A, Lee DS, Saxinger L, Bakal JA. Lessons from the COVID-19 third wave in Canada: the impact of variants of concern and shifting demographics. MedRxiv [Preprint]. 2021.
95. Davies NG, Abbott S, Barnard RC, Jarvis CI, Kucharski AJ, Munday JD, et al. Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. Science. 2021;372(6538).
96. Leung K, Shum MH, Leung GM, Lam TT, Wu JT. Early transmissibility assessment of the N501Y mutant strains of SARS-CoV-2 in the United Kingdom, October to November 2020. Euro Surveill. 2021;26(1).
97. Zhao S, Lou J, Cao L, Zheng H, Chong MKC, Chen Z, et al. Quantifying the transmission advantage associated with N501Y substitution of SARS-CoV-2 in the UK: an early data-driven analysis. J Travel Med. 2021;28(2).
98. Gov.uk [Internet]. NERVTAG paper on COVID-19 variant of concern B.1.1.7. NERVTAG - COVID-19 Public statements. [22 January 2021; cited 7 October 2021] Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/961037/NERVTAG_note_on_B.1.1.7_severity_for_SAGE_77__1_.pdf
99. Challen R, Brooks-Pollock E, Read JM, Dyson L, Tsaneva-Atanasova K, Danon L. Risk of mortality in patients infected with SARS-CoV-2 variant of concern 202012/1: matched cohort study. BMJ. 2021;372:n579.

100. Paredes MI, Lunn SM, Famulare M, Frisbie LA, Painter I, Burstein R, et al. Associations between SARS-CoV-2 variants and risk of COVID-19 hospitalization among confirmed cases in Washington State: a retrospective cohort study. MedRxiv [Preprint]. 2021.
101. Wang P, Nair MS, Liu L, Iketani S, Luo Y, Guo Y, et al. Antibody Resistance of SARS-CoV-2 Variants B.1.351 and B.1.1.7. BioRxiv [Preprint]. 2021:2021.01.25.428137.
102. Wu K, Werner AP, Moliva JI, Koch M, Choi A, Stewart-Jones GBE, et al. mRNA-1273 vaccine induces neutralizing antibodies against spike mutants from global SARS-CoV-2 variants. BioRxiv [Preprint]. 2021.
103. Gallais F, Gantner P, Bruel T, Velay A, Planas D, Wendling M-J, et al. Anti-SARS-CoV-2 Antibodies Persist for up to 13 Months and Reduce Risk of Reinfection. MedRxiv [Preprint]. 2021.
104. Ecdc.europa.eu [Internet]. SARS-CoV-2 variants of concern as of 20 January 2022. European Centre for Disease Prevention and Control. [20 January 2022; cited 24 January 2022] Available from: https://www.ecdc.europa.eu/en/covid-19/variants-concern
105. Gu H, Chen Q, Yang G, He L, Fan H, Deng YQ, et al. Adaptation of SARS-CoV-2 in BALB/c mice for testing vaccine efficacy. Science. 2020;369(6511):1603-7.
106. Plante JA, Liu Y, Liu J, Xia H, Johnson BA, Lokugamage KG, et al. Spike mutation D614G alters SARS-CoV-2 fitness. Nature. 2021;592(7852):116-21.
107. Pearson CA, Russell TW, Davies NG, Kucharski AJ, group CC-w, Edmunds WJ, et al. Estimates of severity and transmissibility of novel South Africa SARS-CoV-2 variant 501Y.V2. Centre for Mathematical Modelling of Infectious Diseases. CMMID Repository [Preprint]. 2021.
108. Wibmer CK, Ayres F, Hermanus T, Madzivhandila M, Kgagudi P, Oosthuysen B, et al. SARS-CoV-2 501Y.V2 escapes neutralization by South African COVID-19 donor plasma. Nat Med. 2021;27(4):622-5.
109. Sinha S, Tam B, Wang SM. Altered interaction between RBD and ACE2 receptor contributes towards the increased transmissibility of SARS CoV-2 delta, kappa, beta, and gamma strains with RBD double mutations. BioRxiv [Preprint]. 2021.
110. Campbell F, Archer B, Laurenson-Schafer H, Jinnai Y, Konings F, Batra N, et al. Increased transmissibility and global spread of SARS-CoV-2 variants of concern as at June 2021. Euro Surveill. 2021;26(24).
111. Ecdc.europa.eu [Internet]. Risk assessment: SARS-CoV-2 - increased circulation of variants of concern and vaccine rollout in the EU/EEA, 14th update. European Centre for Disease Prevention and Control. [15 February 2021; cited 8 October 2021] Available from: https://www.ecdc.europa.eu/en/publications-data/covid-19-risk-assessment-variants-vaccine-fourteenth-update-february-2021
112. Khan A, Zia T, Suleman M, Khan T, Ali SS, Abbasi AA, et al. Higher infectivity of the SARS-CoV-2 new variants is associated with K417N/T, E484K, and N501Y mutants: An insight from structural data. J Cell Physiol. 2021;236(10):7045-57.
113. Baum A, Fulton BO, Wloga E, Copin R, Pascal KE, Russo V, et al. Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies. Science. 2020;369(6506):1014-8.

114. Curran J, Dol J, Boulos L, Somerville M, McCulloch H, MacDonald M, et al. Transmission characteristics of SARS-CoV-2 variants of concern. MedRxiv [Preprint]. 2021.
115. de Faria E, Guedes AR, Oliveira MS, de Godoy Moreira MV, Maia FL, dos Santos Barboza A, et al. Performance of vaccination with CoronaVac in a cohort of healthcare workers (HCW) - preliminary report. MedRxiv [Preprint]. 2021.
116. Freitas ARR, Beckedorff OA, Cavalcanti LPG, Siqueira AM, Castro DB, Costa CFD, et al. The emergence of novel SARS-CoV-2 variant P.1 in Amazonas (Brazil) was temporally associated with a change in the age and sex profile of COVID-19 mortality: A population based ecological study. Lancet Reg Health Am. 2021;1:100021.
117. Funk T, Pharris A, Spiteri G, Bundle N, Melidou A, Carr M, et al. Characteristics of SARS-CoV-2 variants of concern B.1.1.7, B.1.351 or P.1: data from seven EU/EEA countries, weeks 38/2020 to 10/2021. Euro Surveill. 2021;26(16).
118. Sabino EC, Buss LF, Carvalho MPS, Prete CA, Jr., Crispim MAE, Fraiji NA, et al. Resurgence of COVID-19 in Manaus, Brazil, despite high seroprevalence. Lancet. 2021;397(10273):452-5.
119. Dejnirattisai W, Zhou D, Supasa P, Liu C, Mentzer AJ, Ginn HM, et al. Antibody evasion by the P.1 strain of SARS-CoV-2. Cell. 2021;184(11):2939-54 e9.
120. Korber B, Fischer WM, Gnanakaran S, Yoon H, Theiler J, Abfalterer W, et al. Tracking Changes in SARS-CoV-2 Spike: Evidence that D614G Increases Infectivity of the COVID-19 Virus. Cell. 2020;182(4):812-27 e19.
121. Volz E, Hill V, McCrone JT, Price A, Jorgensen D, O'Toole A, et al. Evaluating the Effects of SARS-CoV-2 Spike Mutation D614G on Transmissibility and Pathogenicity. Cell. 2021;184(1):64-75 e11.
122. Augusto G, Mohsen MO, Zinkhan S, Liu X, Vogel M, Bachmann MF. In vitro data suggest that Indian delta variant B.1.617 of SARS-CoV-2 escapes neutralization by both receptor affinity and immune evasion. Allergy. 2021.
123. Tchesnokova V, Kulakesara H, Larson L, Bowers V, Rechkina E, Kisiela D, et al. Acquisition of the L452R mutation in the ACE2-binding interface of Spike protein triggers recent massive expansion of SARS-Cov-2 variants. BioRxiv [Preprint]. 2021.
124. Li Q, Wu J, Nie J, Zhang L, Hao H, Liu S, et al. The Impact of Mutations in SARS-CoV-2 Spike on Viral Infectivity and Antigenicity. Cell. 2020;182(5):1284-94 e9.
125. Di Giacomo S, Mercatelli D, Rakhimov A, Giorgi FM. Preliminary report on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Spike mutation T478K. J Med Virol. 2021;93(9):5638-43.
126. Torjesen I. Covid-19: Delta variant is now UK's most dominant strain and spreading through schools. BMJ. 2021;373:n1445.
127. Reuters.com [Internet]. Delta COVID variant now dominant strain worldwide, U.S. deaths surge -officials. O'donnell C, Mason J, Reuters. [16 July 2021; cited 6 January 2022]. Available from: www.reuters.com
128. Euro.who.int [Internet]. SARS-CoV-2 Delta variant now dominant in much of European region; efforts must be reinforced to prevent transmission, warns WHO Regional Office for Europe and ECDC. World Health Organisation. [23 July 2021; cited 11 October 2021]. Available from: https://www.euro.who.int/en/media-

centre/sections/press-releases/2021/sars-cov-2-delta-variant-now-dominant-in-much-of-european-region-efforts-must-be-reinforced-to-prevent-transmission,-warns-who-regional-office-for-europe-and-ecdc

129. Li B, Deng A, Li K, Hu Y, Li Z, Xiong Q, et al. Viral infection and transmission in a large, well-traced outbreak caused by the SARS-CoV-2 Delta variant MedRxiv [Preprint]. 2021.

130. Teyssou E, Delagreverie H, Visseaux B, Lambert-Niclot S, Brichler S, Ferre V, et al. The Delta SARS-CoV-2 variant has a higher viral load than the Beta and the historical variants in nasopharyngeal samples from newly diagnosed COVID-19 patients. J Infect. 2021;83(4):e1-e3.

131. Kumar A, Asghar A, Raza K, Narayan RK, Jha RK, Satyam A, et al. Demographic characteristics of SARS-CoV-2 B.1.617.2 (Delta) variant infections in Indian population. MedRxiv [Preprint]. 2021.

132. Planas D, Veyer D, Baidaliuk A, Staropoli I, Guivel-Benhassine F, Rajah MM, et al. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. Nature. 2021;596(7871):276-80.

133. Sheikh A, McMenamin J, Taylor B, Robertson C, Public Health S, the EIIC. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. Lancet. 2021;397(10293):2461-2.

134. Fisman DN, Tuite AR. Progressive Increase in Virulence of Novel SARS-CoV-2 Variants in Ontario, Canada. MedRxiv [Preprint]. 2021.

135. Cameroni E, Saliba C, Bowen JE, Rosen LE, Culap K, Pinto D, et al. Broadly neutralizing antibodies overcome SARS-CoV-2 Omicron antigenic shift. BioRxiv [Preprint]. 2021.

136. Shah M, Woo HG. Omicron: A heavily mutated SARS-CoV-2 variant exhibits stronger binding to ACE2 and potently escape approved COVID-19 therapeutic antibodies. BioRxiv [Preprint]. 2021.

137. Wolter N, Jassat W, Walaza S, Welch R, Moultrie H, Groome M, et al. Early assessment of the clinical severity of the SARS-CoV-2 Omicron variant in South Africa. MedRxiv [Preprint]. 2021.

138. Gov.uk [Internet]. Omicron daily overview: 24 December 2021. UK Health Security Agency. [24 December 2021; cited 4 January 2022]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1043866/20211224_OS_Daily_Omicron_Overview.pdf

139. Who.int [Internet]. Enhancing readiness for Omicron (B.1.1.529): Technical brief and priority actions for Member States. World Health Organisation. [23 December 2021; cited 4 January 2022]. Available from: https://www.who.int/docs/default-source/coronaviruse/2021-12-23-global-technical-brief-and-priority-action-on-omicron.pdf?sfvrsn=d0e9fb6c_8

140. Med.hku.hk [Internet]. HKUMed finds Omicron SARS-CoV-2 can infect faster and better than Delta in human bronchus but with less severe infection in lung. The University of Hong Kong, LKS Faculty of Medicine. [15 December 2021; cited 5 January 2022]. Available from: https://www.med.hku.hk/en/news/press/20211215-omicron-sars-cov-2-infection

141. Sheikh A, Kerr S, Woolhouse M, McMenamin J, C. R. Severity of Omicron variant of concern and vaccine effectiveness against symptomatic disease: national cohort with nested test negative design study in Scotland. 2021.
142. Pulliam JRC, van Schalkwyk C, Govender N, von Gottberg A, Cohen C, Groome MJ, et al. Increased risk of SARS-CoV-2 reinfection associated with emergence of the Omicron variant in South Africa. MedRxiv [Preprint]. 2021.
143. Sandile Cele, Laurelle Jackson, Khadija Khan, David Khoury, Thandeka Moyo-Gwete, Houriiyah Tegally, et al. SARS-CoV-2 Omicron has extensive but incomplete escape of Pfizer BNT162b2 elicited neutralization and requires ACE2 for infection. MedRxiv [Preprint]. 2021.
144. Planas D, Saunders N, Maes P, Guivel-Benhassine F, Planchais C, Buchrieser J, et al. Considerable escape of SARS-CoV-2 variant Omicron to antibody neutralization. BioRxiv [Preprint]. 2021.
145. Meng B, Ferreira IATM, Abdullahi A, Saito A, Kimura I, Yamasoba D, et al. SARS-CoV-2 Omicron spike mediated immune escape, infectivity and cell-cell fusion. BioRxiv [Preprint]. 2021.
146. Pfizer.com [Internet]. Pfizer and BioNTech Provide Update on Omicron Variant. Pfizer. [8 December 2021; cited 4 January 2022]. Available from: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-provide-update-omicron-variant
147. Keeton R, Tincho MB, Ngomti A, Baguma R, Benede N, Suzuki A, et al. SARS-CoV-2 spike T cell responses induced upon vaccination or infection remain robust against Omicron. MedRxiv [Preprint]. 2021.
148. Sacoronavirus.co.za [Internet]. Cabinet approves changes to covid-19 regulations. South Africa Department of Health. [30 December 2021; cited 7 January 2022]. Available from: https://sacoronavirus.co.za/2021/12/30/media-release-cabinet-approves-changes-to-covid-19-regulations/
149. Taylor L. Covid-19: Omicron drives weekly record high in global infections. BMJ. 2022;376:o66.
150. Tada T, Zhou H, Dcosta BM, Samanovic MI, Mulligan MJ, Landau NR. SARS-CoV-2 Lambda Variant Remains Susceptible to Neutralization by mRNA Vaccine-elicited Antibodies and Convalescent Serum. BioRxiv [Preprint]. 2021.
151. Acevedo ML, Alonso-Palomares L, Bustamante A, Gaggero A, Paredes F, Cortés CP, et al. Infectivity and immune escape of the new SARS-CoV-2 variant of interest Lambda. MedRxiv [Preprint]. 2021.
152. Laiton-Donato K, Franco-Munoz C, Alvarez-Diaz DA, Ruiz-Moreno HA, Usme-Ciro JA, Prada DA, et al. Characterization of the emerging B.1.621 variant of interest of SARS-CoV-2. Infect Genet Evol. 2021;95:105038.
153. Chen J, Gao K, Wang R, Wei GW. Revealing the Threat of Emerging SARS-CoV-2 Mutations to Antibody Therapies. J Mol Biol. 2021;433(18):167155.
154. Amanat F, Krammer F. SARS-CoV-2 vaccines: status report. Immunity. 2020;52(4):583-9.
155. Who.int [Internet]. COVID-19 vaccine tracker and landscape. World Health Organisation. [25 January 2022; cited 26 January 2022]. Available from: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

156. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020;383(27):2603-15.
157. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh C-L, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020;367(6483):1260-3.
158. Who.int [Internet]. Coronavirus disease (COVID-19): Vaccines. World Health Organisation. [20 January 2022; cited 26 January 2022]. Available from: https://www.who.int/news-room/questions-and-answers/item/coronavirus-disease-(covid-19)-vaccines
159. Sahin U, Muik A, Vogler I, Derhovanessian E, Kranz LM, Vormehr M, et al. BNT162b2 vaccine induces neutralizing antibodies and poly-specific T cells in humans. Nature. 2021;595(7868):572-7.
160. Arunachalam PS, Scott MKD, Hagan T, Li C, Feng Y, Wimmers F, et al. Systems vaccinology of the BNT162b2 mRNA vaccine in humans. Nature. 2021;596(7872):410-6.
161. Walsh EE, Frenck RW, Jr., Falsey AR, Kitchin N, Absalon J, Gurtman A, et al. Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates. N Engl J Med. 2020;383(25):2439-50.
162. Appelman B, van der Straten K, Lavell AHA, Schinkel M, Slim MA, Poniman M, et al. Time since SARS-CoV-2 infection and humoral immune response following BNT162b2 mRNA vaccination. EBioMedicine. 2021;72:103589.
163. Beatty AL, Peyser ND, Butcher XE, Cocohoba JM, Lin F, Olgin JE, et al. Analysis of COVID-19 Vaccine Type and Adverse Effects Following Vaccination. JAMA Netw Open. 2021;4(12):e2140364.
164. Vizcarra P, Haemmerle J, Velasco H, Velasco T, Fernandez-Escribano M, Vallejo A, et al. BNT162b2 mRNA COVID-19 vaccine Reactogenicity: The key role of immunity. Vaccine. 2021;39(51):7367-74.
165. Salmeron Rios S, Mas Romero M, Cortes Zamora EB, Tabernero Sahuquillo MT, Romero Rizos L, Sanchez-Jurado PM, et al. Immunogenicity of the BNT162b2 vaccine in frail or disabled nursing home residents: COVID-A study. J Am Geriatr Soc. 2021;69(6):1441-7.
166. Barda N, Dagan N, Ben-Shlomo Y, Kepten E, Waxman J, Ohana R, et al. Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. N Engl J Med. 2021;385(12):1078-90.
167. Sharma O, Sultan AA, Ding H, Triggle CR. A Review of the Progress and Challenges of Developing a Vaccine for COVID-19. Front Immunol. 2020;11:585354.
168. Who.int [Internet]. WHO lists two additional COVID-19 vaccines for emergency use and COVAX roll-out. World Health Organisation. [15 February 2021; cited 13 October 2021]. Available rom: https://www.who.int/news/item/15-02-2021-who-lists-two-additional-covid-19-vaccines-for-emergency-use-and-covax-roll-out
169. Ewer KJ, Barrett JR, Belij-Rammerstorfer S, Sharpe H, Makinson R, Morter R, et al. T cell and antibody responses induced by a single dose of ChAdOx1 nCoV-19 (AZD1222) vaccine in a phase 1/2 clinical trial. Nat Med. 2021;27(2):270-8.
170. Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij-Rammerstorfer S, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-

CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. Lancet. 2020;396(10249):467-78.
171. Al Khames Aga QA, Alkhaffaf WH, Hatem TH, Nassir KF, Batineh Y, Dahham AT, et al. Safety of COVID-19 vaccines. J Med Virol. 2021;93(12):6588-94.
172. Sadoff J, Gray G, Vandebosch A, Cardenas V, Shukarev G, Grinsztejn B, et al. Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19. N Engl J Med. 2021;384(23):2187-201.
173. Alter G, Yu J, Liu J, Chandrashekar A, Borducchi EN, Tostanoski LH, et al. Immunogenicity of Ad26.COV2.S vaccine against SARS-CoV-2 variants in humans. Nature. 2021;596(7871):268-72.
174. Sadoff J, Le Gars M, Shukarev G, Heerwegh D, Truyers C, de Groot AM, et al. Interim Results of a Phase 1-2a Trial of Ad26.COV2.S Covid-19 Vaccine. N Engl J Med. 2021;384(19):1824-35.
175. Keeton R, Richardson SI, Moyo-Gwete T, Hermanus T, Tincho MB, Benede N, et al. Prior infection with SARS-CoV-2 boosts and broadens Ad26.COV2.S immunogenicity in a variant-dependent manner. Cell Host Microbe. 2021;29(11):1611-9 e5.
176. See I, Su JR, Lale A, Woo EJ, Guh AY, Shimabukuro TT, et al. US Case Reports of Cerebral Venous Sinus Thrombosis With Thrombocytopenia After Ad26.COV2.S Vaccination, March 2 to April 21, 2021. JAMA. 2021;325(24):2448-56.
177. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2021;384(5):403-16.
178. Mukhopadhyay L, Yadav PD, Gupta N, Mohandas S, Patil DY, Shete-Aich A, et al. Comparison of the immunogenicity & protective efficacy of various SARS-CoV-2 vaccine candidates in non-human primates. Indian J Med Res. 2021;153(1 & 2):93-114.
179. Anderson EJ, Rouphael NG, Widge AT, Jackson LA, Roberts PC, Makhene M, et al. Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults. N Engl J Med. 2020;383(25):2427-38.
180. Jackson LA, Anderson EJ, Rouphael NG, Roberts PC, Makhene M, Coler RN, et al. An mRNA Vaccine against SARS-CoV-2 - Preliminary Report. N Engl J Med. 2020;383(20):1920-31.
181. Chu L, McPhee R, Huang W, Bennett H, Pajon R, Nestorova B, et al. A preliminary report of a randomized controlled phase 2 trial of the safety and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine. Vaccine. 2021;39(20):2791-9.
182. Who.int [Internet]. Interim recommendations for use of the inactivated COVID-19 vaccine BIBP developed by China National Biotec Group (CNBG), Sinopharm. World Health Organisation. [28 October 2021; cited 7 January 2022]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-BIBP
183. Who.int [Internet]. Background document on the inactivated vaccine Sinovac-CoronaVac against COVID-19. World Health Organisation. [1 June 2021; cited 13 October 2021]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-Sinovac-CoronaVac-background-2021.1
184. Who.int [Internet]. Background document on the Bharat Biotech BBV152 COVAXIN® (COVID-19) vaccine. World Health Organisation. [3 November 2021;

cited 7 January 2022]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-bbv152-covaxin-background

185. Who.int [Internet]. WHO issues emergency use listing for eighth COVID-19 vaccine. World Health Organisation. [3 November 2021; cited 7 January 2022]. Available from: https://www.who.int/news/item/03-11-2021-who-issues-emergency-use-listing-for-eighth-covid-19-vaccine

186. Who.int [Internet]. WHO lists 9th COVID-19 vaccine for emergency use with aim to increase access to vaccination in lower-income countries. World Health Organisation. [17 December 2021; cited 7 January 2022]. Available from: https://www.who.int/news/item/17-12-2021-who-lists-9th-covid-19-vaccine-for-emergency-use-with-aim-to-increase-access-to-vaccination-in-lower-income-countries

187. Who.int [Internet]. WHO lists 10th COVID-19 vaccine for emergency use: Nuvaxovid. World Health Organisation. [21 December 2021; cited 7 January 2022]. Available from: https://www.who.int/news/item/21-12-2021-who-lists-10th-covid-19-vaccine-for-emergency-use-nuvaxovid

188. Who.int [Internet]. Interim recommendations for use of the Novavax NVX-CoV2373 vaccine against COVID-19. World Health Organisation. [20 December 2021; cited 7 January 2022]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-novavax-nvx-cov2373

189. Mishra SK, Pradhan SK, Pati S, Sahu S, Nanda RK. Waning of Anti-spike Antibodies in AZD1222 (ChAdOx1) Vaccinated Healthcare Providers: A Prospective Longitudinal Study. Cureus. 2021;13(11):e19879.

190. Tre-Hardy M, Cupaiolo R, Wilmet A, Antoine-Moussiaux T, Della Vecchia A, Horeanga A, et al. Immunogenicity of mRNA-1273 COVID vaccine after 6 months surveillance in health care workers; a third dose is necessary. J Infect. 2021;83(5):559-64.

191. Shrotri M, Navaratnam AMD, Nguyen V, Byrne T, Geismar C, Fragaszy E, et al. Spike-antibody waning after second dose of BNT162b2 or ChAdOx1. Lancet. 2021;398(10298):385-7.

192. Chemaitelly H, Tang P, Hasan MR, AlMukdad S, Yassine HM, Benslimane FM, et al. Waning of BNT162b2 Vaccine Protection against SARS-CoV-2 Infection in Qatar. N Engl J Med. 2021.

193. Mizrahi B, Lotan R, Kalkstein N, Peretz A, Perez G, Ben-Tov A, et al. Correlation of SARS-CoV-2 Breakthrough Infections to Time-from-vaccine; Preliminary Study. MedRxiv [Preprint]. 2021.

194. Thomas SJ, Moreira ED, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Six Month Safety and Efficacy of the BNT162b2 mRNA COVID-19 Vaccine. MedRxiv [Preprint]. 2021.

195. Tre-Hardy M, Cupaiolo R, Wilmet A, Antoine-Moussiaux T, Della Vecchia A, Horeanga A, et al. Six-month interim analysis of ongoing immunogenicity surveillance of the mRNA-1273 vaccine in healthcare workers: A third dose is expected. J Infect. 2021.

196. Almendro-Vazquez P, Laguna-Goya R, Ruiz-Ruigomez M, Utrero-Rico A, Lalueza A, Maestro de la Calle G, et al. Longitudinal dynamics of SARS-CoV-2-

specific cellular and humoral immunity after natural infection or BNT162b2 vaccination. PLoS Pathog. 2021;17(12):e1010211.

197. Cohen KW, Linderman SL, Moodie Z, Czartoski J, Lai L, Mantus G, et al. Longitudinal analysis shows durable and broad immune memory after SARS-CoV-2 infection with persisting antibody responses and memory B and T cells. Cell Rep Med. 2021;2(7):100354.

198. Zeng G, Wu Q, Pan H, Li M, Yang J, Wang L, et al. Immunogenicity and safety of a third dose of CoronaVac, and immune persistence of a two-dose schedule, in healthy adults: interim results from two single-centre, double-blind, randomised, placebo-controlled phase 2 clinical trials. Lancet Infect Dis. 2021.

199. Choi A, Koch M, Wu K, Chu L, Ma L, Hill A, et al. Safety and immunogenicity of SARS-CoV-2 variant mRNA vaccine boosters in healthy adults: an interim analysis. Nat Med. 2021.

200. Flaxman A, Marchevsky NG, Jenkin D, Aboagye J, Aley PK, Angus B, et al. Reactogenicity and immunogenicity after a late second dose or a third dose of ChAdOx1 nCoV-19 in the UK: a substudy of two randomised controlled trials (COV001 and COV002). Lancet. 2021;398(10304):981-90.

201. Iketani S, Liu L, Nair MS, Mohri H, Wang M, Huang Y, et al. A third COVID-19 vaccine shot markedly boosts neutralizing antibody potency and breadth MedRxiv [Preprint]. 2021.

202. Garcia-Beltran WF, St Denis KJ, Hoelzemer A, Lam EC, Nitido AD, Sheehan ML, et al. mRNA-based COVID-19 vaccine boosters induce neutralizing immunity against SARS-CoV-2 Omicron variant. MedRxiv [Preprint]. 2021.

203. Yorsaeng R, Suntronwong N, Phowatthanasathian H, Assawakosri S, Kanokudom S, Thongmee T, et al. Immunogenicity of a third dose viral-vectored COVID-19 vaccine after receiving two-dose inactivated vaccines in healthy adults. Vaccine. 2022;40(3):524-30.

204. Munro APS, Janani L, Cornelius V, Aley PK, Babbage G, Baxter D, et al. Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial. Lancet. 2021;398(10318):2258-76.

205. Madelon N, Heikkilä N, Sabater Royo I, Fontannaz P, Breville G, Lauper K, et al. Omicron-specific cytotoxic T-cell responses are boosted following a third dose of mRNA COVID-19 vaccine in anti-CD20-treated multiple sclerosis patients MedRxiv [Preprint]. 2021.

206. Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Kalkstein N, et al. Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel. N Engl J Med. 2021;385(15):1393-400.

207. Barda N, Dagan N, Cohen C, Hernan MA, Lipsitch M, Kohane IS, et al. Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. Lancet. 2021;398(10316):2093-100.

208. Arbel R, Hammerman A, Sergienko R, Friger M, Peretz A, Netzer D, et al. BNT162b2 Vaccine Booster and Mortality Due to Covid-19. N Engl J Med. 2021;385(26):2413-20.

209. Spitzer A, Angel Y, Marudi O, Zeltser D, Saiag E, Goldshmidt H, et al. Association of a Third Dose of BNT162b2 Vaccine With Incidence of SARS-CoV-2 Infection Among Health Care Workers in Israel. JAMA. 2022.
210. Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Alroy-Preis S, et al. Protection against Covid-19 by BNT162b2 Booster across Age Groups. N Engl J Med. 2021;385(26):2421-30.
211. Levine-Tiefenbrun M, Yelin I, Alapi H, Katz R, Herzel E, Kuint J, et al. Viral loads of Delta-variant SARS-CoV-2 breakthrough infections after vaccination and booster with BNT162b2. Nat Med. 2021;27(12):2108-10.
212. Andrews N, Stowe J, Kirsebom F, Toffa S, Rickeard T, Gallagher E, et al. Effectiveness of COVID-19 vaccines against the Omicron (B.1.1.529) variant of concern. medRxiv [Preprint]. 2021.
213. Hansen CH, Schelde AB, Moustsen-Helm IR, Emborg H-D, Krause TG, Mølbak K, et al. Vaccine effectiveness against SARS-CoV-2 infection with the Omicron or Delta variants following a two-dose or booster BNT162b2 or mRNA-1273 vaccination series: A Danish cohort study MedRxiv [Preprint]. 2021.
214. Lusvarghi S, Pollett SD, Neerukonda SN, Wang W, Wang R, Vassell R, et al. SARS-CoV-2 Omicron neutralization by therapeutic antibodies, convalescent sera, and post-mRNA vaccine booster. BioRxiv [Preprint]. 2021.
215. Cdc.gov [Internet]. CDC Recommends Pfizer Booster at 5 Months, Additional Primary Dose for Certain Immunocompromised Children. Centers for Disease Control and Prevention. [4 January 2022; cited 7 January 2022]. Available from: https://www.cdc.gov/media/releases/2022/s0104-Pfizer-Booster.html
216. Wu K, Choi A, Koch M, Elbashir S, Ma L, Lee D, et al. Variant SARS-CoV-2 mRNA vaccines confer broad neutralization as primary or booster series in mice. Vaccine. 2021;39(51):7394-400.
217. Covid19-trials.com [Internet]. Global Coronavirus COVID-19 Clinical Trial Tracker. Cytel Inc. [cited 12 January 2022]. Available from: https://www.covid19-trials.com/
218. Gov.uk [Internet]. First oral antiviral for COVID-19, Lagevrio (molnupiravir), approved by MHRA. Medicines and Healthcare products Regulatory Agency. [4 November 2021; cited 12 January 2022]. Available from: https://www.gov.uk/government/news/first-oral-antiviral-for-covid-19-lagevrio-molnupiravir-approved-by-mhra
219. Gov.uk [Internet]. Oral COVID-19 antiviral, Paxlovid, approved by UK regulator. Medicines and Healthcare products Regulatory Agency. [31 December 2021; cited 12 January 2022]. Available from: https://www.gov.uk/government/news/oral-covid-19-antiviral-paxlovid-approved-by-uk-regulator
220. Fda.gov [Internet]. Coronavirus (COVID-19) Update: FDA Authorizes Additional Oral Antiviral for Treatment of COVID-19 in Certain Adults. U.S. Food and Drug Administration. [23 December 2021; cited 12 January 2022]. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-oral-antiviral-treatment-covid-19-certain
221. Fda.gov [Internet]. Coronavirus (COVID-19) Update: FDA Authorizes First Oral Antiviral for Treatment of COVID-19. U.S. Food and Drug Administration. [22 December 2021; cited 12 January 2022]. Available from: https://www.fda.gov/news-

events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-oral-antiviral-treatment-covid-19

222. ema.europa.eu [Internet]. EMA issues advice on use of Lagevrio (molnupiravir) for the treatment of COVID-19. European Medicines Agency. [19 November 2021.; cited 12 January 2022]. Available from: https://www.ema.europa.eu/en/news/ema-issues-advice-use-lagevrio-molnupiravir-treatment-covid-19

223. ema.europa.eu [Internet]. EMA issues advice on use of Paxlovid (PF-07321332 and ritonavir) for the treatment of COVID-19: rolling review starts in parallel. European Medicines Agency. [16 December 2021.; cited 12 January 2022]. Available from: https://www.ema.europa.eu/en/news/ema-issues-advice-use-paxlovid-pf-07321332-ritonavir-treatment-covid-19-rolling-review-starts

224. Gov.uk [Internet]. MHRA approves Xevudy (sotrovimab), a COVID-19 treatment found to cut hospitalisation and death by 79%. Medicines and Healthcare products Regulatory Agency. [2 December 2021; cited 12 January 2022]. Available from: https://www.gov.uk/government/news/mhra-approves-xevudy-sotrovimab-a-covid-19-treatment-found-to-cut-hospitalisation-and-death-by-79#:~:text=and%20licensing%20guidance-,MHRA%20approves%20Xevudy%20(sotrovimab)%2C%20a%20COVID%2D19%20treatment,risk%20of%20developing%20severe%20disease.

225. Fda.gov [Internet]. Coronavirus (COVID-19) Update: FDA Authorizes Additional Monoclonal Antibody for Treatment of COVID-19. U.S. Food and Drug Administration. [26 May 2021; cited 12 January 2022]. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-monoclonal-antibody-treatment-covid-19

226. ema.europa.eu [Internet]. COVID-19: EMA recommends authorisation of antibody medicine Xevudy. European Medicines Agency. [16 December 2021.; cited 12 January 2022]. Available from: https://www.ema.europa.eu/en/news/covid-19-ema-recommends-authorisation-antibody-medicine-xevudy#:~:text=EMA's%20human%20medicines%20committee%20(CHMP,medicine%20together%20with%20Vir%20Biotechnology.

227. Who.int [Internet]. Therapeutics and COVID-19: living guideline. World Health Organisation. [14 January 2022; cited 21 January 2022] Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022.1

228. Nice.org.uk [Internet]. COVID-19 rapid guideline: managing COVID-19 NICE guideline [NG191]. National Institute for Health and Care Excellence. [16 December 2021; cited 21 January 2022]. Available from: https://www.nice.org.uk/guidance/ng191

229. Gov.uk [Internet]. MHRA guidance on coronavirus (COVID-19). Medicines and Healthcare products Regulatory Agency. [16 September 2021; cited 21 January 2022]. Available from: https://www.gov.uk/government/collections/mhra-guidance-on-coronavirus-covid-19

230. ecdc.europa.eu [Internet]. All resources on COVID-19 – Guidance and technical reports. [2022; cited 21 January 2022]. Available from: https://www.ecdc.europa.eu/en/covid-19/all-reports-covid-19

231. Nih.gov [Internet]. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health [19 January 2022; cited 21 January 2022]. Available from: https://www.covid19treatmentguidelines.nih.gov/
232. Cdc.gov [Internet]. Guidance for COVID-19. Centers for Disease Control and Prevention. [15 March 2021; cited 21 January 2022]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/communication/guidance.html
233. Blundell R, Costa Dias M, Joyce R, Xu X. COVID-19 and Inequalities. Fisc Stud. 2020.
234. Chadeau-Hyam M, Bodinier B, Elliott J, Whitaker MD, Tzoulaki I, Vermeulen R, et al. Risk factors for positive and negative COVID-19 tests: a cautious and in-depth analysis of UK biobank data. Int J Epidemiol. 2020;49(5):1454-67.
235. Patel JA, Nielsen FBH, Badiani AA, Assi S, Unadkat VA, Patel B, et al. Poverty, inequality and COVID-19: the forgotten vulnerable. Public Health. 2020;183:110-1.
236. Cohen J, Rodgers YVM. Contributing factors to personal protective equipment shortages during the COVID-19 pandemic. Prev Med. 2020;141:106263.
237. Who.int [Internet]. Vaccine Equity. World Health Organisation. [cited 10 January 2022]. Available from: https://www.who.int/campaigns/vaccine-equity
238. parliament.uk [Internet]. Coronavirus: lessons learned to date. The House of Commons, Science and Technology Committee, and Health and Social Care Committee. [12 October 2021; cited 10 January 2022]. Available from: https://publications.parliament.uk/pa/cm5802/cmselect/cmsctech/92/9203.htm
239. Ball P. The lightning-fast quest for COVID vaccines - and what it means for other diseases. Nature. 2021;589(7840):16-8.
240. Summers J, Cheng HY, Lin HH, Barnard LT, Kvalsvig A, Wilson N, et al. Potential lessons from the Taiwan and New Zealand health responses to the COVID-19 pandemic. Lancet Reg Health West Pac. 2020;4:100044.
241. Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. N Engl J Med. 2021;384(15):1412-23.
242. Lopez Bernal J, Andrews N, Gower C, Gallagher E, Simmons R, Thelwall S, et al. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. N Engl J Med. 2021;385(7):585-94.
243. Abu-Raddad LJ, Chemaitelly H, Butt AA, National Study Group for C-V. Effectiveness of the BNT162b2 Covid-19 Vaccine against the B.1.1.7 and B.1.351 Variants. N Engl J Med. 2021;385(2):187-9.
244. Chung H, He S, Nasreen S, Sundaram ME, Buchan SA, Wilson SE, et al. Effectiveness of BNT162b2 and mRNA-1273 covid-19 vaccines against symptomatic SARS-CoV-2 infection and severe covid-19 outcomes in Ontario, Canada: test negative design study. BMJ. 2021;374:n1943.
245. Nasreen S, Chung H, He S, Brown KA, Gubbay JB, Buchan SA, et al. Effectiveness of mRNA and ChAdOx1 COVID-19 vaccines against symptomatic SARS CoV-2 infection and severe outcomes with variants of concern in Ontario. MedRxiv [Preprint]. 2021.

246. Puranik A, Lenehan PJ, Silvert E, Niesen MJM, Corchado-Garcia J, O'Horo JC, et al. Comparison of two highly-effective mRNA vaccines for COVID-19 during periods of Alpha and Delta variant prevalence. MedRxiv [Preprint]. 2021.
247. Julia Stowe, Nick Andrews, Charlotte Gower, Eileen Gallagher, Lara Utsi, Ruth Simmons, et al. Effectiveness of COVID-19 vaccines against hospital admission with the Delta (B.1.617.2) variant. Public Health England [preprint]. 2021.
248. Lopez Bernal J, Andrews N, Gower C, Robertson C, Stowe J, Tessier E, et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. BMJ. 2021;373:n1088.
249. Skowronski DM, Setayeshgar S, Zou M, Prystajecky N, Tyson JR, Galanis E, et al. Single-dose mRNA vaccine effectiveness against SARS-CoV-2, including Alpha and Gamma variants: a test-negative design in adults 70 years and older in British Columbia, Canada. Clin Infect Dis. 2021.
250. Carazo S, Talbot D, Boulianne N, Brisson M, Gilca R, Deceuninck G, et al. Single-dose mRNA vaccine effectiveness against SARS-CoV-2 in healthcare workers extending 16 weeks post-vaccination: a test-negative design from Quebec, Canada. Clin Infect Dis. 2021.
251. Charmet T, Schaeffer L, Grant R, Galmiche S, Cheny O, Von Platen C, et al. Impact of original, B.1.1.7, and B.1.351/P.1 SARS-CoV-2 lineages on vaccine effectiveness of two doses of COVID-19 mRNA vaccines: Results from a nationwide case-control study in France. Lancet Reg Health Eur. 2021;8:100171.
252. Tang P, Hasan MR, Chemaitelly H, Yassine HM, Benslimane FM, Al Khatib HA, et al. BNT162b2 and mRNA-1273 COVID-19 vaccine effectiveness against the SARS-CoV-2 Delta variant in Qatar. Nat Med. 2021;27(12):2136-43.
253. Hall VJ, Foulkes S, Saei A, Andrews N, Oguti B, Charlett A, et al. COVID-19 vaccine coverage in health-care workers in England and effectiveness of BNT162b2 mRNA vaccine against infection (SIREN): a prospective, multicentre, cohort study. Lancet. 2021;397(10286):1725-35.
254. Haas EJ, Angulo FJ, McLaughlin JM, Anis E, Singer SR, Khan F, et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. Lancet. 2021;397(10287):1819-29.
255. Nanduri S, Pilishvili T, Derado G, Soe MM, Dollard P, Wu H, et al. Effectiveness of Pfizer-BioNTech and Moderna Vaccines in Preventing SARS-CoV-2 Infection Among Nursing Home Residents Before and During Widespread Circulation of the SARS-CoV-2 B.1.617.2 (Delta) Variant - National Healthcare Safety Network, March 1-August 1, 2021. MMWR Morb Mortal Wkly Rep. 2021;70(34):1163-6.
256. Fowlkes A, Gaglani M, Groover K, Thiese MS, Tyner H, Ellingson K, et al. Effectiveness of COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Frontline Workers Before and During B.1.617.2 (Delta) Variant Predominance - Eight U.S. Locations, December 2020-August 2021. MMWR Morb Mortal Wkly Rep. 2021;70(34):1167-9.

257. Lefevre B, Tondeur L, Madec Y, Grant R, Lina B, van der Werf S, et al. Beta SARS-CoV-2 variant and BNT162b2 vaccine effectiveness in long-term care facilities in France. Lancet Healthy Longev. 2021.
258. Pouwels KB, Pritchard E, Matthews PC, Stoesser N, Eyre DW, Vihta K-D, et al. Effect of Delta variant on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK. Nature Medicine. 2021.
259. Williams C, Al-Bargash D, Macalintal C, Stuart R, Seth A, Latham J, et al. COVID-19 Outbreak Associated with a SARS-CoV-2 P.1 Lineage in a Long-Term Care Home after Implementation of a Vaccination Program - Ontario, April-May 2021. Clin Infect Dis. 2021.
260. Fabiani M, Ramigni M, Gobbetto V, Mateo-Urdiales A, Pezzotti P, Piovesan C. Effectiveness of the Comirnaty (BNT162b2, BioNTech/Pfizer) vaccine in preventing SARS-CoV-2 infection among healthcare workers, Treviso province, Veneto region, Italy, 27 December 2020 to 24 March 2021. Euro Surveill. 2021;26(17).
261. Thomas SJ, Moreira ED, Jr., Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months. N Engl J Med. 2021;385(19):1761-73.
262. Angel Y, Spitzer A, Henig O, Saiag E, Sprecher E, Padova H, et al. Association Between Vaccination With BNT162b2 and Incidence of Symptomatic and Asymptomatic SARS-CoV-2 Infections Among Health Care Workers. JAMA. 2021;325(24):2457-65.
263. Bjork J, Inghammar M, Moghaddassi M, Rasmussen M, Malmqvist U, Kahn F. High level of protection against COVID-19 after two doses of BNT162b2 vaccine in the working age population - first results from a cohort study in Southern Sweden. Infect Dis (Lond). 2022;54(2):128-33.
264. Cabezas C, Coma E, Mora-Fernandez N, Li X, Martinez-Marcos M, Fina F, et al. Associations of BNT162b2 vaccination with SARS-CoV-2 infection and hospital admission and death with covid-19 in nursing homes and healthcare workers in Catalonia: prospective cohort study. BMJ. 2021;374:n1868.
265. Emborg H-D, Valentiner-Branth P, Schelde AB, Nielsen KF, Gram MA, Moustsen-Helms IR, et al. Vaccine effectiveness of the BNT162b2 mRNA COVID-19 vaccine against RT-PCR confirmed SARS-CoV2 infections, hospitalisations and mortality in prioritised risk groups. MedRxiv [Preprint]. 2021.
266. Gras-Valenti P, Chico-Sanchez P, Algado-Selles N, Jimenez-Sepulveda NJ, Gomez-Sotero IL, Fuster-Perez M, et al. [Effectiveness of the first dose of BNT162b2 vaccine to preventing covid-19 in healthcare personnel.]. Rev Esp Salud Publica. 2021;95.
267. Mason TFD, Whitston M, Hodgson J, Watkinson RE, Lau YS, Abdulrazeg O, et al. Effects of BNT162b2 mRNA vaccine on COVID-19 infection and hospitalisation amongst older people: matched case control study for England. BMC Med. 2021;19(1):275.
268. Monge S, Olmedo C, Alejos B, Lapena MF, Sierra MJ, Limia A, et al. Direct and Indirect Effectiveness of mRNA Vaccination against Severe Acute Respiratory Syndrome Coronavirus 2 in Long-Term Care Facilities, Spain. Emerg Infect Dis. 2021;27(10):2595-603.

269. Pritchard E, Matthews PC, Stoesser N, Eyre DW, Gethings O, Vihta KD, et al. Impact of vaccination on new SARS-CoV-2 infections in the United Kingdom. Nat Med. 2021;27(8):1370-8.
270. Regev-Yochay G, Amit S, Bergwerk M, Lipsitch M, Leshem E, Kahn R, et al. Decreased infectivity following BNT162b2 vaccination: A prospective cohort study in Israel. Lancet Reg Health Eur. 2021;7:100150.
271. Shrotri M, Krutikov M, Palmer T, Giddings R, Azmi B, Subbarao S, et al. Vaccine effectiveness of the first dose of ChAdOx1 nCoV-19 and BNT162b2 against SARS-CoV-2 infection in residents of long-term care facilities in England (VIVALDI): a prospective cohort study. Lancet Infect Dis. 2021;21(11):1529-38.
272. Swift MD, Breeher LE, Tande AJ, Tommaso CP, Hainy CM, Chu H, et al. Effectiveness of Messenger RNA Coronavirus Disease 2019 (COVID-19) Vaccines Against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in a Cohort of Healthcare Personnel. Clin Infect Dis. 2021;73(6):e1376-e9.
273. Thompson MG, Burgess JL, Naleway AL, Tyner H, Yoon SK, Meece J, et al. Prevention and Attenuation of Covid-19 with the BNT162b2 and mRNA-1273 Vaccines. N Engl J Med. 2021;385(4):320-9.
274. Frenck RW, Jr., Klein NP, Kitchin N, Gurtman A, Absalon J, Lockhart S, et al. Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents. N Engl J Med. 2021;385(3):239-50.
275. June Choe Y, Yi S, Hwang I, Kim J, Park YJ, Cho E, et al. Safety and effectiveness of BNT162b2 mRNA Covid-19 vaccine in adolescents. Vaccine. 2021.
276. Lutrick K, Rivers P, Yoo YM, Grant L, Hollister J, Jovel K, et al. Interim Estimate of Vaccine Effectiveness of BNT162b2 (Pfizer-BioNTech) Vaccine in Preventing SARS-CoV-2 Infection Among Adolescents Aged 12-17 Years - Arizona, July-December 2021. MMWR Morb Mortal Wkly Rep. 2021;70(5152):1761-5.
277. Glatman-Freedman A, Bromberg M, Dichtiar R, Hershkovitz Y, Keinan-Boker L. The BNT162b2 vaccine effectiveness against new COVID-19 cases and complications of breakthrough cases: A nation-wide retrospective longitudinal multiple cohort analysis using individualised data. EBioMedicine. 2021;72:103574.
278. Pilishvili T, Fleming-Dutra KE, Farrar JL, Gierke R, Mohr NM, Talan DA, et al. Interim Estimates of Vaccine Effectiveness of Pfizer-BioNTech and Moderna COVID-19 Vaccines Among Health Care Personnel - 33 U.S. Sites, January-March 2021. MMWR Morb Mortal Wkly Rep. 2021;70(20):753-8.
279. Martinez-Baz I, Miqueleiz A, Casado I, Navascues A, Trobajo-Sanmartin C, Burgui C, et al. Effectiveness of COVID-19 vaccines in preventing SARS-CoV-2 infection and hospitalisation, Navarre, Spain, January to April 2021. Euro Surveill. 2021;26(21).
280. Vasileiou E, Simpson CR, Shi T, Kerr S, Agrawal U, Akbari A, et al. Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study. Lancet. 2021;397(10285):1646-57.
281. ecdc.europa.eu [Internet]. Interim analysis of COVID-19 vaccine effectiveness against Severe Acute Respiratory Infection due to laboratory-confirmed SARS-CoV-2 among individuals aged 50 years and older, ECDC multi-country study – first update. European Centre for Disease Prevention and Control. [20 January 2022; cited 24

January 2022]. Available from: https://www.ecdc.europa.eu/en/publications-data/interim-analysis-covid-19-vaccine-effectiveness-against-severe-acute-respiratory
282. Rosenberg ES, Dorabawila V, Easton D, Bauer UE, Kumar J, Hoen R, et al. Covid-19 Vaccine Effectiveness in New York State. N Engl J Med. 2022;386(2):116-27.
283. Olson SM, Newhams MM, Halasa NB, Price AM, Boom JA, Sahni LC, et al. Effectiveness of BNT162b2 Vaccine against Critical Covid-19 in Adolescents. N Engl J Med. 2022.
284. Zambrano LD, Newhams MM, Olson SM, Halasa NB, Price AM, Boom JA, et al. Effectiveness of BNT162b2 (Pfizer-BioNTech) mRNA Vaccination Against Multisystem Inflammatory Syndrome in Children Among Persons Aged 12-18 Years - United States, July-December 2021. MMWR Morb Mortal Wkly Rep. 2022;71(2):52-8.
285. Emary KRW, Golubchik T, Aley PK, Ariani CV, Angus B, Bibi S, et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B.1.1.7): an exploratory analysis of a randomised controlled trial. Lancet. 2021;397(10282):1351-62.
286. astrazeneca.com [Internet]. AZD1222 US Phase III trial met primary efficacy endpoint in preventing COVID-19 at interim analysis. AstraZeneca. [22 March 2021; cited 15 October 2021]. Available from: https://www.astrazeneca.com/media-centre/press-releases/2021/astrazeneca-us-vaccine-trial-met-primary-endpoint.html
287. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet. 2021;397(10269):99-111.
288. Madhi SA, Baillie V, Cutland CL, Voysey M, Koen AL, Fairlie L, et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant. N Engl J Med. 2021;384(20):1885-98.
289. Pramod S, Govindan D, Ramasubramani P, Kar SS, Aggarwal R, Manoharan N, et al. Effectiveness of Covishield vaccine in preventing Covid-19 – A test-negative case control study. MedRxiv [Preprint]. 2021.
290. Falsey AR, Sobieszczyk ME, Hirsch I, Sproule S, Robb ML, Corey L, et al. Phase 3 Safety and Efficacy of AZD1222 (ChAdOx1 nCoV-19) Covid-19 Vaccine. N Engl J Med. 2021;385(25):2348-60.
291. Clemens SAC, Folegatti PM, Emary KRW, Weckx LY, Ratcliff J, Bibi S, et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 lineages circulating in Brazil. Nat Commun. 2021;12(1):5861.
292. Voysey M, Costa Clemens SA, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. Lancet. 2021;397(10277):881-91.
293. Bhattacharya A, Ranjan P, Ghosh T, Agarwal H, Seth S, Maher GT, et al. Evaluation of the dose-effect association between the number of doses and duration since the last dose of COVID-19 vaccine, and its efficacy in preventing the disease and reducing disease severity: A single centre, cross-sectional analytical study from India. Diabetes Metab Syndr. 2021;15(5):102238.

294. Malathi Murugesan, Prasad Mathews, Hema Paul, Rajiv Karthik, Joy John Mammen, Rupali. P. Protective Effect Conferred by Prior Infection and Vaccination on COVID-19 in a Healthcare Worker Cohort in South India. SSRN [Preprint]. 2021.
295. Alencar CH, Cavalcanti LPG, Almeida MM, Barbosa PPL, Cavalcante KKS, Melo DN, et al. High Effectiveness of SARS-CoV-2 Vaccines in Reducing COVID-19-Related Deaths in over 75-Year-Olds, Ceara State, Brazil. Trop Med Infect Dis. 2021;6(3).
296. Cerqueira-Silva T, Oliveira VdA, Pescarini J, Bertoldo Júnior J, Machado TM, Flores-Ortiz R, et al. The effectiveness of Vaxzevria and CoronaVac vaccines: A nationwide longitudinal retrospective study of 61 million Brazilians (VigiVac-COVID19). . MedRxiv [Preprint]. 2021.
297. Otavio T Ranzani, Rogério dos Santos Leite, Larissa Domingues Castilho, Crhistinne Cavalheiro Maymone Gonçalves, Geraldo Resende, Rosana Leite de Melo, et al. Vaccine effectiveness of Ad26.COV2.S against symptomatic COVID-19 and clinical outcomes in Brazil: a test-negative study design. MedRxiv [Preprint]. 2021.
298. Corchado-Garcia J, Puyraimond-Zemmour D, Hughes T, Cristea-Platon T, Lenehan P, Pawlowski C, et al. Real-world effectiveness of Ad26.COV2.S adenoviral vector vaccine for COVID-19. MedRxiv [Preprint]. 2021.
299. Barlow RS, Jian K, Larson L. Effectiveness of COVID-19 Vaccines Against SARS-CoV-2 Infection During a Delta Variant Epidemic Surge in Multnomah County, Oregon, July 2021. MedRxiv [Preprint]. 2021.
300. Polinski JM, Weckstein AR, Batech M, Kabelac C, Kamath T, Harvey R, et al. Effectiveness of the Single-Dose Ad26.COV2.S COVID Vaccine. MedRxiv [Preprint]. 2021.
301. Corchado-Garcia J, Zemmour D, Hughes T, Bandi H, Cristea-Platon T, Lenehan P, et al. Analysis of the Effectiveness of the Ad26.COV2.S Adenoviral Vector Vaccine for Preventing COVID-19. JAMA Netw Open. 2021;4(11):e2132540.
302. Chin ET, Leidner D, Zhang Y, Long E, Prince L, Li Y, et al. Effectiveness of the mRNA-1273 Vaccine during a SARS-CoV-2 Delta Outbreak in a Prison. N Engl J Med. 2021;385(24):2300-1.
303. Gupta K, O'Brien WJ, Bellino P, Linsenmeyer K, Doshi SJ, Sprague RS, et al. Incidence of SARS-CoV-2 Infection in Health Care Workers After a Single Dose of mRNA-1273 Vaccine. JAMA Netw Open. 2021;4(6):e2116416.
304. Chemaitelly H, Yassine HM, Benslimane FM, Al Khatib HA, Tang P, Hasan MR, et al. mRNA-1273 COVID-19 vaccine effectiveness against the B.1.1.7 and B.1.351 variants and severe COVID-19 disease in Qatar. Nat Med. 2021;27(9):1614-21.
305. Herlihy R, Bamberg W, Burakoff A, Alden N, Severson R, Bush E, et al. Rapid Increase in Circulation of the SARS-CoV-2 B.1.617.2 (Delta) Variant - Mesa County, Colorado, April-June 2021. MMWR Morb Mortal Wkly Rep. 2021;70(32):1084-7.
306. Bruxvoort KJ, Sy LS, Qian L, Ackerson BK, Luo Y, Lee GS, et al. Real-world effectiveness of the mRNA-1273 vaccine against COVID-19: Interim results from a prospective observational cohort study. Lancet Reg Health Am. 2021:100134.
307. Bruxvoort KJ, Sy LS, Qian L, Ackerson BK, Luo Y, Lee GS, et al. Effectiveness of mRNA-1273 against delta, mu, and other emerging variants of SARS-CoV-2: test negative case-control study. BMJ. 2021;375:e068848.

308. El Sahly HM, Baden LR, Essink B, Doblecki-Lewis S, Martin JM, Anderson EJ, et al. Efficacy of the mRNA-1273 SARS-CoV-2 Vaccine at Completion of Blinded Phase. N Engl J Med. 2021;385(19):1774-85.
309. Li XN, Huang Y, Wang W, Jing QL, Zhang CH, Qin PZ, et al. Effectiveness of inactivated SARS-CoV-2 vaccines against the Delta variant infection in Guangzhou: a test-negative case-control real-world study. Emerg Microbes Infect. 2021;10(1):1751-9.
310. Min Kang, Yao Yi, Yan Li, Limei Sun, Aiping Deng, Ting Hu, et al. Effectiveness of Inactivated COVID-19 Vaccines Against COVID-19 Pneumonia and Severe Illness Caused by the B.1.617.2 (Delta) Variant: Evidence from an Outbreak in Guangdong, China. SSRN [Preprint]. 2021.
311. Silva-Valencia Javier, Soto-Becerra Percy, Escobar-Agreda Stefan, Fernández-Navarro Manuel, Moscoso-Porras Miguel, Solari Lely, et al. Effectiveness of the BBIPB-CorV Vaccine in Preventing Infection and Death in Health Care Workers in Peru 2021. SSRN [Preprint]. 2021.
312. Al Kaabi N, Zhang Y, Xia S, Yang Y, Al Qahtani MM, Abdulrazzaq N, et al. Effect of 2 Inactivated SARS-CoV-2 Vaccines on Symptomatic COVID-19 Infection in Adults: A Randomized Clinical Trial. JAMA. 2021;326(1):35-45.
313. Farida Ismail AlHosani, Anderson Eduardo Stanciole, Bashir Aden, Andrey Timoshkin, Omar Najim, Walid Abbas Zaher, et al. Sinopharm's BBIBP-CorV vaccine effectiveness on preventing hospital admission and deaths: results from a retrospective study in the Emirate of Abu Dhabi, United Arab Emirates (UAE). SSRN [Preprint]. 2021.
314. AlQahtani M, Bhattacharyya S, Alawadi A, Mahmeed HA, Sayed JA, Justman J, et al. Morbidity and mortality from COVID-19 postvaccination breakthrough infections in association with vaccines and the emergence of variants in Bahrain. Research Square [Preprint]. 2021.
315. Jara A, Undurraga EA, Gonzalez C, Paredes F, Fontecilla T, Jara G, et al. Effectiveness of an Inactivated SARS-CoV-2 Vaccine in Chile. N Engl J Med. 2021;385(10):875-84.
316. Ranzani OT, Hitchings MDT, Dorion M, D'Agostini TL, de Paula RC, de Paula OFP, et al. Effectiveness of the CoronaVac vaccine in older adults during a gamma variant associated epidemic of covid-19 in Brazil: test negative case-control study. BMJ. 2021;374:n2015.
317. Hitchings MDT, Ranzani OT, Torres MSS, de Oliveira SB, Almiron M, Said R, et al. Effectiveness of CoronaVac among healthcare workers in the setting of high SARS-CoV-2 Gamma variant transmission in Manaus, Brazil: A test-negative case-control study. Lancet Reg Health Am. 2021;1:100025.
318. Enny S. Paixao, Kerry LM Wong, Flavia Jôse Oliveira Alves, Vinicius de Araújo Oliveira, Thiago Cerqueira-Silva, Juracy Bertoldo Júnior, et al. Effectiveness of the CoronaVac vaccine in prevention of symptomatic and progression to severe Covid-19 in pregnant women in Brazil. SSRN [Preprint]. 2021.
319. Hitchings MDT, Ranzani OT, Scaramuzzini Torres MS, de Oliveira SB, Almiron M, Said R, et al. Effectiveness of CoronaVac in the setting of high SARS-CoV-2 P.1 variant transmission in Brazil: A test-negative case-control study. MedRxiv [Preprint]. 2021.

320. Tanriover MD, Doganay HL, Akova M, Guner HR, Azap A, Akhan S, et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. Lancet. 2021;398(10296):213-22.
321. Palacios R, Batista AP, Albuquerque CSN, Patiño EG, Santos JdP, Tilli Reis Pessoa Conde M, et al. Efficacy and Safety of a COVID-19 Inactivated Vaccine in Healthcare Professionals in Brazil: The PROFISCOV Study. SSRN [Preprint]. 2021.
322. Ella R, Reddy S, Blackwelder W, Potdar V, Yadav P, Sarangi V, et al. Efficacy, safety, and lot-to-lot immunogenicity of an inactivated SARS-CoV-2 vaccine (BBV152): interim results of a randomised, double-blind, controlled, phase 3 trial. Lancet. 2021;398(10317):2173-84.
323. Desai D, Khan AR, Soneja M, Mittal A, Naik S, Kodan P, et al. Effectiveness of an inactivated virus-based SARS-CoV-2 vaccine, BBV152, in India: a test-negative, case-control study. Lancet Infect Dis. 2021.
324. Malhotra S, Mani K, Lodha R, Bakhshi S, Mathur VP, Gupta P, et al. SARS-CoV-2 Reinfection Rate and Estimated Effectiveness of the Inactivated Whole Virion Vaccine BBV152 Against Reinfection Among Health Care Workers in New Delhi, India. JAMA Netw Open. 2022;5(1):e2142210.
325. Heath PT, Galiza EP, Baxter DN, Boffito M, Browne D, Burns F, et al. Safety and Efficacy of NVX-CoV2373 Covid-19 Vaccine. N Engl J Med. 2021;385(13):1172-83.
326. Dunkle LM, Kotloff KL, Gay CL, Anez G, Adelglass JM, Barrat Hernandez AQ, et al. Efficacy and Safety of NVX-CoV2373 in Adults in the United States and Mexico. N Engl J Med. 2021.
327. Toback S, Galiza E, Cosgrove C, Galloway J, Goodman AL, Swift PA, et al. Safety, immunogenicity, and efficacy of a COVID-19 vaccine (NVX-CoV2373) co-administered with seasonal influenza vaccines: an exploratory substudy of a randomised, observer-blinded, placebo-controlled, phase 3 trial. Lancet Respir Med. 2021.
328. Shinde V, Bhikha S, Hoosain Z, Archary M, Bhorat Q, Fairlie L, et al. Efficacy of NVX-CoV2373 Covid-19 Vaccine against the B.1.351 Variant. N Engl J Med. 2021;384(20):1899-909.

COVID-19: Virology, variants, and vaccinations

Keywords: Covid-19, Coronavirus, Virology, SARS-CoV-2 variants, Vaccines.

Megan Young[1†], Harry Crook[1†], Janet Scott[2], Paul Edison[1,3,*]

[1] Faculty of Medicine, Imperial College London, London, UK.
[2] Medical Research Council-University of Glasgow Centre for Virus Research, University of Glasgow, UK
[3] School of Medicine, Cardiff University, Cardiff, UK.

† Both authors contributed equally to the manuscript

*Corresponding author:
Dr Paul Edison, MD, MRCP, PhD, FRCP, FRCPI,
Clinical Senior Lecturer, Imperial College London and Honorary Professor, Cardiff University, UK
Division of Neurology, Faculty of Medicine, Imperial College London
Level 2, Commonwealth Building,
Hammersmith Campus, Imperial College London,
Du Cane Road, London, W12 0NN, UK

Tel: +442075941081
E-mail: paul.edison@imperial.ac.uk

No authors have any competing interests.

Abstract

As of 25th January 2022, there have been over 349 million confirmed cases of COVID-19, with over 5.59 million confirmed deaths associated with the SARS-CoV-2 virus. The COVID-19 pandemic has prompted an extensive, global effort to study the molecular evolution of the virus and develop vaccines to combat its spread. Although rigorous determination of SARS-CoV-2 infectivity remains elusive, due to the continuous evolution of the virus, steps have been made to understand its genome, structure, and emerging genetic mutations. The SARS-CoV-2 genome is composed of ~~a number of~~several open reading frames (ORFs) and structural proteins, including the spike protein, which is essential for entry into host cells. As of 25th January 2022, the WHO reports five variants of concern (VOC) two variants of interest (VOI) and three variants under monitoring (VUM). The mutations harboured in these variants confer an increased transmissibility, severity of disease, and escape from neutralising antibodies compared to the primary strain. The current vaccine strategy, including booster doses, provides protection from severe disease. As of 24th January 2022, there are 33 approved vaccines in use in 197 countries. In this review, we discuss the genetics, structure and transmission methods of SARS-CoV-2 and its variants, highlighting how mutations provide enhanced abilities to spread and inflict disease. We also outline the vaccines currently in use around the world, providing evidence for the immunogenicity and effectiveness of each.

~~1.~~ Introduction

There are seven coronaviruses that infect humans, all belonging to either alpha- or beta-coronavirus subgroups, including 229E (alpha), NL63 (alpha), OC43 (beta), and HKU1 (beta)(1). Over the last two decades, three notable beta-coronaviruses, severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002, Middle East respiratory syndrome coronavirus (MERS-CoV) in 2011, and most recently, severe acute respiratory syndrome 2 (SARS-CoV-2) in 2019, have emerged and caused severe illness resulting in debilitating disease and worldwide fatalities. SARS-CoV-2 is the pathogen responsible for the current Coronavirus 2019 (COVID-19) pandemic and has caused more than 5.59 million deaths in approximately two years and resulted in multisystem illness in several million people(2).

All viruses change and mutate over time, with most changes having little to no impact. However, some mutations may alter its pathogenic or transmission potential and could, therefore, increase disease severity or hinder the effectiveness of vaccines and therapeutic strategies. The World Health Organisation (WHO) (3) classify SARS-CoV-2 variants that increase transmissibility, disease severity or virulence, or decrease the effectiveness of public health measures, diagnostics, therapeutics, or vaccines as variants of concern (VOC). Variants with genetic changes that are predicted to enhance the virulence and transmissibility of the virus which have been identified to cause community transmission in multiple countries posing a possible risk to global public health are defined as variants of interest (VOI). Lastly, the WHO defines variants with genetic changes that are suspected to affect virus characteristics and have currently unclear phenotypic or epidemiological effects as variants under monitoring (VUM). VUM are not typically assigned a name until they are upgraded to VOI or VOC. The full working definitions of VOC, VOI and VUM can be found on the WHO 'tracking SARS-CoV-2 variants' website: www.who.int/en/activities/tracking-SARS-CoV-2-variants/(3). As of 25th January 2022, the WHO reports five VOC; Alpha, Beta, Gamma, Delta and Omicron, two VOI;

Lambda and Mu, and three VUM(3). Former VOC/VOI/VUM have been reclassified as 'formerly monitored variants' due to them either no longer circulating, having little impact on the epidemiological situation, or having no concerning properties(3). Since the beginning of the COVID-19 pandemic, the rapid development of effective COVID-19 vaccines has taken place around the world. As of 24th January 2022, there are 33 approved vaccines in use in 197 countries, with ten vaccines having gained emergency use listing approval from the WHO(4).

In this review, we provide an overview of the genome and structure of SARS-CoV-2, describing how these elements allow the virus to infect and replicate inside of host cells, before outlining how certain mutations harboured by SARS-CoV-2 variants enhance these abilities. Next, we examine the current state of vaccine development around the world and provide evidence of the effectiveness of booster doses.

2. Methods

We searched PubMed and Embase databases for COVID-19-related articles published between 1st January 2020 and 25th January 2022 and for general coronavirus-related articles published from 1st January 2000 onwards. Our search terms included SARS-CoV-2, COVID-19, and specific terms including virology, genome, variants, and vaccine. Additional, specific search terms are outlined in supplementary file 1. We performed further manual searching for additional articles and data using relevant databases, including who.int, gov.uk, and ecdc.europa.eu/en. Due to the rapidly evolving nature of the literature involving SARS-CoV-2, we also searched preprint databases including MedRxiv and BioRxiv. Due to the various topics addressed here, studies were selected through different criteria, details of which can be found in supplementary file 1. Overall, studies were selected based on quality and impact factor of publishing~~journal reputation~~, with real-world studies with large sample sizes of greatest interest.

3. Viral transmission, clinical presentation, and genetic susceptibility of COVID-19

SARS-CoV-2 is predominantly spread via respiratory droplet transmission, spreading between people through close contact, coughing, or sneezing. It has been documented that the virus can also spread through airborne transmission, fomite transmission, and via other modes, such as through biological material including urine and faeces, and through (5, 6). The SARS-CoV-2 virus may survive on surfaces or suspended in air droplets for long periods of time. Indeed, on plastic, stainless steel, and glass surfaces, the half-life of the virus is around 5.3, 4.4, and 4.2 hours, respectively(7), with no difference seen between SARS-CoV-2 variants(8). Although SARS-CoV-2 can be detected on inanimate surfaces for hours and days, due to the evaporation of water droplets, the viruses' living environment, the concentration of the virus plummets rapidly(9). Protective measures, including using personal protective equipment (PPE), maintaining indoor ventilation, and disinfecting hands and surfaces, can effectively limit the spread of SARS-CoV-2(10).

Once inside the airways, SARS-CoV-2 can directly or indirectly infect ciliated, mucus-secreting, and club cells of bronchial epithelium, type 1 pneumocytes within the lungs, and the conjunctival mucosa(11). The clinical presentation of COVID-19 is non-specific, heterogeneous, and infection can result in a wide spectrum of symptoms. Following an incubation period of 4-14 days, symptoms develop ranging from mild to severe disease and, in

some cases, can result in death(12). The most common COVID-19 symptoms include fever, cough, dyspnoea, and fatigue(13, 14), while myalgia, gastrointestinal issues, cognitive deficits, and other symptoms are reported. Asymptomatic individuals can also test positive for COVID-19(15, 16). Although the entire population is susceptible to COVID-19 infection, some subgroups within the general population exist that are more susceptible to developing poorer clinical outcomes.

Risk factors associated with increased risk of hospitalisation, severe disease, and fatal outcome with COVID-19 have been identified. Older age(17-19), male sex(20, 21), non-white ethnicity(21, 22), comorbidities including diabetes, hypertension, and lung disease(18, 23-25), malignancy and immunodeficiency(26-28) have all been associated with more severe COVID-19. The duration of symptoms endured by COVID-19 patients, as well as the treatment they receive will also have profound influences on the severity of disease they experience and both the acute and long-term outcomes following recovery. The host genetic background is thought to have an influence on the susceptibility and severity of COVID-19, possibly explaining the broad spectrum of clinical manifestations that can develop in seemingly similar individuals. A study examining individuals with COVID-19 across numerous ancestry groups identified four gene loci associated with susceptibility to COVID-19; SLC6A20, RPL24, ABO, PLEKHA4, and nine associated with increased risk of severe COVID-19; LZTFL1, FOXP4, TMEM65, OAS1, KANSL1, TAC4, DPP9, RAVER1, and IFNAR2(29). Meanwhile, genome-wide association studies spanning across Europe, the United States (US), and the United Kingdom (UK) identified a gene cluster on chromosome three (chr3p21.31) as being strongly linked with susceptibility and severity of COVID-19(30, 31). Polymorphisms in the angiotensin-converting enzyme 2 (ACE2) receptor and transmembrane protease serine 2 (TMPRSS2) have also been shown to enhance SARS-CoV-2 viral entry(32, 33), with differential polymorphisms seen across ethnic populations, which may partly explain why certain ethnic groups are more susceptible to severe COVID-19. Increased ACE2 receptor levels have also been associated with other risk factors of COVID-19 including smoking and increasing age(34). The ~~utilisation~~ use –of polygenetic risk scores (PRS) may be useful in determining an individual's risk for developing severe disease caused by COVID-19(35). A PRS infers a person's risk of susceptibility to, or development of a certain disease based on the total number of genomic variations they possess. Determining PRS with the inclusion of comorbidities, such as chronic obstructive pulmonary disease(36), or other aspects, such as coagulation factors(37), may improve the usefulness of PRS in determining a person's risk of severe COVID-19.

4. Virology of SARS-CoV-2

SARS-CoV-2 is a positive-stranded ribonucleic acid (RNA) virus belonging to Coronaviridae family. Coronaviruses, which have crownlike appearances, are the largest known RNA viruses and are thought to primarily infect vertebrates(38, 39). SARS-CoV-2 belongs to the beta genus of the coronaviruses and has a genome varying from 29.8kb to 29.9kb in size(40). Human coronaviruses (HCoV) genomes consist of a variable number of open reading frames (ORFs). Following the typical 5'-3' order, the beginning two-thirds of the SARS-CoV-2 genome contains two ORFs, ORF1a and ORF1b which, inside the host cell, are translated at the rough endoplasmic reticulum into polyprotein 1a (pp1a) and polyprotein 1ab (pp1ab), respectively(40). These polyproteins are cleaved into 16 non-structural proteins (nsp);

nsp1-11, from pp1a and nsp12-16, from pp1ab. The proteolytic release of nsp1 occurs rapidly, which enables it to interfere with translation processes of the host cell by inducing cellular mRNA degradation(41-43). Nsp2-16 contain the viruses' replication and transcription complex (RTC) and encode multiple enzymes with many functions including, proteases, helicase, polymerase, exo- and endo-nuclease, N7- and 2'O-methyltransferases, and de-ubiquitination enzymes(44, 45). The final third of HCoV genomes contain genes that encode structural and accessory proteins. The four major structural proteins encoded here are the nucleocapsid (N), membrane (M), envelope (E), and spike glycoprotein (S) proteins(46, 47). The N protein is associated with the viral RNA genome and is involved in RNA synthesis regulation and interacts with the M protein during viral budding(39, 48). The M protein is important for viral assembly, it contains a short N-terminal domain that projects onto the external surface of the envelope and a long internal C terminus(39). The E protein function is largely unknown; however, along with the N and M proteins, it is required for viral assembly and release(47) . Lastly, the S protein gives coronaviruses their characteristic spikes that compose their crownlike appearance. This protein projects through the viral envelope, is heavily glycosylated, and regulates host cell membrane receptor binding and fusion of the viral and cellular membrane(49). The functions of the eleven accessory proteins encoded within the one-third closest to the 3' end of the SARS-CoV-2 genome are not fully understood. These accessory proteins are encoded by the ORF3a, ORF3b, ORF3c, ORF3d, ORF6, ORF7a, ORF7b, ORF8, ORF9b, ORC9c, and ORF10 genes. Some of these proteins, including ORF3b, ORF6, ORF7a and ORF8 are interferon antagonists which impair the host cell immune response(50-53), while ORF3a may promote virus release(54) and is involved in apoptosis of host cells through caspase-3 activation(55). ORF9b and ORF9c are known to supress the host antiviral response by interacting with host cell organelles(56-58), while a clear understanding of the functions of ORF3c, ORF7b, and ORF10 remains elusive(59). ***Figure 1*** (A and B) depicts the genome and structure of SARS-CoV-2.

The S glycoprotein is composed of two functionally distinct subunits (S1 and S2) and is essential for viral entry into host cells. The N-terminal S1 domain of the protein contains the receptor-binding domain (RBD) that directly interacts with the ACE2 receptor on the host cell, the primary receptor that SARS-Cov-2 utilises for cell entry(60). The C-terminal S2 domain fuses the host and viral membranes to allow for entry of the viral genome into the host cell(61). The subunits of the trimeric S complex are either in a closed (pre-fusion stage) or open (post-fusion stage) conformation(62), with one subunit always in an open conformation to allow for ACE2 recognition and binding(63). The RBD itself consists of five anti-parallel β-strands surrounded by several α-helices(64). From closed to open conformation, the RBD undergoes structural rearrangement whereby the globular head region rotates clockwise, which alters is elecropotential surface(64). Once positioned, numerous residues within the RBD form either hydrogen bonds or salt bridges with residues of the ACE2 receptor, allowing for tight binding(65), while the concave structure of the RBD allows for three distinct binding regions(64). Following binding between the S protein and the host cell receptor, host cell proteases cleave the S protein, causing the release of the S2 domain which allows for fusion and cell entry(66). ***Figure 1*** (C and D) demonstrate the structure and function of the S protein.

The ACE2 receptor is expressed in numerous cell types throughout the human body, including in the lungs, oral and nasal mucosa, heart, gastrointestinal tract, kidneys, liver,

spleen, and brain(67), highlighting the widespread infection that SARS-CoV-2 can inflict. Meanwhile, TMPRSS2, a host cell protease, facilitates fusion of the viral and host cell membranes(68), and may play a role in the spread of the virus in the airways(68). Host cell cathepsin L may also aid in SARS-CoV-2 cell entry by cleaving the S protein(69). Indeed, a clinically approved protease inhibitor has been shown to block SARS-CoV-2 cell entry(70). ***Figure 2*** depicts the mechanism by which SARS-CoV-2 gains entry into and replicates inside host cells, and ~~overviews~~ summarises the host cell immune response.

~~5.~~ Variants of SARS-CoV-2

Most viral mutations have a limited impact on the viruses' ability to infect, replicate, escape host immunity, and transmit, however, certain mutations may give a viral strain a competitive advantage and, through natural selection, give it the ability to become dominant. Many of the mutations observed in SARS-CoV-2 variants are found within the RBD or the N-terminal domain of the S protein, which alters the three-dimensional structure of the S protein. Not only can these changes affect the transmission abilities of the virus but can also allow it to better escape the immune response, including from neutralising antibodies either elicited through vaccine administration or natural infection.

The SARS-CoV-2 virus has mutated numerous times, with estimates suggesting that circulating lineages acquire nucleotide mutations at rates of around one to two mutations per month(71). The current method of identifying variants relies on the use of genomic testing such as whole genome sequencing, partial S-gene sequencing, or nucleic acid amplification technique (NAAT)-based assays(72). The aspects of different variants that most people experience, however, is the clinical symptoms they inflict. Certain variants induce a greater risk of severe disease and death, such as Alpha and Delta(73), while others are more likely to induce milder symptoms, such as Omicron(74, 75). Moreover, individual symptoms can differ between variants. For example, the Gamma variant is associated inflicting anosmia and dysgeusia(76), which is less commonly seen in Omicron infections. Moving forward, the clinical themes and symptoms associated with emerging variants should be elucidated rapidly ~~in order for the~~ so that the public and healthcare professionals can ~~to~~ rapidly identify possible cases of COVID-19.

The WHO have tracked and monitored SARS-CoV-2 variants since the COVID-19 pandemic began to identify VOCs. As of 25th January 2022, the WHO reports five VOC, two VOI, and three VUM(3) (***Table 1***). Herein, we report studies that compare SARS-CoV-2 variants to the 'primary' virus strain. 'Primary strain' refers to the strain of the virus that first emerged in Wuhan, China at the end of 2019 and spread around the world in the first wave of infections, which is often also referred to as the Wuhan-Hu-1, B.1, or wild-type strain.

~~5.1~~ Variants of concern

~~*5.1.1*~~ *Alpha*

The Alpha SARS-CoV-2 variant, of the B.1.1.7 lineage, was first documented in the UK in September 2020 and classified as a VOC on 18th December 2020(3, 77). This variant contains S protein mutations which have potential biological effects. Firstly, the S protein residue 501, a key contact residue within the RBD, forms a portion of the binding loop in the contact region of the ACE2 receptor, forms a hydrogen bond with the Y41 residue of the ACE2

receptor, and stabilises the ACE2 K353 residue(65, 78, 79). Alpha harbours an N501Y mutation which increases the binding affinity of the RBD to the ACE2 receptor(80). Next, the P681H mutation contained within the Alpha variant is located immediately adjacent to the 682-685 furin cleavage site, at the interface of the S1 and S2 domains(81). The S1/S2 furin cleavage site prompts entry into respiratory epithelial cells and partly determines the transmissibility of the virus(82-84), while the P681H mutation makes the furin cleavage site less acidic, meaning it is more effectively recognised and cleaved(85, 86). Alpha also contains a D614G mutation, located within the S1/S2 furin cleavage site, which increases SARS-CoV-2 binding affinity to the ACE2 receptor and increases infectivity(87). Other mutations harboured within the Alpha variant enhance the ability of the virus to escape antibody detection, such as the two amino acid deletion at the sites 69-70 in the N-terminal domain of the S protein(88, 89), while other mutations demonstrate limited or no effects(90). In February 2021, viruses of the B.1.1.7 lineage with the added S protein mutation E484K were identified, which may have threatened vaccine effectiveness due to the mutation conferring an increased resistance to neutralising vaccine-elicited and monoclonal antibodies(91). This mutation had limited effects, however, and variants containing it failed to dominate.

Epidemiological studies explored the Alpha variant, with a case-control study of 27,633 respiratory samples originating from 20 primary care centres in Madrid, Spain, finding that the probability of admission to an intensive care unit (ICU) was twice as high in patients infected with the Alpha variant compared to those infected with the primary strain(92).~~,~~ Furthermore,~~while~~ this variant became the dominant strain within four months, and led to an increase in disease burden as a result(92).

Meanwhile in Cannes, France, infection with the Alpha variant was associated with a 3.8-fold higher risk of transfer to an ICU or death compared to the primary strain, as determined through a retrospective cohort study of 158 COVID-19 patients(93). A large retrospective cohort study found that, d~~D~~uring the third COVID-19 wave in ~~Ontario,~~ Canada, where 91% of infections were caused by the Alpha variant, the risk of both hospitalisation (adjusted odds ratio (aOR)=1.57) and death (aOR=1.52) was higher compared to primary strain infections(94). Overall, the Alpha variant was approximately 50-70% more transmissible and was associated with a 30-60% increased risk of hospitalisation and death compared to the primary strain(95-100).

The Alpha variant was found to have a minimal impact on the effectiveness of current vaccines(101, 102), while the risk of reinfection remained similar for this variant as with previous ones(103). On 3rd September 2021, the European Centre for Disease Prevention and Control (ECDC) reclassified the Alpha, and the Alpha+E484K mutation variants from a VOC to a 'de-escalated variant' (104).

~~5.1.2~~ *Beta*

The Beta SARS-CoV-2 variant, of the B.1.351 lineage, was first documented in South Africa in May 2020(3). This variant contains five S protein mutations of interest: N501Y, E484K, D614G, K417N, and A701V. Like the Alpha variant, Beta contains the mutations N501Y, E484K, and D614G, which increase ACE2 receptor binding affinity(80, 87), increase virulence(105), and enhance resistance to neutralising antibodies(91, 106). The K417 residue of the SARS-CoV-2 S protein interacts with the D30 residue of the ACE2 receptor, forming a

salt bridge across the central contact region(65, 78), however, the K417N mutation appears to have a limited impact on ACE2 receptor binding(80). The A701V mutation is located close to the furin cleavage site but has a minimal impact on transmissibility or antibody resistance(101).

In a genomic and epidemiological study, it was concluded that the Beta SARS-CoV-2 variant had a selective advantage over previous variants from its increased transmissibility and immune escape abilities(107, 108), while the E484K/N501K mutations significantly enhanced the binding affinity of Beta and, hence, increased its transmissibility(109). A retrospective cohort study of 22,068 participants found that infection with the Beta variant was associated with an increased hospitalisation risk compared to an infection with a non-VOC (hazard ratio (HR)=2.30)(100). Overall, Beta is approximately 25-50% more transmissible, is associated with a possible increase in risk of hospital mortality, and has enhanced resistance to antibody neutralisation compared to previous variants(107, 108, 110).

~~5.1.3~~ *Gamma*

The Gamma variant is of the P.1 lineage and was first reported in November 2020 from travellers returning to Japan from Brazil, and was later discovered in Brazil(3, 111). This variant contains the S protein mutations of interest; K417T, E484K, N501Y, D614G, and H655Y(104). As mentioned, the N501Y and D614G mutations increase ACE2 receptor binding affinity and increase infectivity of the virus(80, 87). The N501Y, K417N/T, and E484K mutation trinity, meanwhile, is shared by both Gamma and Beta variants, and is associated with enhanced infectivity and lethality compared to the N501Y mutation alone, possibly due to tighter binding of the S protein to the ACE2 receptor due to increased electrostatic contribution(112). Gamma also possesses the H655Y mutation which was found to provide enhanced viral escape abilities from multiple human monoclonal antibodies *in vitro*(113).

The Gamma variant is associated with heightened transmissibility(109, 110, 114), with one study concluding that it possesses a 1.7- to 2.4-fold increased transmissibility compared to previous variants(115). Additionally, the wave of infections caused by the Gamma variant in Brazil was associated with a 13% increase in death rate compared to the previous wave, suggesting the greater virulence held by Gamma compared to previous viral strains(116).

A surveillance study from seven European countries concluded that the Gamma variant was associated with a higher risk of hospitalisation (aOR=2.6) and admission to an ICU (aOR=2.2) when compared to non-VOC cases(117). In Manaus, Brazil the resurgence of COVID-19, despite high seroprevalence, suggested that the Gamma variant had a moderate resistance to neutralising antibodies(118), however, Gamma has been shown to be significantly less resistant to neutralising antibodies, compared to other variants, including Beta(119).

~~5.1.~~*4 Delta*

The Delta variant, from the B.1.617.2 lineage, was first documented in India in October 2020 and was classified as a VOC on 11th May 2021(3). Of the S protein mutations of interest, the aforementioned P681H and D614G are also harboured by the Delta variant(104) and similarly impacts its ACE2 receptor binding affinity and transmissibility(106, 120, 121). Unlike the E484K mutation seen in previous variants, Delta contains the E484Q mutation which, along with a L452R mutation also located within the RBD, causes significantly higher affinity for the ACE2 receptor than the primary strain or the E484K mutation alone(122). The

L452R mutation alone results in greater RBD-ACE2 receptor binding affinity and enhanced escape from neutralising antibodies(123, 124). Lastly, the Delta variant contains the T478K mutation, located on the interface between the S protein and the ACE2 receptor when bound, which increases the electrostatic potential of the S protein and enhances binding affinity(125).

The Delta variant quickly became the dominant variant in the UK(126), US(127), Europe, and around the world(128). The mutations present in the Delta variant, enhanced the transmissibility of the virus as a result of increased binding affinity to the ACE2 receptor(109). It was estimated that the reproduction number of the Delta variant is 97% greater than non-VOC/VOI and approximately three times that of the Alpha, Beta, and Gamma variants(110), which highlights the competitive advantage that this variant had over earlier ones and how it rapidly became the dominant strain globally. The fast replication rate of Delta likely contributes to its increased transmissibility compared to Alpha, Beta, and Gamma. From infected individuals, the Delta variant has been able to be detected by polymerase chain reaction (PCR) within the first four days from exposure, while non-Delta infections could only be detected after six days(129). Furthermore, viral loads of people infected with the Delta variant were found to be significantly higher than people infected with other strains(129), including Beta(130). Delta is also thought to better escape neutralisation, with the frequency of post-vaccination infections much higher for the Delta variant than infections with the primary strain in India(131) and blood sera samples from individuals who had received one dose of a COVID-19 vaccine showing minimal neutralisation of the Delta variant(132).

The Delta variant is also associated with an increased disease severity. In Scotland, infection with the Delta variant was associated with an increased risk of hospitalisation (HR=1.85) compared to infection with the Alpha variant(133). Compared to non-VOC infections, North American retrospective cohort studies demonstrated that infection with Delta was associated with a 108%(134) or HR=2.3(100) increased risk of hospitalisation, a 234% increased risk for admission to an ICU, and a 132% increased risk of death(134). Lastly, a cross-sectional study of 6238 Delta and 3262 primary strain cases in India found that the risk of death was around 1.8 times higher for Delta infections, while Delta also infected and induced symptoms in a greater proportion of younger people (0-19 years old), compared to the primary strain(131).

~~5.1.5~~ Omicron

The Omicron variant is of the B.1.1.529 lineage and was first discovered in November 2021 in South Africa and Botswana before being detected in multiple countries and classified as a VOC on 26th November 2021(3). This variant contains over 30 S protein mutations(104), 23 of which have been previously identified, including K417N, T478K, E484A, D614G, H655Y, P681H, and N501Y(135). 15 Omicron mutations are contained within the RBD(17) providing the variant with a significantly enhanced binding affinity to the ACE2 receptor(135, 136). In addition, various single mutations harboured with the RBD of the Omicron variant impair the effectiveness of neutralising antibodies, including K417N, N440K, G446S, E484A, Q493K, G496S, G339D, S371L, and S375F(17).

The emergence of Omicron has been followed by a tidal wave of infections worldwide. Early data from South Africa demonstrated that the proportion of COVID-19 cases caused by

the Omicron variant rose from 3% in early October, to 98% by early December(137). In late December 2021, meanwhile, the doubling time for number of positive Omicron cases was between two and three in the UK, US, and much of Europe(138, 139), highlighting the transmissibility of this variant. The mutations harboured by Omicron that enhance its binding affinity(135, 136) and ability to escape neutralising antibodies(17) likely drove its rapid spread, as did its fast replication rate, which is around 70 times faster than the Delta and primary strains(140). The reinfection rate of Omicron has also been found to be significantly higher than that of previous variants in studies from Scotland(141) and South Africa(142).

The Omicron variant has extensive but incomplete escape from naturally acquired and vaccine-induced immunity(143, 144). Compared to the Delta variant, Omicron requires around a ten-fold increased antibody titre to be neutralised, following vaccination with either Oxford-AstraZeneca or Pfizer/BioNtech vaccines(145). Indeed, blood sera from individuals who had received two doses of the Pfizer/BioNtech vaccine exhibited more than a 25-fold reduction in neutralising antibody titres against the Omicron variant compared to the primary strain(146). T-cell responses to Omicron may remain intact, however. One preprint study demonstrated that 70-80% of the T-cell response targeting the S protein was maintained in those vaccinated or with prior infection, while the magnitude of Omicron cross-reactive T-cells was like that of both Delta and Beta variants(147). Furthermore, data from Pfizer/BioNtech revealed that 80% of the epitopes in the Omicron variant S protein that are recognised by CD8+ T-cells were not affected by this variant's mutations, following two-doses of the vaccine(146). T-cell responses induced from vaccine administration or prior infection may, therefore, provide some protection from severe disease.

Recent real-world evidence has implied that Omicron infection is milder in severity than previous variants. In an early South African analysis, the risk of hospitalisation (aOR=0.2) was lower for Omicron infections compared to non-Omicron SARS-CoV-2 infections(137) while, compared to earlier infections associated with the Delta variant, Omicron-infected individuals had a lower risk of severe disease (aOR=0.3)(137). In December 2021 in England, Omicron cases were found to induce a significantly reduced risk of hospitalisation or presentation for emergency care in comparison to Delta cases(74, 75). The decreased disease severity inflicted by Omicron may be due to its reduced capacity for replication in lung tissue, which was found to be more than ten times less in lung tissue compared to Delta(140). Concordantly, the S protein of the Omicron variant is less efficient at cleaving the ACE2 receptor and entering cells of lung organoids(145), while is also less able to cause fusion between lung cells compared to Delta(145), which is often observed in cases of severe COVID-19. The reduction in replication within the lungs, and the preservation of T-cell responses likely contribute to the milder disease exerted by the Omicron variant.

Although the Omicron variant appears to manifest in mild disease, high case numbers may still result in many hospitalisations and deaths in those vulnerable to the virus. Omicron case numbers may be beginning to peak, however. In South Africa, a 29.7% decrease in weekly COVID-19 cases were reported in the week ending 25th December 2021, compared to the previous week, and the Omicron wave is said to have passed(148). Concerningly, global case numbers continue to rise rapidly(149) and many countries will continue to feel the pressure exerted by the wave of Omicron infections.

~~5.2~~ Variants of interest

~~5.2.1~~ *Lambda*

The Lambda variant, of the C.37 lineage, was first documented in Peru in December 2020 and was designated as a VOI on 14th June 2021(3). This variant contains the S protein mutations; D614G, L452Q, and F490S(104). The L452Q mutation, located within the RBD, enhances binding affinity to the ACE2 receptor and increases the infectivity of Lambda(150), while, together L452Q and F490S increase the resistance of this variant to vaccine-elicited antibody neutralisation(150). Furthermore, F490S was identified as being a high-risk mutation for enhancing abilities to escape neutralisation(150).

Infectivity of the Lambda variant may be higher than that of Alpha, Gamma, and other D614G containing variants(151), suggesting that Lambda could potentially spread more rapidly and effectively. Additionally, compared to the primary SARS-CoV-2 virus, antibody neutralisation was found to be decreased by 3.05-fold for the Lambda variant, higher than that for Gamma (2.33-fold) and Alpha (2.03-fold) variants(151). However, findings suggest that the Lambda variant can be neutralised by monoclonal antibodies and current vaccines are protective against this variant(150).

~~5.2.2~~ *Mu*

The Mu variant, from the B.1.621 lineage, was first documented in Columbia in January 2021 before receiving designation as a VOI on 30th August 2021(3). This variant contains the aforementioned S protein mutations E484K, N501Y, D614G, and P681H(104). Mu also contains the S protein mutation R346K, located within the RBD(104, 152), which may induce large binding free energy changes that disrupt the binding of antibodies to the S protein and enhance the ability of the variant to escape neutralisation(153). As discussed, the E484K, N501Y, D614G, and P681H mutations have been shown to increase transmissibility(80, 85, 87, 105, 109, 112, 120, 121) and neutralisation escape(91, 106) suggesting that the Mu SARS-CoV-2 variant is likely to be more infectious than the primary strain.

Although the Lambda and Mu variants have been outcompeted by Delta and now Omicron, the development and spread of VOIs will need to be closely monitored and studied to appreciate their pathogenicity, transmissibility, and virulence.

~~5.3~~ VUM

As of 25th January 2022, there are three VUM listed by the WHO(3) ***(table 1)***.

~~6.~~ Vaccinations

The COVID-19 pandemic prompted a rapid international search for safe and effective vaccines against the SARS-CoV-2 virus. In line with previous vaccine development, including for both SARS-CoV and MERS-CoV, the S protein was a key target for COVID-19 vaccine development(154). As of 24th January 2022, 33 approved vaccines are in use in 197 countries, with ten vaccines having gained emergency use listing approval from the WHO(4), (***table 2***). As of 25th January 2022 there are 194 vaccines in pre-clinical development and 140 in clinical

development(155). Numerous studies have explored the effectiveness of approved vaccines, however, large variations in vaccine effectiveness are reported. This variability is likely due to several factors in the studies including, the country, date, and population size of the study, as well as the SARS-CoV-2 variants circulating during the study period. These factors, along with how the effectiveness is reported, mean that it is difficult to compare vaccines and fully understand how effective each vaccine is. Here, we review the COVID-19 vaccines in use around the world.

~~6.1~~ *Pfizer/BioNtech - BNT162b2*

The BNT162b2 vaccine (Comirnaty) is a lipid nanoparticle-formulated, nucleoside-modified mRNA vaccine encoding a modified SARS-CoV-2 S protein which was developed through a collaborative effort between Pfizer (New York, US) and BioNTech (Mainz, Germany)(156, 157). BNT162b2 gained WHO emergency use listing on 31st December 2020(158) and, as of 24th January 2022, has been approved for use in 136 countries(4).

Following administration of BNT162b2, a Th1-biased response is observed, with tumour necrosis factor alpha (TNFα), interferon gamma (IFNγ), and interleukin-2 (IL-2) all elevated following vaccination, compared to placebo(159, 160). Highest neutralisation titres are found between seven and fourteen days following the second dose(161), while those previously infected with COVID-19 showed a four-fold increase in antibody binding and a 18-fold increase in neutralisation titres compared to previously uninfected individuals following two-doses(162). The BNT162b vaccine is well tolerated, with limited reactogenicity. Redness and swelling at injection site have been reported, however mild or moderate pain at the injection site is the most commonly reported reaction to vaccination(161). Fatigue, muscle pain, headache and chills are other commonly reported symptoms following BNT162b2 administration(163). The rate of systemic reactions after a second dose of BNT162b has been found to be 1.7 to 2 times higher than after a first dose, possibly suggesting an immunity-boosting effect(164). Many safety reports of this vaccine describe no serious adverse events(161, 164, 165), however, a large study found that BNT162b2 was associated with an increased risk of myocarditis, lymphadenopathy, appendicitis, and herpes zoster infection(166). Although rare, allergic reaction or anaphylaxis has also been reported following administration of the BNT162b2 vaccine(163). ***Table 2*** outlines clinical trial and real-world data for vaccine effectiveness.

~~6.2~~ *Oxford-AstraZeneca – AZD1222*

The AZD1222 vaccine (Vaxzevria) is a non-replicating vector of the chimpanzee adenovirus ChAdOx1, modified to encode the SARS-CoV-2 S protein(167). Developed through collaboration between the University of Oxford and AstraZeneca (Cambridge, UK), this vaccine was given WHO emergency use listing on 16th February 2021(158) and has been approved for use in 137 countries, as of 24th January 2022(4). The WHO has granted emergency use listing to two versions of this vaccine (AZD1222 and Covishield) in order to utilise Covishield as part of their worldwide COVAX initiate, which is being produced by the Serum Institute of India and AstraZeneca-SKBio (Republic of Korea)(168).

Following administration of AZD1222, significant antibody production, predominantly of IgG1 and IgG3 subclasses, and a Th-1 cell response, with increased expression of IFNγ and TNFα, is seen(122, 169). One dose of AZD1222 has been shown to produce a neutralising antibody response in 91% of participants, while a second dose resulted in 100% of participants producing neutralising antibodies(170). Mild and moderate itch, pain, redness, swelling, tenderness, and warmth are common local reactions, while chills, fatigue, fever, headache, muscle ache, and nausea are commonly reported systemic reactions following AZD1222 administration(170). Rare symptoms, including severe chest pain, nasal bleeding, and allergic reaction have been reported following AZD1222 administration(171). ***Table 2*** outlines clinical trial and real-world data for vaccine effectiveness.

~~6.3~~ *Johnson & Johnson - Ad26.COV.2.S*

The Ad26.COV.2.S vaccine is a non-replicating adenovirus vector, modified to contain the SARS-CoV-2 S protein in a prefusion-stabilised conformation and requires a single dose(172). This vector was developed from the recombinant human adenovirus type 26 by the Janssen pharmaceutical company of Johnson & Johnson (New Brunswick, New Jersey, US)(172) and was listed for WHO emergency use listing on 12th March 2021(158). As of 24th January 2022, Ad26.COV.2.S has been approved for use in 106 countries(4).

The Ad26.COV.2.S vaccine induces the production of a variety of antibody subclasses, such as IgG, IgM, and IgA, and promotes several non-neutralising antibody responses, including activation of CD4+ and CD8+ Th1-cells and production if IFNγ, IL-2, and TNFα(173, 174). Although neutralising antibody responses induced by Ad26.COV2.S are reduced against SARS-CoV-2 variants, non-neutralising antibody and T-cell responses have been found to be preserved against VOC(173), while a prior COVID-19 infection significantly increases levels of S protein-binding antibodies, antibody-dependent cellular cytotoxicity, and neutralising antibodies against VOCs including Beta and Delta(175). Ad26.COV.2.S is safe and well tolerated, with a large clinical trial demonstrating that headache, fatigue, and myalgia, are the most common systemic reactions, while injection-site pain is the most common local reaction following administration(172). Like other vaccines, Ad26.COV.2.S has been associated with serious adverse events, such as allergic reactions and cerebral venous sinus thrombosis, however, these are rare(163, 176). ***Table 2*** outlines clinical trial and real-world data for vaccine effectiveness.

~~6.4~~ *Moderna – mRNA-1273*

The mRNA-1273 vaccine (Spikevax) developed by Moderna (Massachusetts, US) is a lipid-nanoparticle-encapsulated mRNA vaccine expressing the SARS-CoV-2 S protein that has been prefusion-stabilised(177). This vaccine gained WHO emergency use listing on 30th April 2021(158), and as of 24th January 2022, has been approved for use in 85 countries(4).

The mRNA-1273 vaccine elicits a strong CD4+ Th-1 cell response, with TNFα, IFNγ, and IL-2 expression increased following administration(178-180), while neutralising antibody titres have been shown to significantly increase up until around 28 days following the second dose of the vaccine, and afterwards remain consistently high(181). Fatigue, muscle pain, headache, chills, joint pain, and injection-site pain/reaction are common adverse effects caused by the mRNA-1273 vaccine(163, 177), while serious adverse effects are often avoided(177,

181). Serious adverse events, including allergic reaction and anaphylaxis are rare, but not inconceivable following mRNA-1273 administration(163). ***Table 2*** outlines clinical trial and real-world data for vaccine effectiveness.

~~6.5~~ *Other WHO emergency use listed COVID-19 vaccines*

In addition to the five COVID-19 vaccines described previously, five other vaccines have gained emergency use listing by the WHO. First, the Sinopharm BBIBP-CorV COVID-19 vaccine (Covilo) was developed by the Beijing Bio-Institute of Biological Products, a subsidiary of China National Biotec Group, and was given WHO emergency use listing on 7th May 2021(158). This vaccine is a 19nCoV-CDC-Tan-HB02 strain SARS-CoV-2 antigen that is produced in Vero cells, inactivated by β-propiolactone, and then purified and absorbed with aluminium hydroxide(182). Next, the CoronaVac vaccine, developed by Sinovac Biotech (Beijing, China), was listed for WHO emergency use on 1st June 2021(158). Like the BBIBP-CorV vaccine, this vaccine is a Vero cell-based, aluminium hydroxide-adjuvanted, β-propiolactone-inactivated vaccine, however, it is based on the SARS-CoV-2 CZ02 strain(183). Covaxin (BBV152) is a whole virion inactivated SARS-CoV-2 vaccine formula developed by Bharat Biotech International ltd (India)(184) which gained emergency use listing from the WHO On 3rd November 2021(185). Lastly, Covovax and its originator, Nuvaxovid (NVX-CoV2372), were both developed by Novavax (Maryland, United States) and the Coalition for Epidemic Preparedness Innovations (Oslo, Norway), and gained emergency use listing on 17st and 21th December 2021, respectively(186, 187). Both vaccines are manufactured using the same technology, and consist of a recombinant SARS-CoV-2 S protein nanoparticle administered with the adjuvant Matrix-M as a co-formulation(188). These vaccines produce similar immune responses to those already discussed. Studies assessing the efficacy of these vaccines are outlined in ***table 2***.

~~6.10~~ *Other approved vaccines*

In addition to the vaccines that have received emergency use listing from the WHO, around the world, vaccines have been developed, tested, and approved to combat COVID-19. As of 24th January 2022, 33 vaccines, including the ten described above, have been approved in at least one country(4). The remaining 23 approved vaccines are outlined in ***table 3***.

~~6.11~~ *Waning immunity and boosters*

Throughout the COVID-19 pandemic, emerging variants have threatened the effectiveness of vaccines (***table 2***). Simultaneously, waning immunity following vaccination questions how long vaccines remain effective and highlights the importance of booster doses. Indeed, protection against SARS-CoV-2 following vaccination decreases over time, both in terms of antibody titres(189-191) and vaccine effectiveness(192-195). However, c~~C~~ellular responses, such as T-cell immunity, may persist for longer periods~~, however~~(196, 197). With a gradual loss of protection from SARS-CoV-2 following COVID-19 vaccination, many countries are now rolling out booster programmes with the aim of raising levels of immunity.

Since booster programmes began, evidence that a booster vaccine dose enhances antibody and cellular responses has accumulated. Following a third dose of vaccine, neutralising antibody titres increase significantly(198-201) and, in some cases, to higher levels

than after the primary two doses(198). Additionally, boosters have also been found to increase neutralising antibody titres against Beta, Gamma, Delta, and Omicron variants(199, 202, 203). T-cell response is also enhanced following a third dose(200, 204, 205). Together, enhancing neutralising antibody and cellular responses with a booster vaccine dose is likely to provide a greater level of protection than relying on immunity built through a primary regimen.

The antibody and cellular responses observed following booster vaccinations have been found to correlate with increased levels of protection against SAR-CoV-2 infection and severe illness. On 30th July 2021, Israel was the first country to offer a third dose of BNT162b2 to certain groups. Subsequently, several studies have revealed that those who received a third vaccine dose were significantly less likely to be infected or have severe disease with SARS-CoV-2 compared to those who received two-doses(206-209). In those aged 60 or older, an observational study demonstrated that the rate of severe COVID-19 and death was lower in the boosted group by a factor of 17.9 and 14.7, respectively, compared to the non-boosted group(210). Booster doses of COVID-19 vaccine have been shown to be effective against infection with Delta(211, 212) and, to a lesser degree, Omicron variants(75, 145, 146, 212-214) despite the numerous mutations harboured by these variants. Overall, increasing evidence is pointing towards the benefits of booster doses of COVID-19 vaccines, therefore it is expected that booster programmes will continue to roll out across the globe. Based on current evidence, the CDC recommend that the time interval for receiving a booster following the primary regiment is five months for Pfizer/BioNTech BNT162b2 primary regimen, six months for Moderna mRNA-1273 primary regimen, and two months for Johnson & Johnson Ad26.COV2.S primary regimen(215). As the pandemic progresses and new variants emerge, variant-specific vaccines may require development, with pre-clinical studies demonstrating their efficacy(216) and pharmaceutical companies, such as Pfizer, advancing in variant-specific vaccine development(146). Policy makers should also consider when vaccine boosters will be given in the future and who will receive booster doses in the long-term.

~~7.~~ Emerging Treatments

As more is learnt about the virus, the therapeutic strategy against COVID-19 develops. There are currently over two thousand ongoing trials assessing certain treatment strategies for COVID-19(217). Recently, antivirals including molnupiravir (Lagevrio) and nirmatrelvir/ritonavir (Paxlovid) have been approved in the UK(218, 219), US(220, 221), and Europe(222, 223) for treating COVID-19 in certain risk groups. Similarly, sotrovimab (Xevudy), a monoclonal antibody treatment, has recently been approved for use in treating certain COVID-19 patients in the UK(224), US(225), and Europe(226). These drugs have been shown to be effective at preventing poor clinical outcomes, including death, in those vulnerable to severe COVID-19 infection. Other drug treatments, such as janus kinase inhibitors, corticosteroids, and anti-inflammatories have contrasting evidence to support their use, and therefore, the use of specific drugs is either recommended for or against by certain treatment and management guidelines, which are discussed below.

~~8.~~ Guidelines

The treatment and management of COVID-19 is a continually evolving topic, however, health authorities have published and continue to update guidelines and recommendations for

treating COVID-19. The WHO living guideline on COVID-19 and therapeutics is regularly updated, with the latest version, published on 14th January 2022 containing 14 recommendations on COVID-19 treatment(227). In the UK, the National Institute for Health and Care Excellence (NICE)(228) and Medicines and Healthcare products Regulatory Agency (MHRA)(229) provide updated guidelines on COVID-19 treatment, while in Europe, the ECDC regularly publishes several guidelines providing recommendations on a range of COVID-19 related topics(230). In the US, the National Institutes of Health (NIH)(231) and the CDC(232) provide guidance on COVID-19 treatment and management, with the CDC supplying guidelines for specific groups including, employers, schools, health departments, and governments.

9. Considerations for the future

Novel infectious diseases and pandemics are an unpredictable but inevitable aspect of nature and it is, therefore, important that we learn from past pandemics to prepare for future ones. Firstly, the COVID-19 pandemic has highlighted and amplified the existing inequalities within society(233), with non-white ethnicity, social disadvantage, and unemployment all risk factors for testing positive for COVID-19(234) and those most economically deprived found to be particularly vulnerable(235). These inequalities require addressing to be better prepared for similar situations in the future.

Next, to progress through a pandemic we should be racing the pathogen, not each other. This statement becomes apparent when you consider the problems countries faced when seeking out PPE(236), and the vaccine inequity seen around the world(237), with developed countries often better placed to be able to purchase these items. Initiatives such as the WHO's COVAX programme are vital to protect those most vulnerable and reduce the global spread of disease. In October 2021, the UK government released a publication outlining where the policies implemented to reduce the impact of the COVID-19 pandemic failed, and the lessons learned from these failures (238). Here, ~~it is clear that~~ there is room for improvement, with the publication presenting conclusions and recommendations on how to enhance pandemic preparedness, lockdown and social distancing measures, testing and contact tracing, social care, and vaccines. In countries such as the UK, US, and much of Europe, where the COVID-19 death rate has been high, steps need to be taken and lessons need to be learnt in order to be better prepared for the next pandemic. The responsibility of improving pandemic response lies with policy makers, the medical/scientific community, and the public, and will ultimately require a collaborative approach.

However, c~~C~~ertain aspects of the response to the COVID-19 pandemic have been a triumph~~, however~~. One of the major victories was the rapid development and rollout of vaccines(239), which continue to be effective. The rollout of rapid testing and quarantine for positive cases was also important to at least disrupt the spread of the virus, especially given that asymptomatic individuals can contribute to the spread. Furthermore, the swift identification and sharing of knowledge of SARS-CoV-2 variants between countries should be applauded. Lessons can be learned from countries where COVID-19 was controlled. In Taiwan, managing the pandemic as directed by pre-COVID-19 pandemic plans prompted an immediate response; screening of all airline passengers arriving from Wuhan and high risk areas, restricting entry for non-Taiwanese citizens, 14-day quarantine period for contacts of

confirmed cases or returning travellers, a ban on large gatherings, and widespread mask wearing were some of the quickly implemented management strategies(240). New Zealand implemented similarly effective restrictions, with the addition of a national lockdown(240). Many of the pandemic control components that kept case and death numbers low in Taiwan and New Zealand could be adopted by other countries in the future and may lead to greater outcomes in terms of protecting both health of individuals and the health and wellbeing of the country. Overall, there is much to be learnt from the COVID-19 pandemic and, as we emerge from it, inspection of which policies failed, and which succeeded are imperative.

~~10.~~ Conclusion

COVID-19 remains prevalent and life-threatening. Although rollout of vaccines has been successful~~, we must aim to address unmet goals, such~~ as attaining a high global vaccination coverage and ensuring that all healthcare systems have the capacity to cope with seasonal waves are essential. With Omicron highly prevalent, we must continue to learn, develop therapeutics, and remain vigilant to new VOCs. Here, we have provided an overview of the virology of SARS-CoV-2, including the mutations harboured by variants of the virus and how these mutations effect its transmissibility and virulence. Lastly, we discussed the vaccines that have been developed and administered around the world and provided evidence supporting the rollout of booster doses. Future priorities should focus on continuing vaccination programmes and developing variant-specific vaccines as new mutations emerge. This, along with the expansion of our knowledge of SARS-CoV-2 and which therapies are most successful to treat infections with it will ultimately lead to favourable outcomes moving forward.

Research Questions

1) How will the SARS-CoV-2 virus mutate in the future, and which mutations will give a competitive advantage that will allow the virus to inflict disease to many people?
2) How do we keep up with the rapidly changing SARS-CoV-2 environment and ensure that vaccines remain effective?
3) How do we manage the booster programme and when will future booster vaccinations be required in order to maintain high levels of immunity?
4) How can we learn from the current and past pandemics so that we are better prepared for the next one?

Patient Involvement: Patients who had been infected with covid-19 were contacted and requested to review the initial drafts of this manuscript. The received feedback was mostly positive and assisted in developing and focusing our review. Final drafts were also reviewed by patients who had had covid-19 and similar positive feedback was received.

Contributorship statement and guarantor: MY and HC performed the literature search and drafted the manuscript. HC revised and finalised the manuscript. JS reviewed and revised the manuscript. PE was responsible for the concept and design of the work. PE reviewed, revised, and finalised the manuscript. PE is the guarantor.

Competing interests: We have read and understood the BMJ policy on declaration of interests and declare the following interests: PE was funded by the Medical Research Council and now by Higher Education Funding Council for England (HEFCE). He has also received grants from Alzheimer's Research, UK, Alzheimer's Drug Discovery Foundation, Alzheimer's Society, UK, Medical Research Council, Alzheimer's Association US, Van-Geest foundation, and European Union grants. PE is a consultant to Roche, Pfizer, and Novo Nordisk. He has received educational and research grants from GE Healthcare, Novo Nordisk, Piramal Life Science/Life Molecular Imaging, Avid Radiopharmaceuticals and Eli Lilly. He is a member of the Scientific Advisory Board at Novo Nordisk. None of these were related to COVID-19

Figure Legends:

Figure 1: Genome and structure of SARS-CoV-2. A) SARS-CoV-2 genome and S protein amino acid composition. The SARS-CoV-2 genome is approximately 30,000 base pairs (bp) long and consists of open reading frames (ORF) and elements that are essential for the virus' structure. The spike S protein is responsible for binding and entry into host cells. SARS-CoV-2 variants of concern (VOC) contain various S protein non-synonymous mutations that result in amino acid changes in the receptor binding domain (orange text) and the S1/S2 subunit interface (black text) which have been demonstrated to enhance transmissibility of the virus. VOC include Alpha (α), Beta (β), Gamma (γ), and Delta (δ). **B) SARS-CoV-2 structure.** SARS-CoV-2 is a RNA virus that has a crown-like appearance and contains four major structural proteins: nucleocapsid (N), spike (S), envelope (E), and membrane (M). **C) S and ACE2 interaction.** The SARS-CoV-2 S protein directly interacts with human angiotensin-converting enzyme 2 (ACE2) receptors in order to gain entry into host cells. The receptor binding domain (RBD) of the S protein tightly binds to ACE2. **D) Spike protein structure.** The S protein protrudes out from the main SARS-CoV-2 bulk and is comprised of two subunits: S1 and S2. S1 contains the RBD which directly interacts with the human ACE2 receptor, while the S1/S2 interface contains a furin cleavage site which is cleaved to allow S2 to fuse with the host cell membrane. Both the RBD and the S1/S2 interface contain transmissibility increasing mutations that are harboured in variants of concern.

Figure 2: Viral entry and host response. A) At the alveolar epithelial cell layer. Epithelial cells in the lungs express both angiotensin-converting enzyme 2 (ACE2) receptors and transmembrane protease serine 2 (TMPRSS2), allowing for infection by SARS-CoV-2. Replication of the virus within these cells induces an intense immune response that attracts monocytes, T-cells and macrophages and, in some cases, can result in a cytokine storm. **B) Within nearby blood vessels.** Cytokines produced by the epithelial cell layer are released

into blood vessels supplying the infected tissue, which causes the recruitment of further immune cells to the area, driving the damaging inflammatory response further. Circulating cytokines also create a systemic inflammatory environment. **C) Adaptive immune response.** Circulating lymphocytes carry viral antigens to lymph nodes and bone marrow to begin the adaptive immune system processes whereby B-cells, and later antibodies, are activated. **D) SARS-CoV2 host replication.** The SARS-CoV-2 virus utilises the ACE2 receptor and TMPRSS2 to gain entry into human cells. Following release of the viral RNA within the host cell, the virus utilises the host endoplasmic reticulum (ER) and Golgi apparatus to produce and manufacture new viral particles, which are released out of the cell to infect other cells and new hosts.

Table 1: SARS-CoV-2 variants and their S protein mutations. *first detection worldwide. Information correct as of 24th January 2022.

Table 2: Vaccine effectiveness of vaccines that have gained WHO emergency use listing. *Adjusted for covariates when reported by study, dates are reported in dd/mm/yyyy format. Vaccine effectiveness days/months refers to days/months since vaccination dose. Information correct as of reported conclusion date of each study.

Table 3: COVID-19 vaccines approved in at least one country. Information correct as of 24th January 2022.

References

1. CDC.org [Internet]. Human Coronavirus Types. Centres for Disease Control and Prevention. [15 February 2020; cited 12 October 2021]. Available from: https://www.cdc.gov/coronavirus/types.html
2. Who.int [Internet]. Weekly operational update on COVID-19 - 25 January 2022. World Health Organisation. [25 January 2022; cited 26 January 2022]. Available from: https://www.who.int/publications/m/item/weekly-operational-update-on-covid-19---25-january-2022
3. Who.int [Internet]. Tracking SARS-CoV-2 variants. World Health Organisation. [25 January 2022; cited 26 January 2022]. Available from: https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/
4. covid19.trackvaccines.org [Internet]. COVID-19 Vaccine Tracker. [24 January 2022; cited 26 January 2022]. Available from: https://covid19.trackvaccines.org/
5. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet. 2020;395(10223):514-23.
6. Who.int [Internet]. Transmission of SARS-CoV-2: implications for infection prevention precautions - Scientific Brief. World Health Organisation. [9 July 2020; cited 28 October 2021]. Available from: https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions
7. Gidari A, Sabbatini S, Bastianelli S, Pierucci S, Busti C, Bartolini D, et al. SARS-CoV-2 Survival on Surfaces and the Effect of UV-C Light. Viruses. 2021;13(3).

8. Pottage T, Garratt I, Onianwa O, Spencer A, Paton S, Verlander NQ, et al. A comparison of persistence of SARS-CoV-2 variants on stainless steel. J Hosp Infect. 2021;114:163-6.
9. Guo L, Wang M, Zhang L, Mao N, An C, Xu L, et al. Transmission risk of viruses in large mucosalivary droplets on the surface of objects: A time-based analysis. Infect Dis Now. 2021;51(3):219-27.
10. Carraturo F, Del Giudice C, Morelli M, Cerullo V, Libralato G, Galdiero E, et al. Persistence of SARS-CoV-2 in the environment and COVID-19 transmission risk from environmental matrices and surfaces. Environ Pollut. 2020;265(Pt B):115010.
11. Hui KP, Cheung M-C, Perera RA, Ng K-C, Bui CH, Ho JC, et al. Tropism, replication competence, and innate immune responses of the coronavirus SARS-CoV-2 in human respiratory tract and conjunctiva: an analysis in ex-vivo and in-vitro cultures. The Lancet Respiratory Medicine. 2020;8(7):687-95.
12. McAloon C, Collins A, Hunt K, Barber A, Byrne AW, Butler F, et al. Incubation period of COVID-19: a rapid systematic review and meta-analysis of observational research. BMJ Open. 2020;10(8):e039652.
13. Bliddal S, Banasik K, Pedersen OB, Nissen J, Cantwell L, Schwinn M, et al. Acute and persistent symptoms in non-hospitalized PCR-confirmed COVID-19 patients. Sci Rep. 2021;11(1):13153.
14. Grant MC, Geoghegan L, Arbyn M, Mohammed Z, McGuinness L, Clarke EL, et al. The prevalence of symptoms in 24,410 adults infected by the novel coronavirus (SARS-CoV-2; COVID-19): A systematic review and meta-analysis of 148 studies from 9 countries. PLoS One. 2020;15(6):e0234765.
15. Kronbichler A, Kresse D, Yoon S, Lee KH, Effenberger M, Shin JI. Asymptomatic patients as a source of COVID-19 infections: A systematic review and meta-analysis. Int J Infect Dis. 2020;98:180-6.
16. Arons MM, Hatfield KM, Reddy SC, Kimball A, James A, Jacobs JR, et al. Presymptomatic SARS-CoV-2 Infections and Transmission in a Skilled Nursing Facility. N Engl J Med. 2020;382(22):2081-90.
17. Cao Y, Wang J, Jian F, Xiao T, Song W, Yisimayi A, et al. B.1.1.529 escapes the majority of SARS-CoV-2 neutralizing antibodies of diverse epitopes. BioRxiv [Preprint]. 2021.
18. Wolff D, Nee S, Hickey NS, Marschollek M. Risk factors for Covid-19 severity and fatality: a structured literature review. Infection. 2021;49(1):15-28.
19. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62.
20. Zhang J, Wang X, Jia X, Li J, Hu K, Chen G, et al. Risk factors for disease severity, unimprovement, and mortality in COVID-19 patients in Wuhan, China. Clin Microbiol Infect. 2020;26(6):767-72.
21. Ebinger JE, Achamallah N, Ji H, Claggett BL, Sun N, Botting P, et al. Pre-existing traits associated with Covid-19 illness severity. PLoS One. 2020;15(7):e0236240.
22. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;584(7821):430-6.

23. Li R, Tian J, Yang F, Lv L, Yu J, Sun G, et al. Clinical characteristics of 225 patients with COVID-19 in a tertiary Hospital near Wuhan, China. J Clin Virol. 2020;127:104363.
24. Guo L, Shi Z, Zhang Y, Wang C, Do Vale Moreira NC, Zuo H, et al. Comorbid diabetes and the risk of disease severity or death among 8807 COVID-19 patients in China: A meta-analysis. Diabetes Res Clin Pract. 2020;166:108346.
25. Feng Y, Ling Y, Bai T, Xie Y, Huang J, Li J, et al. COVID-19 with Different Severities: A Multicenter Study of Clinical Features. Am J Respir Crit Care Med. 2020;201(11):1380-8.
26. Tian J, Yuan X, Xiao J, Zhong Q, Yang C, Liu B, et al. Clinical characteristics and risk factors associated with COVID-19 disease severity in patients with cancer in Wuhan, China: a multicentre, retrospective, cohort study. Lancet Oncol. 2020;21(7):893-903.
27. Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020;21(3):335-7.
28. Vizcarra P, Perez-Elias MJ, Quereda C, Moreno A, Vivancos MJ, Dronda F, et al. Description of COVID-19 in HIV-infected individuals: a single-centre, prospective cohort. Lancet HIV. 2020;7(8):e554-e64.
29. Baillie JK, Wilson JF, Bulteel N, Hayward C, Klaric L, Porteous DJ, et al. Mapping the human genetic architecture of COVID-19. Nature. 2021.
30. Shelton JF, Shastri AJ, Ye C, Weldon CH, Filshtein-Somnez T, Coker D, et al. Trans-ethnic analysis reveals genetic and non-genetic associations with COVID-19 susceptibility and severity. MedRxiv [Preprint]. 2020.
31. Ellinghaus D, Degenhardt F, Bujanda L, Buti M, Albillos A, Invernizzi P, et al. Genomewide association study of severe covid-19 with respiratory failure/[...]. New England Journal of Medicine Boston: Massachusetts Medical Society, 2020, vol 383, no 16. 2020.
32. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. cell. 2020;181(2):271-80. e8.
33. Hou Y, Zhao J, Martin W, Kallianpur A, Chung MK, Jehi L, et al. New insights into genetic susceptibility of COVID-19: an ACE2 and TMPRSS2 polymorphism analysis. BMC medicine. 2020;18(1):1-8.
34. Barbry P, Muus C, Luecken M, Eraslan G, Waghray A, Heimberg G, et al. Integrated analyses of single-cell atlases reveal age, gender, and smoking status associations with cell type-specific expression of mediators of SARS-CoV-2 viral entry and highlights inflammatory programs in putative target cells. BioRxiv [Preprint]. 2020.
35. Prakrithi P, Lakra P, Sundar D, Kapoor M, Mukerji M, Gupta I, et al. Genetic Risk Prediction of COVID-19 Susceptibility and Severity in the Indian Population. Front Genet. 2021;12:714185.
36. Huang QM, Zhang PD, Li ZH, Zhou JM, Liu D, Zhang XR, et al. Genetic Risk and Chronic Obstructive Pulmonary Disease Independently Predict the Risk of Incident Severe COVID-19. Ann Am Thorac Soc. 2022;19(1):58-65.
37. Zhou Y, Qian X, Liu Z, Yang H, Liu T, Chen K, et al. Coagulation factors and the incidence of COVID-19 severity: Mendelian randomization analyses and supporting evidence. Signal Transduct Target Ther. 2021;6(1):222.
38. Payne S. Family Coronaviridae. Viruses 2017. p. 149-58.

39. Masters PS, Kuo L, Ye R, Hurst KR, Koetzner CA, Hsue B. Genetic and molecular biological analysis of protein-protein interactions in coronavirus assembly. Adv Exp Med Biol. 2006;581:163-73.
40. Khailany RA, Safdar M, Ozaslan M. Genomic characterization of a novel SARS-CoV-2. Gene Rep. 2020;19:100682.
41. Thoms M, Buschauer R, Ameismeier M, Koepke L, Denk T, Hirschenberger M, et al. Structural basis for translational shutdown and immune evasion by the Nsp1 protein of SARS-CoV-2. Science. 2020;369(6508):1249-55.
42. Schubert K, Karousis ED, Jomaa A, Scaiola A, Echeverria B, Gurzeler LA, et al. SARS-CoV-2 Nsp1 binds the ribosomal mRNA channel to inhibit translation. Nat Struct Mol Biol. 2020;27(10):959-66.
43. Huang C, Lokugamage KG, Rozovics JM, Narayanan K, Semler BL, Makino S. SARS coronavirus nsp1 protein induces template-dependent endonucleolytic cleavage of mRNAs: viral mRNAs are resistant to nsp1-induced RNA cleavage. PLoS Pathog. 2011;7(12):e1002433.
44. Snijder EJ, Decroly E, Ziebuhr J. The Nonstructural Proteins Directing Coronavirus RNA Synthesis and Processing. Adv Virus Res. 2016;96:59-126.
45. V'Kovski P, Gerber M, Kelly J, Pfaender S, Ebert N, Braga Lagache S, et al. Determination of host proteins composing the microenvironment of coronavirus replicase complexes by proximity-labeling. Elife. 2019;8.
46. Masters PS. The molecular biology of coronaviruses. Advances in virus research. 2006;66:193-292.
47. Siu Y, Teoh K, Lo J, Chan C, Kien F, Escriou N, et al. The M, E, and N structural proteins of the severe acute respiratory syndrome coronavirus are required for efficient assembly, trafficking, and release of virus-like particles. Journal of virology. 2008;82(22):11318-30.
48. Kuo L, Masters PS. Genetic evidence for a structural interaction between the carboxy termini of the membrane and nucleocapsid proteins of mouse hepatitis virus. J Virol. 2002;76(10):4987-99.
49. Hulswit RJ, de Haan CA, Bosch BJ. Coronavirus Spike Protein and Tropism Changes. Adv Virus Res. 2016;96:29-57.
50. Konno Y, Kimura I, Uriu K, Fukushi M, Irie T, Koyanagi Y, et al. SARS-CoV-2 ORF3b Is a Potent Interferon Antagonist Whose Activity Is Increased by a Naturally Occurring Elongation Variant. Cell Rep. 2020;32(12):108185.
51. Kopecky-Bromberg SA, Martinez-Sobrido L, Frieman M, Baric RA, Palese P. Severe acute respiratory syndrome coronavirus open reading frame (ORF) 3b, ORF 6, and nucleocapsid proteins function as interferon antagonists. J Virol. 2007;81(2):548-57.
52. Xia H, Cao Z, Xie X, Zhang X, Chen JY, Wang H, et al. Evasion of Type I Interferon by SARS-CoV-2. Cell Rep. 2020;33(1):108234.
53. Wong HH, Fung TS, Fang S, Huang M, Le MT, Liu DX. Accessory proteins 8b and 8ab of severe acute respiratory syndrome coronavirus suppress the interferon signaling pathway by mediating ubiquitin-dependent rapid degradation of interferon regulatory factor 3. Virology. 2018;515:165-75.
54. Azad GK, Khan PK. Variations in Orf3a protein of SARS-CoV-2 alter its structure and function. Biochem Biophys Rep. 2021;26:100933.

55. Ren Y, Shu T, Wu D, Mu J, Wang C, Huang M, et al. The ORF3a protein of SARS-CoV-2 induces apoptosis in cells. Cell Mol Immunol. 2020;17(8):881-3.
56. Kreimendahl S, Rassow J. The Mitochondrial Outer Membrane Protein Tom70-Mediator in Protein Traffic, Membrane Contact Sites and Innate Immunity. Int J Mol Sci. 2020;21(19).
57. Gordon DE, Jang GM, Bouhaddou M, Xu J, Obernier K, White KM, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. Nature. 2020;583(7816):459-68.
58. Dominguez Andres A, Feng Y, Campos AR, Yin J, Yang CC, James B, et al. SARS-CoV-2 ORF9c Is a Membrane-Associated Protein that Suppresses Antiviral Responses in Cells. BioRxiv [Preprint]. 2020.
59. Redondo N, Zaldivar-Lopez S, Garrido JJ, Montoya M. SARS-CoV-2 Accessory Proteins in Viral Pathogenesis: Knowns and Unknowns. Front Immunol. 2021;12:708264.
60. Bosch BJ, van der Zee R, de Haan CA, Rottier PJ. The coronavirus spike protein is a class I virus fusion protein: structural and functional characterization of the fusion core complex. J Virol. 2003;77(16):8801-11.
61. Li F. Structure, Function, and Evolution of Coronavirus Spike Proteins. Annu Rev Virol. 2016;3(1):237-61.
62. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020;367(6483):1260-3.
63. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. Cell. 2020;181(2):281-92 e6.
64. Khare S, Azevedo M, Parajuli P, Gokulan K. Conformational Changes of the Receptor Binding Domain of SARS-CoV-2 Spike Protein and Prediction of a B-Cell Antigenic Epitope Using Structural Data. Front Artif Intell. 2021;4:630955.
65. Lan J, Ge J, Yu J, Shan S, Zhou H, Fan S, et al. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. Nature. 2020;581(7807):215-20.
66. Millet JK, Whittaker GR. Host cell proteases: Critical determinants of coronavirus tropism and pathogenesis. Virus Res. 2015;202:120-34.
67. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004;203(2):631-7.
68. Glowacka I, Bertram S, Muller MA, Allen P, Soilleux E, Pfefferle S, et al. Evidence that TMPRSS2 activates the severe acute respiratory syndrome coronavirus spike protein for membrane fusion and reduces viral control by the humoral immune response. J Virol. 2011;85(9):4122-34.
69. Zhao MM, Yang WL, Yang FY, Zhang L, Huang WJ, Hou W, et al. Cathepsin L plays a key role in SARS-CoV-2 infection in humans and humanized mice and is a promising target for new drug development. Signal Transduct Target Ther. 2021;6(1):134.
70. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020;181(2):271-80 e8.

71. Duchene S, Featherstone L, Haritopoulou-Sinanidou M, Rambaut A, Lemey P, Baele G. Temporal signal and the phylodynamic threshold of SARS-CoV-2. Virus Evol. 2020;6(2):veaa061.
72. Ecdc.europa.eu [Internet]. Methods for the detection and characterisation of SARS-CoV-2 variants - first update. European Centre for Disease Prevention and Control. [20 December 2021; cited 7 January 2022]. Available from: https://www.ecdc.europa.eu/en/publications-data/methods-detection-and-characterisation-sars-cov-2-variants-first-update
73. Cdc.gov [Internet]. COVID-19: About Variants. Centers for Disease Control and Prevention. [13 December 2021; cited 7 January 2022]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/variants/about-variants.html
74. Imperial.ac.uk [Internet]. Report 50 - Hospitalisation risk for Omicron cases in England. Imperial College London, MRC Centre for Global Infectious Disease Analysis. [22 December 2021; cited 10 January 2022]. Available from: https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/covid-19/report-50-severity-omicron/
75. Gov.uk [Internet]. SARS-CoV-2 variants of concern and variants under investigation in England - Technical briefing 33. UK Health Security Agency. [23 December 2021; cited 10 January 2022]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1043807/technical-briefing-33.pdf
76. Luna-Muschi A, Borges IC, de Faria E, Barboza AS, Maia FL, Leme MD, et al. Clinical features of COVID-19 by SARS-CoV-2 Gamma variant: A prospective cohort study of vaccinated and unvaccinated healthcare workers. J Infect. 2021.
77. Gov.uk [Internet]. Investigation of novel SARS-CoV-2 variant - Variant of Concern 202012/01 - Technical briefing 5. UK Health Security Agency (formerly Public Health England). [14 January 2021; cited 10 January 2022]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/959426/Variant_of_Concern_VOC_202012_01_Technical_Briefing_5.pdf
78. Wang Y, Liu M, Gao J. Enhanced receptor binding of SARS-CoV-2 through networks of hydrogen-bonding and hydrophobic interactions. Proc Natl Acad Sci U S A. 2020;117(25):13967-74.
79. Yi C, Sun X, Ye J, Ding L, Liu M, Yang Z, et al. Key residues of the receptor binding motif in the spike protein of SARS-CoV-2 that interact with ACE2 and neutralizing antibodies. Cell Mol Immunol. 2020;17(6):621-30.
80. Starr TN, Greaney AJ, Hilton SK, Ellis D, Crawford KHD, Dingens AS, et al. Deep Mutational Scanning of SARS-CoV-2 Receptor Binding Domain Reveals Constraints on Folding and ACE2 Binding. Cell. 2020;182(5):1295-310 e20.
81. Huang Y, Yang C, Xu XF, Xu W, Liu SW. Structural and functional properties of SARS-CoV-2 spike protein: potential antivirus drug development for COVID-19. Acta Pharmacol Sin. 2020;41(9):1141-9.
82. Hoffmann M, Kleine-Weber H, Pohlmann S. A Multibasic Cleavage Site in the Spike Protein of SARS-CoV-2 Is Essential for Infection of Human Lung Cells. Mol Cell. 2020;78(4):779-84 e5.

83. Peacock TP, Goldhill DH, Zhou J, Baillon L, Frise R, Swann OC, et al. The furin cleavage site of SARS-CoV-2 spike protein is a key determinant for transmission due to enhanced replication in airway cells. BioRxiv [Preprint]. 2020.
84. Zhu Y, Feng F, Hu G, Wang Y, Yu Y, Zhu Y, et al. The S1/S2 boundary of SARS-CoV-2 spike protein modulates cell entry pathways and transmission. BioRxiv [Preprint]. 2020.
85. Scudellari M. How the coronavirus infects cells - and why Delta is so dangerous. Nature. 2021;595(7869):640-4.
86. Wang Q, Qiu Y, Li JY, Zhou ZJ, Liao CH, Ge XY. A Unique Protease Cleavage Site Predicted in the Spike Protein of the Novel Pneumonia Coronavirus (2019-nCoV) Potentially Related to Viral Transmissibility. Virol Sin. 2020;35(3):337-9.
87. Yurkovetskiy L, Wang X, Pascal KE, Tomkins-Tinch C, Nyalile TP, Wang Y, et al. Structural and Functional Analysis of the D614G SARS-CoV-2 Spike Protein Variant. Cell. 2020;183(3):739-51 e8.
88. McCarthy KR, Rennick LJ, Nambulli S, Robinson-McCarthy LR, Bain WG, Haidar G, et al. Natural deletions in the SARS-CoV-2 spike glycoprotein drive antibody escape. BioRxiv [Preprint]. 2021.
89. Kemp SA, Collier DA, Datir R, Ferreira I, Gayed S, Jahun A, et al. Neutralising antibodies in Spike mediated SARS-CoV-2 adaptation. MedRxiv [Preprint]. 2020.
90. Gamage AM, Tan KS, Chan WOY, Liu J, Tan CW, Ong YK, et al. Infection of human Nasal Epithelial Cells with SARS-CoV-2 and a 382-nt deletion isolate lacking ORF8 reveals similar viral kinetics and host transcriptional profiles. PLoS Pathog. 2020;16(12):e1009130.
91. Collier DA, De Marco A, Ferreira I, Meng B, Datir RP, Walls AC, et al. Sensitivity of SARS-CoV-2 B.1.1.7 to mRNA vaccine-elicited antibodies. Nature. 2021;593(7857):136-41.
92. Martínez-García L, Espinel MA, Abreu M, González-Alba JM, Gijón D, McGee A, et al. Emergence and Spread of B. 1.1. 7 Lineage in Primary Care and Clinical Impact in the Morbi-Mortality among Hospitalized Patients in Madrid, Spain. Microorganisms. 2021;9(7):1517.
93. Vassallo M, Manni S, Klotz C, Fabre R, Pini P, Blanchouin E, et al. Patients Admitted for Variant Alpha COVID-19 Have Poorer Outcomes than Those Infected with the Old Strain. J Clin Med. 2021;10(16).
94. McAlister FA, Nabipoor M, Chu A, Lee DS, Saxinger L, Bakal JA. Lessons from the COVID-19 third wave in Canada: the impact of variants of concern and shifting demographics. MedRxiv [Preprint]. 2021.
95. Davies NG, Abbott S, Barnard RC, Jarvis CI, Kucharski AJ, Munday JD, et al. Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. Science. 2021;372(6538).
96. Leung K, Shum MH, Leung GM, Lam TT, Wu JT. Early transmissibility assessment of the N501Y mutant strains of SARS-CoV-2 in the United Kingdom, October to November 2020. Euro Surveill. 2021;26(1).
97. Zhao S, Lou J, Cao L, Zheng H, Chong MKC, Chen Z, et al. Quantifying the transmission advantage associated with N501Y substitution of SARS-CoV-2 in the UK: an early data-driven analysis. J Travel Med. 2021;28(2).

98. Gov.uk [Internet]. NERVTAG paper on COVID-19 variant of concern B.1.1.7. NERVTAG - COVID-19 Public statements. [22 January 2021; cited 7 October 2021] Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/961037/NERVTAG_note_on_B.1.1.7_severity_for_SAGE_77__1_.pdf
99. Challen R, Brooks-Pollock E, Read JM, Dyson L, Tsaneva-Atanasova K, Danon L. Risk of mortality in patients infected with SARS-CoV-2 variant of concern 202012/1: matched cohort study. BMJ. 2021;372:n579.
100. Paredes MI, Lunn SM, Famulare M, Frisbie LA, Painter I, Burstein R, et al. Associations between SARS-CoV-2 variants and risk of COVID-19 hospitalization among confirmed cases in Washington State: a retrospective cohort study. MedRxiv [Preprint]. 2021.
101. Wang P, Nair MS, Liu L, Iketani S, Luo Y, Guo Y, et al. Antibody Resistance of SARS-CoV-2 Variants B.1.351 and B.1.1.7. BioRxiv [Preprint]. 2021:2021.01.25.428137.
102. Wu K, Werner AP, Moliva JI, Koch M, Choi A, Stewart-Jones GBE, et al. mRNA-1273 vaccine induces neutralizing antibodies against spike mutants from global SARS-CoV-2 variants. BioRxiv [Preprint]. 2021.
103. Gallais F, Gantner P, Bruel T, Velay A, Planas D, Wendling M-J, et al. Anti-SARS-CoV-2 Antibodies Persist for up to 13 Months and Reduce Risk of Reinfection. MedRxiv [Preprint]. 2021.
104. Ecdc.europa.eu [Internet]. SARS-CoV-2 variants of concern as of 20 January 2022. European Centre for Disease Prevention and Control. [20 January 2022; cited 24 January 2022] Available from: https://www.ecdc.europa.eu/en/covid-19/variants-concern
105. Gu H, Chen Q, Yang G, He L, Fan H, Deng YQ, et al. Adaptation of SARS-CoV-2 in BALB/c mice for testing vaccine efficacy. Science. 2020;369(6511):1603-7.
106. Plante JA, Liu Y, Liu J, Xia H, Johnson BA, Lokugamage KG, et al. Spike mutation D614G alters SARS-CoV-2 fitness. Nature. 2021;592(7852):116-21.
107. Pearson CA, Russell TW, Davies NG, Kucharski AJ, group CC-w, Edmunds WJ, et al. Estimates of severity and transmissibility of novel South Africa SARS-CoV-2 variant 501Y.V2. Centre for Mathematical Modelling of Infectious Diseases. CMMID Repository [Preprint]. 2021.
108. Wibmer CK, Ayres F, Hermanus T, Madzivhandila M, Kgagudi P, Oosthuysen B, et al. SARS-CoV-2 501Y.V2 escapes neutralization by South African COVID-19 donor plasma. Nat Med. 2021;27(4):622-5.
109. Sinha S, Tam B, Wang SM. Altered interaction between RBD and ACE2 receptor contributes towards the increased transmissibility of SARS CoV-2 delta, kappa, beta, and gamma strains with RBD double mutations. BioRxiv [Preprint]. 2021.
110. Campbell F, Archer B, Laurenson-Schafer H, Jinnai Y, Konings F, Batra N, et al. Increased transmissibility and global spread of SARS-CoV-2 variants of concern as at June 2021. Euro Surveill. 2021;26(24).
111. Ecdc.europa.eu [Internet]. Risk assessment: SARS-CoV-2 - increased circulation of variants of concern and vaccine rollout in the EU/EEA, 14th update. European Centre for Disease Prevention and Control. [15 February 2021; cited 8

October 2021] Available from: https://www.ecdc.europa.eu/en/publications-data/covid-19-risk-assessment-variants-vaccine-fourteenth-update-february-2021

112. Khan A, Zia T, Suleman M, Khan T, Ali SS, Abbasi AA, et al. Higher infectivity of the SARS-CoV-2 new variants is associated with K417N/T, E484K, and N501Y mutants: An insight from structural data. J Cell Physiol. 2021;236(10):7045-57.
113. Baum A, Fulton BO, Wloga E, Copin R, Pascal KE, Russo V, et al. Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies. Science. 2020;369(6506):1014-8.
114. Curran J, Dol J, Boulos L, Somerville M, McCulloch H, MacDonald M, et al. Transmission characteristics of SARS-CoV-2 variants of concern. MedRxiv [Preprint]. 2021.
115. de Faria E, Guedes AR, Oliveira MS, de Godoy Moreira MV, Maia FL, dos Santos Barboza A, et al. Performance of vaccination with CoronaVac in a cohort of healthcare workers (HCW) - preliminary report. MedRxiv [Preprint]. 2021.
116. Freitas ARR, Beckedorff OA, Cavalcanti LPG, Siqueira AM, Castro DB, Costa CFD, et al. The emergence of novel SARS-CoV-2 variant P.1 in Amazonas (Brazil) was temporally associated with a change in the age and sex profile of COVID-19 mortality: A population based ecological study. Lancet Reg Health Am. 2021;1:100021.
117. Funk T, Pharris A, Spiteri G, Bundle N, Melidou A, Carr M, et al. Characteristics of SARS-CoV-2 variants of concern B.1.1.7, B.1.351 or P.1: data from seven EU/EEA countries, weeks 38/2020 to 10/2021. Euro Surveill. 2021;26(16).
118. Sabino EC, Buss LF, Carvalho MPS, Prete CA, Jr., Crispim MAE, Fraiji NA, et al. Resurgence of COVID-19 in Manaus, Brazil, despite high seroprevalence. Lancet. 2021;397(10273):452-5.
119. Dejnirattisai W, Zhou D, Supasa P, Liu C, Mentzer AJ, Ginn HM, et al. Antibody evasion by the P.1 strain of SARS-CoV-2. Cell. 2021;184(11):2939-54 e9.
120. Korber B, Fischer WM, Gnanakaran S, Yoon H, Theiler J, Abfalterer W, et al. Tracking Changes in SARS-CoV-2 Spike: Evidence that D614G Increases Infectivity of the COVID-19 Virus. Cell. 2020;182(4):812-27 e19.
121. Volz E, Hill V, McCrone JT, Price A, Jorgensen D, O'Toole A, et al. Evaluating the Effects of SARS-CoV-2 Spike Mutation D614G on Transmissibility and Pathogenicity. Cell. 2021;184(1):64-75 e11.
122. Augusto G, Mohsen MO, Zinkhan S, Liu X, Vogel M, Bachmann MF. In vitro data suggest that Indian delta variant B.1.617 of SARS-CoV-2 escapes neutralization by both receptor affinity and immune evasion. Allergy. 2021.
123. Tchesnokova V, Kulakesara H, Larson L, Bowers V, Rechkina E, Kisiela D, et al. Acquisition of the L452R mutation in the ACE2-binding interface of Spike protein triggers recent massive expansion of SARS-Cov-2 variants. BioRxiv [Preprint]. 2021.
124. Li Q, Wu J, Nie J, Zhang L, Hao H, Liu S, et al. The Impact of Mutations in SARS-CoV-2 Spike on Viral Infectivity and Antigenicity. Cell. 2020;182(5):1284-94 e9.
125. Di Giacomo S, Mercatelli D, Rakhimov A, Giorgi FM. Preliminary report on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Spike mutation T478K. J Med Virol. 2021;93(9):5638-43.

126. Torjesen I. Covid-19: Delta variant is now UK's most dominant strain and spreading through schools. BMJ. 2021;373:n1445.
127. Reuters.com [Internet]. Delta COVID variant now dominant strain worldwide, U.S. deaths surge -officials. O'donnell C, Mason J, Reuters. [16 July 2021; cited 6 January 2022]. Available from: www.reuters.com
128. Euro.who.int [Internet]. SARS-CoV-2 Delta variant now dominant in much of European region; efforts must be reinforced to prevent transmission, warns WHO Regional Office for Europe and ECDC. World Health Organisation. [23 July 2021; cited 11 October 2021]. Available from: https://www.euro.who.int/en/media-centre/sections/press-releases/2021/sars-cov-2-delta-variant-now-dominant-in-much-of-european-region-efforts-must-be-reinforced-to-prevent-transmission,-warns-who-regional-office-for-europe-and-ecdc
129. Li B, Deng A, Li K, Hu Y, Li Z, Xiong Q, et al. Viral infection and transmission in a large, well-traced outbreak caused by the SARS-CoV-2 Delta variant MedRxiv [Preprint]. 2021.
130. Teyssou E, Delagreverie H, Visseaux B, Lambert-Niclot S, Brichler S, Ferre V, et al. The Delta SARS-CoV-2 variant has a higher viral load than the Beta and the historical variants in nasopharyngeal samples from newly diagnosed COVID-19 patients. J Infect. 2021;83(4):e1-e3.
131. Kumar A, Asghar A, Raza K, Narayan RK, Jha RK, Satyam A, et al. Demographic characteristics of SARS-CoV-2 B.1.617.2 (Delta) variant infections in Indian population. MedRxiv [Preprint]. 2021.
132. Planas D, Veyer D, Baidaliuk A, Staropoli I, Guivel-Benhassine F, Rajah MM, et al. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. Nature. 2021;596(7871):276-80.
133. Sheikh A, McMenamin J, Taylor B, Robertson C, Public Health S, the EIIC. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. Lancet. 2021;397(10293):2461-2.
134. Fisman DN, Tuite AR. Progressive Increase in Virulence of Novel SARS-CoV-2 Variants in Ontario, Canada. MedRxiv [Preprint]. 2021.
135. Cameroni E, Saliba C, Bowen JE, Rosen LE, Culap K, Pinto D, et al. Broadly neutralizing antibodies overcome SARS-CoV-2 Omicron antigenic shift. BioRxiv [Preprint]. 2021.
136. Shah M, Woo HG. Omicron: A heavily mutated SARS-CoV-2 variant exhibits stronger binding to ACE2 and potently escape approved COVID-19 therapeutic antibodies. BioRxiv [Preprint]. 2021.
137. Wolter N, Jassat W, Walaza S, Welch R, Moultrie H, Groome M, et al. Early assessment of the clinical severity of the SARS-CoV-2 Omicron variant in South Africa. MedRxiv [Preprint]. 2021.
138. Gov.uk [Internet]. Omicron daily overview: 24 December 2021. UK Health Security Agency. [24 December 2021; cited 4 January 2022]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1043866/20211224_OS_Daily_Omicron_Overview.pdf
139. Who.int [Internet]. Enhancing readiness for Omicron (B.1.1.529): Technical brief and priority actions for Member States. World Health Organisation. [23 December 2021; cited 4 January 2022]. Available from: https://www.who.int/docs/default-

source/coronaviruse/2021-12-23-global-technical-brief-and-priority-action-on-omicron.pdf?sfvrsn=d0e9fb6c_8

140. Med.hku.hk [Internet]. HKUMed finds Omicron SARS-CoV-2 can infect faster and better than Delta in human bronchus but with less severe infection in lung. The University of Hong Kong, LKS Faculty of Medicine. [15 December 2021; cited 5 January 2022]. Available from: https://www.med.hku.hk/en/news/press/20211215-omicron-sars-cov-2-infection

141. Sheikh A, Kerr S, Woolhouse M, McMenamin J, C. R. Severity of Omicron variant of concern and vaccine effectiveness against symptomatic disease: national cohort with nested test negative design study in Scotland. 2021.

142. Pulliam JRC, van Schalkwyk C, Govender N, von Gottberg A, Cohen C, Groome MJ, et al. Increased risk of SARS-CoV-2 reinfection associated with emergence of the Omicron variant in South Africa. MedRxiv [Preprint]. 2021.

143. Sandile Cele, Laurelle Jackson, Khadija Khan, David Khoury, Thandeka Moyo-Gwete, Houriiyah Tegally, et al. SARS-CoV-2 Omicron has extensive but incomplete escape of Pfizer BNT162b2 elicited neutralization and requires ACE2 for infection. MedRxiv [Preprint]. 2021.

144. Planas D, Saunders N, Maes P, Guivel-Benhassine F, Planchais C, Buchrieser J, et al. Considerable escape of SARS-CoV-2 variant Omicron to antibody neutralization. BioRxiv [Preprint]. 2021.

145. Meng B, Ferreira IATM, Abdullahi A, Saito A, Kimura I, Yamasoba D, et al. SARS-CoV-2 Omicron spike mediated immune escape, infectivity and cell-cell fusion. BioRxiv [Preprint]. 2021.

146. Pfizer.com [Internet]. Pfizer and BioNTech Provide Update on Omicron Variant. Pfizer. [8 December 2021; cited 4 January 2022]. Available from: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-provide-update-omicron-variant

147. Keeton R, Tincho MB, Ngomti A, Baguma R, Benede N, Suzuki A, et al. SARS-CoV-2 spike T cell responses induced upon vaccination or infection remain robust against Omicron. MedRxiv [Preprint]. 2021.

148. Sacoronavirus.co.za [Internet]. Cabinet approves changes to covid-19 regulations. South Africa Department of Health. [30 December 2021; cited 7 January 2022]. Available from: https://sacoronavirus.co.za/2021/12/30/media-release-cabinet-approves-changes-to-covid-19-regulations/

149. Taylor L. Covid-19: Omicron drives weekly record high in global infections. BMJ. 2022;376:o66.

150. Tada T, Zhou H, Dcosta BM, Samanovic MI, Mulligan MJ, Landau NR. SARS-CoV-2 Lambda Variant Remains Susceptible to Neutralization by mRNA Vaccine-elicited Antibodies and Convalescent Serum. BioRxiv [Preprint]. 2021.

151. Acevedo ML, Alonso-Palomares L, Bustamante A, Gaggero A, Paredes F, Cortés CP, et al. Infectivity and immune escape of the new SARS-CoV-2 variant of interest Lambda. MedRxiv [Preprint]. 2021.

152. Laiton-Donato K, Franco-Munoz C, Alvarez-Diaz DA, Ruiz-Moreno HA, Usme-Ciro JA, Prada DA, et al. Characterization of the emerging B.1.621 variant of interest of SARS-CoV-2. Infect Genet Evol. 2021;95:105038.

153. Chen J, Gao K, Wang R, Wei GW. Revealing the Threat of Emerging SARS-CoV-2 Mutations to Antibody Therapies. J Mol Biol. 2021;433(18):167155.
154. Amanat F, Krammer F. SARS-CoV-2 vaccines: status report. Immunity. 2020;52(4):583-9.
155. Who.int [Internet]. COVID-19 vaccine tracker and landscape. World Health Organisation. [25 January 2022; cited 26 January 2022]. Available from: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines
156. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020;383(27):2603-15.
157. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh C-L, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020;367(6483):1260-3.
158. Who.int [Internet]. Coronavirus disease (COVID-19): Vaccines. World Health Organisation. [20 January 2022; cited 26 January 2022]. Available from: https://www.who.int/news-room/questions-and-answers/item/coronavirus-disease-(covid-19)-vaccines
159. Sahin U, Muik A, Vogler I, Derhovanessian E, Kranz LM, Vormehr M, et al. BNT162b2 vaccine induces neutralizing antibodies and poly-specific T cells in humans. Nature. 2021;595(7868):572-7.
160. Arunachalam PS, Scott MKD, Hagan T, Li C, Feng Y, Wimmers F, et al. Systems vaccinology of the BNT162b2 mRNA vaccine in humans. Nature. 2021;596(7872):410-6.
161. Walsh EE, Frenck RW, Jr., Falsey AR, Kitchin N, Absalon J, Gurtman A, et al. Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates. N Engl J Med. 2020;383(25):2439-50.
162. Appelman B, van der Straten K, Lavell AHA, Schinkel M, Slim MA, Poniman M, et al. Time since SARS-CoV-2 infection and humoral immune response following BNT162b2 mRNA vaccination. EBioMedicine. 2021;72:103589.
163. Beatty AL, Peyser ND, Butcher XE, Cocohoba JM, Lin F, Olgin JE, et al. Analysis of COVID-19 Vaccine Type and Adverse Effects Following Vaccination. JAMA Netw Open. 2021;4(12):e2140364.
164. Vizcarra P, Haemmerle J, Velasco H, Velasco T, Fernandez-Escribano M, Vallejo A, et al. BNT162b2 mRNA COVID-19 vaccine Reactogenicity: The key role of immunity. Vaccine. 2021;39(51):7367-74.
165. Salmeron Rios S, Mas Romero M, Cortes Zamora EB, Tabernero Sahuquillo MT, Romero Rizos L, Sanchez-Jurado PM, et al. Immunogenicity of the BNT162b2 vaccine in frail or disabled nursing home residents: COVID-A study. J Am Geriatr Soc. 2021;69(6):1441-7.
166. Barda N, Dagan N, Ben-Shlomo Y, Kepten E, Waxman J, Ohana R, et al. Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. N Engl J Med. 2021;385(12):1078-90.
167. Sharma O, Sultan AA, Ding H, Triggle CR. A Review of the Progress and Challenges of Developing a Vaccine for COVID-19. Front Immunol. 2020;11:585354.

168. Who.int [Internet]. WHO lists two additional COVID-19 vaccines for emergency use and COVAX roll-out. World Health Organisation. [15 February 2021; cited 13 October 2021]. Available rom: https://www.who.int/news/item/15-02-2021-who-lists-two-additional-covid-19-vaccines-for-emergency-use-and-covax-roll-out
169. Ewer KJ, Barrett JR, Belij-Rammerstorfer S, Sharpe H, Makinson R, Morter R, et al. T cell and antibody responses induced by a single dose of ChAdOx1 nCoV-19 (AZD1222) vaccine in a phase 1/2 clinical trial. Nat Med. 2021;27(2):270-8.
170. Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij-Rammerstorfer S, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. Lancet. 2020;396(10249):467-78.
171. Al Khames Aga QA, Alkhaffaf WH, Hatem TH, Nassir KF, Batineh Y, Dahham AT, et al. Safety of COVID-19 vaccines. J Med Virol. 2021;93(12):6588-94.
172. Sadoff J, Gray G, Vandebosch A, Cardenas V, Shukarev G, Grinsztejn B, et al. Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19. N Engl J Med. 2021;384(23):2187-201.
173. Alter G, Yu J, Liu J, Chandrashekar A, Borducchi EN, Tostanoski LH, et al. Immunogenicity of Ad26.COV2.S vaccine against SARS-CoV-2 variants in humans. Nature. 2021;596(7871):268-72.
174. Sadoff J, Le Gars M, Shukarev G, Heerwegh D, Truyers C, de Groot AM, et al. Interim Results of a Phase 1-2a Trial of Ad26.COV2.S Covid-19 Vaccine. N Engl J Med. 2021;384(19):1824-35.
175. Keeton R, Richardson SI, Moyo-Gwete T, Hermanus T, Tincho MB, Benede N, et al. Prior infection with SARS-CoV-2 boosts and broadens Ad26.COV2.S immunogenicity in a variant-dependent manner. Cell Host Microbe. 2021;29(11):1611-9 e5.
176. See I, Su JR, Lale A, Woo EJ, Guh AY, Shimabukuro TT, et al. US Case Reports of Cerebral Venous Sinus Thrombosis With Thrombocytopenia After Ad26.COV2.S Vaccination, March 2 to April 21, 2021. JAMA. 2021;325(24):2448-56.
177. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2021;384(5):403-16.
178. Mukhopadhyay L, Yadav PD, Gupta N, Mohandas S, Patil DY, Shete-Aich A, et al. Comparison of the immunogenicity & protective efficacy of various SARS-CoV-2 vaccine candidates in non-human primates. Indian J Med Res. 2021;153(1 & 2):93-114.
179. Anderson EJ, Rouphael NG, Widge AT, Jackson LA, Roberts PC, Makhene M, et al. Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults. N Engl J Med. 2020;383(25):2427-38.
180. Jackson LA, Anderson EJ, Rouphael NG, Roberts PC, Makhene M, Coler RN, et al. An mRNA Vaccine against SARS-CoV-2 - Preliminary Report. N Engl J Med. 2020;383(20):1920-31.
181. Chu L, McPhee R, Huang W, Bennett H, Pajon R, Nestorova B, et al. A preliminary report of a randomized controlled phase 2 trial of the safety and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine. Vaccine. 2021;39(20):2791-9.
182. Who.int [Internet]. Interim recommendations for use of the inactivated COVID-19 vaccine BIBP developed by China National Biotec Group (CNBG), Sinopharm.

World Health Organisation. [28 October 2021; cited 7 January 2022]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-BIBP

183. Who.int [Internet]. Background document on the inactivated vaccine Sinovac-CoronaVac against COVID-19. World Health Organisation. [1 June 2021; cited 13 October 2021]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-Sinovac-CoronaVac-background-2021.1
184. Who.int [Internet]. Background document on the Bharat Biotech BBV152 COVAXIN® (COVID-19) vaccine. World Health Organisation. [3 November 2021; cited 7 January 2022]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-bbv152-covaxin-background
185. Who.int [Internet]. WHO issues emergency use listing for eighth COVID-19 vaccine. World Health Organisation. [3 November 2021; cited 7 January 2022]. Available from: https://www.who.int/news/item/03-11-2021-who-issues-emergency-use-listing-for-eighth-covid-19-vaccine
186. Who.int [Internet]. WHO lists 9th COVID-19 vaccine for emergency use with aim to increase access to vaccination in lower-income countries. World Health Organisation. [17 December 2021; cited 7 January 2022]. Available from: https://www.who.int/news/item/17-12-2021-who-lists-9th-covid-19-vaccine-for-emergency-use-with-aim-to-increase-access-to-vaccination-in-lower-income-countries
187. Who.int [Internet]. WHO lists 10th COVID-19 vaccine for emergency use: Nuvaxovid. World Health Organisation. [21 December 2021; cited 7 January 2022]. Available from: https://www.who.int/news/item/21-12-2021-who-lists-10th-covid-19-vaccine-for-emergency-use-nuvaxovid
188. Who.int [Internet]. Interim recommendations for use of the Novavax NVX-CoV2373 vaccine against COVID-19. World Health Organisation. [20 December 2021; cited 7 January 2022]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-novavax-nvx-cov2373
189. Mishra SK, Pradhan SK, Pati S, Sahu S, Nanda RK. Waning of Anti-spike Antibodies in AZD1222 (ChAdOx1) Vaccinated Healthcare Providers: A Prospective Longitudinal Study. Cureus. 2021;13(11):e19879.
190. Tre-Hardy M, Cupaiolo R, Wilmet A, Antoine-Moussiaux T, Della Vecchia A, Horeanga A, et al. Immunogenicity of mRNA-1273 COVID vaccine after 6 months surveillance in health care workers; a third dose is necessary. J Infect. 2021;83(5):559-64.
191. Shrotri M, Navaratnam AMD, Nguyen V, Byrne T, Geismar C, Fragaszy E, et al. Spike-antibody waning after second dose of BNT162b2 or ChAdOx1. Lancet. 2021;398(10298):385-7.
192. Chemaitelly H, Tang P, Hasan MR, AlMukdad S, Yassine HM, Benslimane FM, et al. Waning of BNT162b2 Vaccine Protection against SARS-CoV-2 Infection in Qatar. N Engl J Med. 2021.
193. Mizrahi B, Lotan R, Kalkstein N, Peretz A, Perez G, Ben-Tov A, et al. Correlation of SARS-CoV-2 Breakthrough Infections to Time-from-vaccine; Preliminary Study. MedRxiv [Preprint]. 2021.

194. Thomas SJ, Moreira ED, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Six Month Safety and Efficacy of the BNT162b2 mRNA COVID-19 Vaccine. MedRxiv [Preprint]. 2021.
195. Tre-Hardy M, Cupaiolo R, Wilmet A, Antoine-Moussiaux T, Della Vecchia A, Horeanga A, et al. Six-month interim analysis of ongoing immunogenicity surveillance of the mRNA-1273 vaccine in healthcare workers: A third dose is expected. J Infect. 2021.
196. Almendro-Vazquez P, Laguna-Goya R, Ruiz-Ruigomez M, Utrero-Rico A, Lalueza A, Maestro de la Calle G, et al. Longitudinal dynamics of SARS-CoV-2-specific cellular and humoral immunity after natural infection or BNT162b2 vaccination. PLoS Pathog. 2021;17(12):e1010211.
197. Cohen KW, Linderman SL, Moodie Z, Czartoski J, Lai L, Mantus G, et al. Longitudinal analysis shows durable and broad immune memory after SARS-CoV-2 infection with persisting antibody responses and memory B and T cells. Cell Rep Med. 2021;2(7):100354.
198. Zeng G, Wu Q, Pan H, Li M, Yang J, Wang L, et al. Immunogenicity and safety of a third dose of CoronaVac, and immune persistence of a two-dose schedule, in healthy adults: interim results from two single-centre, double-blind, randomised, placebo-controlled phase 2 clinical trials. Lancet Infect Dis. 2021.
199. Choi A, Koch M, Wu K, Chu L, Ma L, Hill A, et al. Safety and immunogenicity of SARS-CoV-2 variant mRNA vaccine boosters in healthy adults: an interim analysis. Nat Med. 2021.
200. Flaxman A, Marchevsky NG, Jenkin D, Aboagye J, Aley PK, Angus B, et al. Reactogenicity and immunogenicity after a late second dose or a third dose of ChAdOx1 nCoV-19 in the UK: a substudy of two randomised controlled trials (COV001 and COV002). Lancet. 2021;398(10304):981-90.
201. Iketani S, Liu L, Nair MS, Mohri H, Wang M, Huang Y, et al. A third COVID-19 vaccine shot markedly boosts neutralizing antibody potency and breadth MedRxiv [Preprint]. 2021.
202. Garcia-Beltran WF, St Denis KJ, Hoelzemer A, Lam EC, Nitido AD, Sheehan ML, et al. mRNA-based COVID-19 vaccine boosters induce neutralizing immunity against SARS-CoV-2 Omicron variant. MedRxiv [Preprint]. 2021.
203. Yorsaeng R, Suntronwong N, Phowatthanasathian H, Assawakosri S, Kanokudom S, Thongmee T, et al. Immunogenicity of a third dose viral-vectored COVID-19 vaccine after receiving two-dose inactivated vaccines in healthy adults. Vaccine. 2022;40(3):524-30.
204. Munro APS, Janani L, Cornelius V, Aley PK, Babbage G, Baxter D, et al. Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial. Lancet. 2021;398(10318):2258-76.
205. Madelon N, Heikkilä N, Sabater Royo I, Fontannaz P, Breville G, Lauper K, et al. Omicron-specific cytotoxic T-cell responses are boosted following a third dose of mRNA COVID-19 vaccine in anti-CD20-treated multiple sclerosis patients MedRxiv [Preprint]. 2021.

206. Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Kalkstein N, et al. Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel. N Engl J Med. 2021;385(15):1393-400.
207. Barda N, Dagan N, Cohen C, Hernan MA, Lipsitch M, Kohane IS, et al. Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. Lancet. 2021;398(10316):2093-100.
208. Arbel R, Hammerman A, Sergienko R, Friger M, Peretz A, Netzer D, et al. BNT162b2 Vaccine Booster and Mortality Due to Covid-19. N Engl J Med. 2021;385(26):2413-20.
209. Spitzer A, Angel Y, Marudi O, Zeltser D, Saiag E, Goldshmidt H, et al. Association of a Third Dose of BNT162b2 Vaccine With Incidence of SARS-CoV-2 Infection Among Health Care Workers in Israel. JAMA. 2022.
210. Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Alroy-Preis S, et al. Protection against Covid-19 by BNT162b2 Booster across Age Groups. N Engl J Med. 2021;385(26):2421-30.
211. Levine-Tiefenbrun M, Yelin I, Alapi H, Katz R, Herzel E, Kuint J, et al. Viral loads of Delta-variant SARS-CoV-2 breakthrough infections after vaccination and booster with BNT162b2. Nat Med. 2021;27(12):2108-10.
212. Andrews N, Stowe J, Kirsebom F, Toffa S, Rickeard T, Gallagher E, et al. Effectiveness of COVID-19 vaccines against the Omicron (B.1.1.529) variant of concern. medRxiv [Preprint]. 2021.
213. Hansen CH, Schelde AB, Moustsen-Helm IR, Emborg H-D, Krause TG, Mølbak K, et al. Vaccine effectiveness against SARS-CoV-2 infection with the Omicron or Delta variants following a two-dose or booster BNT162b2 or mRNA-1273 vaccination series: A Danish cohort study MedRxiv [Preprint]. 2021.
214. Lusvarghi S, Pollett SD, Neerukonda SN, Wang W, Wang R, Vassell R, et al. SARS-CoV-2 Omicron neutralization by therapeutic antibodies, convalescent sera, and post-mRNA vaccine booster. BioRxiv [Preprint]. 2021.
215. Cdc.gov [Internet]. CDC Recommends Pfizer Booster at 5 Months, Additional Primary Dose for Certain Immunocompromised Children. Centers for Disease Control and Prevention. [4 January 2022; cited 7 January 2022]. Available from: https://www.cdc.gov/media/releases/2022/s0104-Pfizer-Booster.html
216. Wu K, Choi A, Koch M, Elbashir S, Ma L, Lee D, et al. Variant SARS-CoV-2 mRNA vaccines confer broad neutralization as primary or booster series in mice. Vaccine. 2021;39(51):7394-400.
217. Covid19-trials.com [Internet]. Global Coronavirus COVID-19 Clinical Trial Tracker. Cytel Inc. [cited 12 January 2022]. Available from: https://www.covid19-trials.com/
218. Gov.uk [Internet]. First oral antiviral for COVID-19, Lagevrio (molnupiravir), approved by MHRA. Medicines and Healthcare products Regulatory Agency. [4 November 2021; cited 12 January 2022]. Available from: https://www.gov.uk/government/news/first-oral-antiviral-for-covid-19-lagevrio-molnupiravir-approved-by-mhra
219. Gov.uk [Internet]. Oral COVID-19 antiviral, Paxlovid, approved by UK regulator. Medicines and Healthcare products Regulatory Agency. [31 December 2021;

cited 12 January 2022]. Available from: https://www.gov.uk/government/news/oral-covid-19-antiviral-paxlovid-approved-by-uk-regulator

220. Fda.gov [Internet]. Coronavirus (COVID-19) Update: FDA Authorizes Additional Oral Antiviral for Treatment of COVID-19 in Certain Adults. U.S. Food and Drug Administration. [23 December 2021; cited 12 January 2022]. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-oral-antiviral-treatment-covid-19-certain

221. Fda.gov [Internet]. Coronavirus (COVID-19) Update: FDA Authorizes First Oral Antiviral for Treatment of COVID-19. U.S. Food and Drug Administration. [22 December 2021; cited 12 January 2022]. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-oral-antiviral-treatment-covid-19

222. ema.europa.eu [Internet]. EMA issues advice on use of Lagevrio (molnupiravir) for the treatment of COVID-19. European Medicines Agency. [19 November 2021.; cited 12 January 2022]. Available from: https://www.ema.europa.eu/en/news/ema-issues-advice-use-lagevrio-molnupiravir-treatment-covid-19

223. ema.europa.eu [Internet]. EMA issues advice on use of Paxlovid (PF-07321332 and ritonavir) for the treatment of COVID-19: rolling review starts in parallel. European Medicines Agency. [16 December 2021.; cited 12 January 2022]. Available from: https://www.ema.europa.eu/en/news/ema-issues-advice-use-paxlovid-pf-07321332-ritonavir-treatment-covid-19-rolling-review-starts

224. Gov.uk [Internet]. MHRA approves Xevudy (sotrovimab), a COVID-19 treatment found to cut hospitalisation and death by 79%. Medicines and Healthcare products Regulatory Agency. [2 December 2021; cited 12 January 2022]. Available from: https://www.gov.uk/government/news/mhra-approves-xevudy-sotrovimab-a-covid-19-treatment-found-to-cut-hospitalisation-and-death-by-79#:~:text=and%20licensing%20guidance-,MHRA%20approves%20Xevudy%20(sotrovimab)%2C%20a%20COVID%2D19%20treatment,risk%20of%20developing%20severe%20disease.

225. Fda.gov [Internet]. Coronavirus (COVID-19) Update: FDA Authorizes Additional Monoclonal Antibody for Treatment of COVID-19. U.S. Food and Drug Administration. [26 May 2021; cited 12 January 2022]. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-monoclonal-antibody-treatment-covid-19

226. ema.europa.eu [Internet]. COVID-19: EMA recommends authorisation of antibody medicine Xevudy. European Medicines Agency. [16 December 2021.; cited 12 January 2022]. Available from: https://www.ema.europa.eu/en/news/covid-19-ema-recommends-authorisation-antibody-medicine-xevudy#:~:text=EMA's%20human%20medicines%20committee%20(CHMP,medicine%20together%20with%20Vir%20Biotechnology.

227. Who.int [Internet]. Therapeutics and COVID-19: living guideline. World Health Organisation. [14 January 2022; cited 21 January 2022] Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022.1

228. Nice.org.uk [Internet]. COVID-19 rapid guideline: managing COVID-19 NICE guideline [NG191]. National Institute for Health and Care Excellence. [16 December

2021; cited 21 January 2022]. Available from: https://www.nice.org.uk/guidance/ng191
229. Gov.uk [Internet]. MHRA guidance on coronavirus (COVID-19). Medicines and Healthcare products Regulatory Agency. [16 September 2021; cited 21 January 2022]. Available from: https://www.gov.uk/government/collections/mhra-guidance-on-coronavirus-covid-19
230. ecdc.europa.eu [Internet]. All resources on COVID-19 – Guidance and technical reports. [2022; cited 21 January 2022]. Available from: https://www.ecdc.europa.eu/en/covid-19/all-reports-covid-19
231. Nih.gov [Internet]. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health [19 January 2022; cited 21 January 2022]. Available from: https://www.covid19treatmentguidelines.nih.gov/
232. Cdc.gov [Internet]. Guidance for COVID-19. Centers for Disease Control and Prevention. [15 March 2021; cited 21 January 2022]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/communication/guidance.html
233. Blundell R, Costa Dias M, Joyce R, Xu X. COVID-19 and Inequalities. Fisc Stud. 2020.
234. Chadeau-Hyam M, Bodinier B, Elliott J, Whitaker MD, Tzoulaki I, Vermeulen R, et al. Risk factors for positive and negative COVID-19 tests: a cautious and in-depth analysis of UK biobank data. Int J Epidemiol. 2020;49(5):1454-67.
235. Patel JA, Nielsen FBH, Badiani AA, Assi S, Unadkat VA, Patel B, et al. Poverty, inequality and COVID-19: the forgotten vulnerable. Public Health. 2020;183:110-1.
236. Cohen J, Rodgers YVM. Contributing factors to personal protective equipment shortages during the COVID-19 pandemic. Prev Med. 2020;141:106263.
237. Who.int [Internet]. Vaccine Equity. World Health Organisation. [cited 10 January 2022]. Available from: https://www.who.int/campaigns/vaccine-equity
238. parliament.uk [Internet]. Coronavirus: lessons learned to date. The House of Commons, Science and Technology Committee, and Health and Social Care Committee. [12 October 2021; cited 10 January 2022]. Available from: https://publications.parliament.uk/pa/cm5802/cmselect/cmsctech/92/9203.htm
239. Ball P. The lightning-fast quest for COVID vaccines - and what it means for other diseases. Nature. 2021;589(7840):16-8.
240. Summers J, Cheng HY, Lin HH, Barnard LT, Kvalsvig A, Wilson N, et al. Potential lessons from the Taiwan and New Zealand health responses to the COVID-19 pandemic. Lancet Reg Health West Pac. 2020;4:100044.
241. Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. N Engl J Med. 2021;384(15):1412-23.
242. Lopez Bernal J, Andrews N, Gower C, Gallagher E, Simmons R, Thelwall S, et al. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. N Engl J Med. 2021;385(7):585-94.
243. Abu-Raddad LJ, Chemaitelly H, Butt AA, National Study Group for C-V. Effectiveness of the BNT162b2 Covid-19 Vaccine against the B.1.1.7 and B.1.351 Variants. N Engl J Med. 2021;385(2):187-9.

244. Chung H, He S, Nasreen S, Sundaram ME, Buchan SA, Wilson SE, et al. Effectiveness of BNT162b2 and mRNA-1273 covid-19 vaccines against symptomatic SARS-CoV-2 infection and severe covid-19 outcomes in Ontario, Canada: test negative design study. BMJ. 2021;374:n1943.
245. Nasreen S, Chung H, He S, Brown KA, Gubbay JB, Buchan SA, et al. Effectiveness of mRNA and ChAdOx1 COVID-19 vaccines against symptomatic SARS CoV-2 infection and severe outcomes with variants of concern in Ontario. MedRxiv [Preprint]. 2021.
246. Puranik A, Lenehan PJ, Silvert E, Niesen MJM, Corchado-Garcia J, O'Horo JC, et al. Comparison of two highly-effective mRNA vaccines for COVID-19 during periods of Alpha and Delta variant prevalence. MedRxiv [Preprint]. 2021.
247. Julia Stowe, Nick Andrews, Charlotte Gower, Eileen Gallagher, Lara Utsi, Ruth Simmons, et al. Effectiveness of COVID-19 vaccines against hospital admission with the Delta (B.1.617.2) variant. Public Health England [preprint]. 2021.
248. Lopez Bernal J, Andrews N, Gower C, Robertson C, Stowe J, Tessier E, et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. BMJ. 2021;373:n1088.
249. Skowronski DM, Setayeshgar S, Zou M, Prystajecky N, Tyson JR, Galanis E, et al. Single-dose mRNA vaccine effectiveness against SARS-CoV-2, including Alpha and Gamma variants: a test-negative design in adults 70 years and older in British Columbia, Canada. Clin Infect Dis. 2021.
250. Carazo S, Talbot D, Boulianne N, Brisson M, Gilca R, Deceuninck G, et al. Single-dose mRNA vaccine effectiveness against SARS-CoV-2 in healthcare workers extending 16 weeks post-vaccination: a test-negative design from Quebec, Canada. Clin Infect Dis. 2021.
251. Charmet T, Schaeffer L, Grant R, Galmiche S, Cheny O, Von Platen C, et al. Impact of original, B.1.1.7, and B.1.351/P.1 SARS-CoV-2 lineages on vaccine effectiveness of two doses of COVID-19 mRNA vaccines: Results from a nationwide case-control study in France. Lancet Reg Health Eur. 2021;8:100171.
252. Tang P, Hasan MR, Chemaitelly H, Yassine HM, Benslimane FM, Al Khatib HA, et al. BNT162b2 and mRNA-1273 COVID-19 vaccine effectiveness against the SARS-CoV-2 Delta variant in Qatar. Nat Med. 2021;27(12):2136-43.
253. Hall VJ, Foulkes S, Saei A, Andrews N, Oguti B, Charlett A, et al. COVID-19 vaccine coverage in health-care workers in England and effectiveness of BNT162b2 mRNA vaccine against infection (SIREN): a prospective, multicentre, cohort study. Lancet. 2021;397(10286):1725-35.
254. Haas EJ, Angulo FJ, McLaughlin JM, Anis E, Singer SR, Khan F, et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. Lancet. 2021;397(10287):1819-29.
255. Nanduri S, Pilishvili T, Derado G, Soe MM, Dollard P, Wu H, et al. Effectiveness of Pfizer-BioNTech and Moderna Vaccines in Preventing SARS-CoV-2 Infection Among Nursing Home Residents Before and During Widespread Circulation

of the SARS-CoV-2 B.1.617.2 (Delta) Variant - National Healthcare Safety Network, March 1-August 1, 2021. MMWR Morb Mortal Wkly Rep. 2021;70(34):1163-6.
256. Fowlkes A, Gaglani M, Groover K, Thiese MS, Tyner H, Ellingson K, et al. Effectiveness of COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Frontline Workers Before and During B.1.617.2 (Delta) Variant Predominance - Eight U.S. Locations, December 2020-August 2021. MMWR Morb Mortal Wkly Rep. 2021;70(34):1167-9.
257. Lefevre B, Tondeur L, Madec Y, Grant R, Lina B, van der Werf S, et al. Beta SARS-CoV-2 variant and BNT162b2 vaccine effectiveness in long-term care facilities in France. Lancet Healthy Longev. 2021.
258. Pouwels KB, Pritchard E, Matthews PC, Stoesser N, Eyre DW, Vihta K-D, et al. Effect of Delta variant on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK. Nature Medicine. 2021.
259. Williams C, Al-Bargash D, Macalintal C, Stuart R, Seth A, Latham J, et al. COVID-19 Outbreak Associated with a SARS-CoV-2 P.1 Lineage in a Long-Term Care Home after Implementation of a Vaccination Program - Ontario, April-May 2021. Clin Infect Dis. 2021.
260. Fabiani M, Ramigni M, Gobbetto V, Mateo-Urdiales A, Pezzotti P, Piovesan C. Effectiveness of the Comirnaty (BNT162b2, BioNTech/Pfizer) vaccine in preventing SARS-CoV-2 infection among healthcare workers, Treviso province, Veneto region, Italy, 27 December 2020 to 24 March 2021. Euro Surveill. 2021;26(17).
261. Thomas SJ, Moreira ED, Jr., Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months. N Engl J Med. 2021;385(19):1761-73.
262. Angel Y, Spitzer A, Henig O, Saiag E, Sprecher E, Padova H, et al. Association Between Vaccination With BNT162b2 and Incidence of Symptomatic and Asymptomatic SARS-CoV-2 Infections Among Health Care Workers. JAMA. 2021;325(24):2457-65.
263. Bjork J, Inghammar M, Moghaddassi M, Rasmussen M, Malmqvist U, Kahn F. High level of protection against COVID-19 after two doses of BNT162b2 vaccine in the working age population - first results from a cohort study in Southern Sweden. Infect Dis (Lond). 2022;54(2):128-33.
264. Cabezas C, Coma E, Mora-Fernandez N, Li X, Martinez-Marcos M, Fina F, et al. Associations of BNT162b2 vaccination with SARS-CoV-2 infection and hospital admission and death with covid-19 in nursing homes and healthcare workers in Catalonia: prospective cohort study. BMJ. 2021;374:n1868.
265. Emborg H-D, Valentiner-Branth P, Schelde AB, Nielsen KF, Gram MA, Moustsen-Helms IR, et al. Vaccine effectiveness of the BNT162b2 mRNA COVID-19 vaccine against RT-PCR confirmed SARS-CoV2 infections, hospitalisations and mortality in prioritised risk groups. MedRxiv [Preprint]. 2021.
266. Gras-Valenti P, Chico-Sanchez P, Algado-Selles N, Jimenez-Sepulveda NJ, Gomez-Sotero IL, Fuster-Perez M, et al. [Effectiveness of the first dose of BNT162b2 vaccine to preventing covid-19 in healthcare personnel.]. Rev Esp Salud Publica. 2021;95.
267. Mason TFD, Whitston M, Hodgson J, Watkinson RE, Lau YS, Abdulrazeg O, et al. Effects of BNT162b2 mRNA vaccine on COVID-19 infection and hospitalisation

amongst older people: matched case control study for England. BMC Med. 2021;19(1):275.
268. Monge S, Olmedo C, Alejos B, Lapena MF, Sierra MJ, Limia A, et al. Direct and Indirect Effectiveness of mRNA Vaccination against Severe Acute Respiratory Syndrome Coronavirus 2 in Long-Term Care Facilities, Spain. Emerg Infect Dis. 2021;27(10):2595-603.
269. Pritchard E, Matthews PC, Stoesser N, Eyre DW, Gethings O, Vihta KD, et al. Impact of vaccination on new SARS-CoV-2 infections in the United Kingdom. Nat Med. 2021;27(8):1370-8.
270. Regev-Yochay G, Amit S, Bergwerk M, Lipsitch M, Leshem E, Kahn R, et al. Decreased infectivity following BNT162b2 vaccination: A prospective cohort study in Israel. Lancet Reg Health Eur. 2021;7:100150.
271. Shrotri M, Krutikov M, Palmer T, Giddings R, Azmi B, Subbarao S, et al. Vaccine effectiveness of the first dose of ChAdOx1 nCoV-19 and BNT162b2 against SARS-CoV-2 infection in residents of long-term care facilities in England (VIVALDI): a prospective cohort study. Lancet Infect Dis. 2021;21(11):1529-38.
272. Swift MD, Breeher LE, Tande AJ, Tommaso CP, Hainy CM, Chu H, et al. Effectiveness of Messenger RNA Coronavirus Disease 2019 (COVID-19) Vaccines Against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in a Cohort of Healthcare Personnel. Clin Infect Dis. 2021;73(6):e1376-e9.
273. Thompson MG, Burgess JL, Naleway AL, Tyner H, Yoon SK, Meece J, et al. Prevention and Attenuation of Covid-19 with the BNT162b2 and mRNA-1273 Vaccines. N Engl J Med. 2021;385(4):320-9.
274. Frenck RW, Jr., Klein NP, Kitchin N, Gurtman A, Absalon J, Lockhart S, et al. Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents. N Engl J Med. 2021;385(3):239-50.
275. June Choe Y, Yi S, Hwang I, Kim J, Park YJ, Cho E, et al. Safety and effectiveness of BNT162b2 mRNA Covid-19 vaccine in adolescents. Vaccine. 2021.
276. Lutrick K, Rivers P, Yoo YM, Grant L, Hollister J, Jovel K, et al. Interim Estimate of Vaccine Effectiveness of BNT162b2 (Pfizer-BioNTech) Vaccine in Preventing SARS-CoV-2 Infection Among Adolescents Aged 12-17 Years - Arizona, July-December 2021. MMWR Morb Mortal Wkly Rep. 2021;70(5152):1761-5.
277. Glatman-Freedman A, Bromberg M, Dichtiar R, Hershkovitz Y, Keinan-Boker L. The BNT162b2 vaccine effectiveness against new COVID-19 cases and complications of breakthrough cases: A nation-wide retrospective longitudinal multiple cohort analysis using individualised data. EBioMedicine. 2021;72:103574.
278. Pilishvili T, Fleming-Dutra KE, Farrar JL, Gierke R, Mohr NM, Talan DA, et al. Interim Estimates of Vaccine Effectiveness of Pfizer-BioNTech and Moderna COVID-19 Vaccines Among Health Care Personnel - 33 U.S. Sites, January-March 2021. MMWR Morb Mortal Wkly Rep. 2021;70(20):753-8.
279. Martinez-Baz I, Miqueleiz A, Casado I, Navascues A, Trobajo-Sanmartin C, Burgui C, et al. Effectiveness of COVID-19 vaccines in preventing SARS-CoV-2 infection and hospitalisation, Navarre, Spain, January to April 2021. Euro Surveill. 2021;26(21).
280. Vasileiou E, Simpson CR, Shi T, Kerr S, Agrawal U, Akbari A, et al. Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital

admissions in Scotland: a national prospective cohort study. Lancet. 2021;397(10285):1646-57.
281. ecdc.europa.eu [Internet]. Interim analysis of COVID-19 vaccine effectiveness against Severe Acute Respiratory Infection due to laboratory-confirmed SARS-CoV-2 among individuals aged 50 years and older, ECDC multi-country study – first update. European Centre for Disease Prevention and Control. [20 January 2022; cited 24 January 2022]. Available from: https://www.ecdc.europa.eu/en/publications-data/interim-analysis-covid-19-vaccine-effectiveness-against-severe-acute-respiratory
282. Rosenberg ES, Dorabawila V, Easton D, Bauer UE, Kumar J, Hoen R, et al. Covid-19 Vaccine Effectiveness in New York State. N Engl J Med. 2022;386(2):116-27.
283. Olson SM, Newhams MM, Halasa NB, Price AM, Boom JA, Sahni LC, et al. Effectiveness of BNT162b2 Vaccine against Critical Covid-19 in Adolescents. N Engl J Med. 2022.
284. Zambrano LD, Newhams MM, Olson SM, Halasa NB, Price AM, Boom JA, et al. Effectiveness of BNT162b2 (Pfizer-BioNTech) mRNA Vaccination Against Multisystem Inflammatory Syndrome in Children Among Persons Aged 12-18 Years - United States, July-December 2021. MMWR Morb Mortal Wkly Rep. 2022;71(2):52-8.
285. Emary KRW, Golubchik T, Aley PK, Ariani CV, Angus B, Bibi S, et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B.1.1.7): an exploratory analysis of a randomised controlled trial. Lancet. 2021;397(10282):1351-62.
286. astrazeneca.com [Internet]. AZD1222 US Phase III trial met primary efficacy endpoint in preventing COVID-19 at interim analysis. AstraZeneca. [22 March 2021; cited 15 October 2021]. Available from: https://www.astrazeneca.com/media-centre/press-releases/2021/astrazeneca-us-vaccine-trial-met-primary-endpoint.html
287. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet. 2021;397(10269):99-111.
288. Madhi SA, Baillie V, Cutland CL, Voysey M, Koen AL, Fairlie L, et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant. N Engl J Med. 2021;384(20):1885-98.
289. Pramod S, Govindan D, Ramasubramani P, Kar SS, Aggarwal R, Manoharan N, et al. Effectiveness of Covishield vaccine in preventing Covid-19 – A test-negative case control study. MedRxiv [Preprint]. 2021.
290. Falsey AR, Sobieszczyk ME, Hirsch I, Sproule S, Robb ML, Corey L, et al. Phase 3 Safety and Efficacy of AZD1222 (ChAdOx1 nCoV-19) Covid-19 Vaccine. N Engl J Med. 2021;385(25):2348-60.
291. Clemens SAC, Folegatti PM, Emary KRW, Weckx LY, Ratcliff J, Bibi S, et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 lineages circulating in Brazil. Nat Commun. 2021;12(1):5861.
292. Voysey M, Costa Clemens SA, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Single-dose administration and the influence of the timing of the booster dose on

immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. Lancet. 2021;397(10277):881-91.
293. Bhattacharya A, Ranjan P, Ghosh T, Agarwal H, Seth S, Maher GT, et al. Evaluation of the dose-effect association between the number of doses and duration since the last dose of COVID-19 vaccine, and its efficacy in preventing the disease and reducing disease severity: A single centre, cross-sectional analytical study from India. Diabetes Metab Syndr. 2021;15(5):102238.
294. Malathi Murugesan, Prasad Mathews, Hema Paul, Rajiv Karthik, Joy John Mammen, Rupali. P. Protective Effect Conferred by Prior Infection and Vaccination on COVID-19 in a Healthcare Worker Cohort in South India. SSRN [Preprint]. 2021.
295. Alencar CH, Cavalcanti LPG, Almeida MM, Barbosa PPL, Cavalcante KKS, Melo DN, et al. High Effectiveness of SARS-CoV-2 Vaccines in Reducing COVID-19-Related Deaths in over 75-Year-Olds, Ceara State, Brazil. Trop Med Infect Dis. 2021;6(3).
296. Cerqueira-Silva T, Oliveira VdA, Pescarini J, Bertoldo Júnior J, Machado TM, Flores-Ortiz R, et al. The effectiveness of Vaxzevria and CoronaVac vaccines: A nationwide longitudinal retrospective study of 61 million Brazilians (VigiVac-COVID19). . MedRxiv [Preprint]. 2021.
297. Otavio T Ranzani, Rogério dos Santos Leite, Larissa Domingues Castilho, Crhistinne Cavalheiro Maymone Gonçalves, Geraldo Resende, Rosana Leite de Melo, et al. Vaccine effectiveness of Ad26.COV2.S against symptomatic COVID-19 and clinical outcomes in Brazil: a test-negative study design. MedRxiv [Preprint]. 2021.
298. Corchado-Garcia J, Puyraimond-Zemmour D, Hughes T, Cristea-Platon T, Lenehan P, Pawlowski C, et al. Real-world effectiveness of Ad26.COV2.S adenoviral vector vaccine for COVID-19. MedRxiv [Preprint]. 2021.
299. Barlow RS, Jian K, Larson L. Effectiveness of COVID-19 Vaccines Against SARS-CoV-2 Infection During a Delta Variant Epidemic Surge in Multnomah County, Oregon, July 2021. MedRxiv [Preprint]. 2021.
300. Polinski JM, Weckstein AR, Batech M, Kabelac C, Kamath T, Harvey R, et al. Effectiveness of the Single-Dose Ad26.COV2.S COVID Vaccine. MedRxiv [Preprint]. 2021.
301. Corchado-Garcia J, Zemmour D, Hughes T, Bandi H, Cristea-Platon T, Lenehan P, et al. Analysis of the Effectiveness of the Ad26.COV2.S Adenoviral Vector Vaccine for Preventing COVID-19. JAMA Netw Open. 2021;4(11):e2132540.
302. Chin ET, Leidner D, Zhang Y, Long E, Prince L, Li Y, et al. Effectiveness of the mRNA-1273 Vaccine during a SARS-CoV-2 Delta Outbreak in a Prison. N Engl J Med. 2021;385(24):2300-1.
303. Gupta K, O'Brien WJ, Bellino P, Linsenmeyer K, Doshi SJ, Sprague RS, et al. Incidence of SARS-CoV-2 Infection in Health Care Workers After a Single Dose of mRNA-1273 Vaccine. JAMA Netw Open. 2021;4(6):e2116416.
304. Chemaitelly H, Yassine HM, Benslimane FM, Al Khatib HA, Tang P, Hasan MR, et al. mRNA-1273 COVID-19 vaccine effectiveness against the B.1.1.7 and B.1.351 variants and severe COVID-19 disease in Qatar. Nat Med. 2021;27(9):1614-21.

305. Herlihy R, Bamberg W, Burakoff A, Alden N, Severson R, Bush E, et al. Rapid Increase in Circulation of the SARS-CoV-2 B.1.617.2 (Delta) Variant - Mesa County, Colorado, April-June 2021. MMWR Morb Mortal Wkly Rep. 2021;70(32):1084-7.
306. Bruxvoort KJ, Sy LS, Qian L, Ackerson BK, Luo Y, Lee GS, et al. Real-world effectiveness of the mRNA-1273 vaccine against COVID-19: Interim results from a prospective observational cohort study. Lancet Reg Health Am. 2021:100134.
307. Bruxvoort KJ, Sy LS, Qian L, Ackerson BK, Luo Y, Lee GS, et al. Effectiveness of mRNA-1273 against delta, mu, and other emerging variants of SARS-CoV-2: test negative case-control study. BMJ. 2021;375:e068848.
308. El Sahly HM, Baden LR, Essink B, Doblecki-Lewis S, Martin JM, Anderson EJ, et al. Efficacy of the mRNA-1273 SARS-CoV-2 Vaccine at Completion of Blinded Phase. N Engl J Med. 2021;385(19):1774-85.
309. Li XN, Huang Y, Wang W, Jing QL, Zhang CH, Qin PZ, et al. Effectiveness of inactivated SARS-CoV-2 vaccines against the Delta variant infection in Guangzhou: a test-negative case-control real-world study. Emerg Microbes Infect. 2021;10(1):1751-9.
310. Min Kang, Yao Yi, Yan Li, Limei Sun, Aiping Deng, Ting Hu, et al. Effectiveness of Inactivated COVID-19 Vaccines Against COVID-19 Pneumonia and Severe Illness Caused by the B.1.617.2 (Delta) Variant: Evidence from an Outbreak in Guangdong, China. SSRN [Preprint]. 2021.
311. Silva-Valencia Javier, Soto-Becerra Percy, Escobar-Agreda Stefan, Fernández-Navarro Manuel, Moscoso-Porras Miguel, Solari Lely, et al. Effectiveness of the BBIPB-CorV Vaccine in Preventing Infection and Death in Health Care Workers in Peru 2021. SSRN [Preprint]. 2021.
312. Al Kaabi N, Zhang Y, Xia S, Yang Y, Al Qahtani MM, Abdulrazzaq N, et al. Effect of 2 Inactivated SARS-CoV-2 Vaccines on Symptomatic COVID-19 Infection in Adults: A Randomized Clinical Trial. JAMA. 2021;326(1):35-45.
313. Farida Ismail AlHosani, Anderson Eduardo Stanciole, Bashir Aden, Andrey Timoshkin, Omar Najim, Walid Abbas Zaher, et al. Sinopharm's BBIBP-CorV vaccine effectiveness on preventing hospital admission and deaths: results from a retrospective study in the Emirate of Abu Dhabi, United Arab Emirates (UAE). SSRN [Preprint]. 2021.
314. AlQahtani M, Bhattacharyya S, Alawadi A, Mahmeed HA, Sayed JA, Justman J, et al. Morbidity and mortality from COVID-19 postvaccination breakthrough infections in association with vaccines and the emergence of variants in Bahrain. Research Square [Preprint]. 2021.
315. Jara A, Undurraga EA, Gonzalez C, Paredes F, Fontecilla T, Jara G, et al. Effectiveness of an Inactivated SARS-CoV-2 Vaccine in Chile. N Engl J Med. 2021;385(10):875-84.
316. Ranzani OT, Hitchings MDT, Dorion M, D'Agostini TL, de Paula RC, de Paula OFP, et al. Effectiveness of the CoronaVac vaccine in older adults during a gamma variant associated epidemic of covid-19 in Brazil: test negative case-control study. BMJ. 2021;374:n2015.
317. Hitchings MDT, Ranzani OT, Torres MSS, de Oliveira SB, Almiron M, Said R, et al. Effectiveness of CoronaVac among healthcare workers in the setting of high

SARS-CoV-2 Gamma variant transmission in Manaus, Brazil: A test-negative case-control study. Lancet Reg Health Am. 2021;1:100025.

318. Enny S. Paixao, Kerry LM Wong, Flavia Jôse Oliveira Alves, Vinicius de Araújo Oliveira, Thiago Cerqueira-Silva, Juracy Bertoldo Júnior, et al. Effectiveness of the CoronaVac vaccine in prevention of symptomatic and progression to severe Covid-19 in pregnant women in Brazil. SSRN [Preprint]. 2021.

319. Hitchings MDT, Ranzani OT, Scaramuzzini Torres MS, de Oliveira SB, Almiron M, Said R, et al. Effectiveness of CoronaVac in the setting of high SARS-CoV-2 P.1 variant transmission in Brazil: A test-negative case-control study. MedRxiv [Preprint]. 2021.

320. Tanriover MD, Doganay HL, Akova M, Guner HR, Azap A, Akhan S, et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. Lancet. 2021;398(10296):213-22.

321. Palacios R, Batista AP, Albuquerque CSN, Patiño EG, Santos JdP, Tilli Reis Pessoa Conde M, et al. Efficacy and Safety of a COVID-19 Inactivated Vaccine in Healthcare Professionals in Brazil: The PROFISCOV Study. SSRN [Preprint]. 2021.

322. Ella R, Reddy S, Blackwelder W, Potdar V, Yadav P, Sarangi V, et al. Efficacy, safety, and lot-to-lot immunogenicity of an inactivated SARS-CoV-2 vaccine (BBV152): interim results of a randomised, double-blind, controlled, phase 3 trial. Lancet. 2021;398(10317):2173-84.

323. Desai D, Khan AR, Soneja M, Mittal A, Naik S, Kodan P, et al. Effectiveness of an inactivated virus-based SARS-CoV-2 vaccine, BBV152, in India: a test-negative, case-control study. Lancet Infect Dis. 2021.

324. Malhotra S, Mani K, Lodha R, Bakhshi S, Mathur VP, Gupta P, et al. SARS-CoV-2 Reinfection Rate and Estimated Effectiveness of the Inactivated Whole Virion Vaccine BBV152 Against Reinfection Among Health Care Workers in New Delhi, India. JAMA Netw Open. 2022;5(1):e2142210.

325. Heath PT, Galiza EP, Baxter DN, Boffito M, Browne D, Burns F, et al. Safety and Efficacy of NVX-CoV2373 Covid-19 Vaccine. N Engl J Med. 2021;385(13):1172-83.

326. Dunkle LM, Kotloff KL, Gay CL, Anez G, Adelglass JM, Barrat Hernandez AQ, et al. Efficacy and Safety of NVX-CoV2373 in Adults in the United States and Mexico. N Engl J Med. 2021.

327. Toback S, Galiza E, Cosgrove C, Galloway J, Goodman AL, Swift PA, et al. Safety, immunogenicity, and efficacy of a COVID-19 vaccine (NVX-CoV2373) co-administered with seasonal influenza vaccines: an exploratory substudy of a randomised, observer-blinded, placebo-controlled, phase 3 trial. Lancet Respir Med. 2021.

328. Shinde V, Bhikha S, Hoosain Z, Archary M, Bhorat Q, Fairlie L, et al. Efficacy of NVX-CoV2373 Covid-19 Vaccine against the B.1.351 Variant. N Engl J Med. 2021;384(20):1899-909.

Response to Reviewers - COVID-19: Virology, variants, and vaccines

We would like to thank the editor and reviewers for their insightful and useful comments on our review. We have addressed the comments within the article and outlined the changes we have made below. We believe these alterations and changes have significantly improved the review as a result. The reviewer's comments are preceded by "**Comment**" and our response is preceded by "**Response**". Where possible, we have included the in-text amendments after each response in italics. Any changes or additions to the text are also highlighted in the manuscript.

Editors' comments:

Comment

1. Please provide a **document labelled 'response to reviewers'** which gives a point-by-point response to both the referees comments and those of the editors.

Response

Thank you. This document provides a point-by-point response of both the editors and reviewers comments.

Comment

2. Abstract: as the review is not a systematic review and therefore not classed as original Research, please remove the structured headings. The abstract should just summarise what the review is about in 2-300 words (ie the same as your BMJ review).

Response

Thank you for the suggestion. We have updated the abstract and removed the structed headings. It now reads as following:

*"**Abstract***

As of 25th January 2022, there have been over 349 million confirmed cases of COVID-19, with over 5.59 million confirmed deaths associated with the SARS-CoV-2 virus. The COVID-19 pandemic has prompted an extensive, global effort to study the molecular evolution of the virus and develop vaccines to combat its spread. Although rigorous determination of SARS-CoV-2 infectivity remains elusive, due to the continuous evolution of the virus, steps have been made to understand its genome, structure, and emerging genetic mutations. The SARS-CoV-2 genome is composed of a number of open reading frames (ORFs) and structural proteins, including the spike protein, which is essential for entry into host cells. As of the 25th January 2022, the WHO reports five variants of concern (VOC) two variants of interest (VOI) and three variants under monitoring (VUM). The mutations harboured in these variants confer an increased transmissibility, severity of disease, and escape from neutralising antibodies compared to the primary strain. The current vaccine strategy, including booster doses, provides protection from severe disease. As of 24th January 2022, there are 33 approved vaccines in use in 197 countries. In this review, we discuss the genetics, structure and transmission methods of SARS-CoV-2 and its variants, highlighting how mutations provide enhanced abilities to spread and inflict disease. We also outline the vaccines currently in use around the world, providing evidence for the immunogenicity and effectiveness of each."

Comment

3. Methods: please include the dates you searched from and to. Due to the additions requested below the end search date will be more current. Please provide more detail about the exclusion criteria (study design etc).

Response

We have updated the dates we searched to and from.
Due to the restrictions on the word count, we have provided some more information on selection criteria within the methods section, however, we have also provided a supplementary file describing the specific search terms and the inclusion/exclusion criteria that we used.

The methods section now reads as:

"We searched PubMed and Embase databases for COVID-19-related articles published between 1st January 2020 and 25th January 2022 and for general coronavirus-related articles published from 1st January 2000 onwards. Our search terms included SARS-CoV-2, COVID-19, and specific terms including virology, genome, variants, and vaccine. Additional, specific search terms are outlined in supplementary file 1. We performed further manual searching for additional articles and data using relevant databases, including who.int, gov.uk, and ecdc.europa.eu/en. Due to the rapidly evolving nature of the literature involving SARS-CoV-2, we also searched preprint databases including MedRxiv and BioRxiv. Due to the various topics addressed here, studies were selected through different criteria, details of which can be found in supplementary file 1. Overall, studies were selected based on quality and journal reputation, with real-world studies with large sample sizes of greatest interest."

Comment

4. **OMICRON**: Please can you include in relevant sections throughout the review what is known about the new OMICRON variant, and any other variants of interest.

Response

We have included a section dedicated to the Omicron variant in the variants of concern section, while relevant omicron studies have been included and discussed elsewhere, e.g. in the waning immunity and boosters section.

This section now reads as:

"5.1.5 Omicron

The Omicron variant is of the B.1.1.529 lineage and was first discovered in November 2021 in South Africa and Botswana before being detected in multiple countries and classified as a VOC on 26th November 2021(3). This variant contains over 30 S protein mutations(100), 23 of which have been previously identified, including K417N, T478K, E484A, D614G, H655Y, P681H, and N501Y(131). 15 Omicron mutations are contained within the RBD(17) providing the variant with a significantly enhanced binding affinity to the ACE2 receptor(131, 132). In addition, various single mutations harboured with the RBD of the Omicron variant impair the effectiveness of neutralising antibodies, including K417N, N440K, G446S, E484A, Q493K, G496S, G339D, S371L, and S375F(17).

The emergence of Omicron has been followed by a tidal wave of infections worldwide. Early data from South Africa demonstrated that the proportion of COVID-19 cases caused by the Omicron variant rose from 3% in early October, to 98% by early December(133). In late December 2021, meanwhile, the doubling time for number of positive Omicron cases was between two and three in the UK, US, and much of Europe(134, 135), highlighting the transmissibility of this variant. The mutations harboured by Omicron that enhance its binding affinity(131, 132) and ability to escape neutralising antibodies(17) likely drove its rapid spread, as did its fast replication rate, which is around 70 times faster than the Delta and wild-type strains(136). The reinfection rate of Omicron has also been found to be significantly higher than that of previous variants in studies from Scotland(137) and South Africa(138).

The Omicron variant has extensive but incomplete escape from naturally acquired and vaccine-induced immunity(139, 140). Compared to the Delta variant, Omicron requires around a ten-fold

increased antibody titre to be neutralised, following vaccination with either Oxford-AstraZeneca or Pfizer/BioNtech vaccines(141). Indeed, blood sera from individuals who had received two doses of the Pfizer/BioNtech vaccine exhibited more than a 25-fold reduction in neutralising antibody titres against the Omicron variant compared to the wild-type strain(142). T-cell responses to Omicron may remain intact, however. One preprint study demonstrated that 70-80% of the T-cell response targeting the S protein was maintained in those vaccinated or with prior infection, while the magnitude of Omicron cross-reactive T-cells was similar to that of both Delta and Beta variants(143). Furthermore, data from Pfizer/BioNtech revealed that 80% of the epitopes in the Omicron variant S protein that are recognised by CD8+ T-cells were not affected by this variant's mutations, following two-doses of the vaccine(142). T-cell responses induced from vaccine administration or prior infection may, therefore, provide some protection from severe disease.

Recent real-world evidence has implied that Omicron infection is milder in severity than previous variants. In an early South African analysis, the risk of hospitalisation (aOR=0.2) was lower for Omicron infections compared to non-Omicron SARS-CoV-2 infections(133) while, compared to earlier infections associated with the Delta variant, Omicron-infected individuals had a lower risk of severe disease (aOR=0.3)(133). In December 2021 in England, Omicron cases were found to induce a significantly reduced risk of hospitalisation or presentation for emergency care in comparison to Delta cases(144, 145). The decreased disease severity inflicted by Omicron may be due to its reduced capacity for replication in lung tissue, which was found to be more than ten times less in lung tissue compared to Delta(136). Concordantly, the S protein of the Omicron variant is less efficient at cleaving the ACE2 receptor and entering cells of lung organoids(141), while is also less able to cause fusion between lung cells compared to Delta(141), which is often observed in cases of severe COVID-19. The reduction in replication within the lungs, and the preservation of T-cell responses likely contribute to the milder disease exerted by the Omicron variant.

Although the Omicron variant appears to manifest in mild disease, high case numbers may still result in a large number of hospitalisations and deaths in those vulnerable to the virus. Omicron case numbers may be beginning to peak, however. In South Africa, a 29.7% decrease in weekly COVID-19 cases were reported in the week ending 25th December 2021, compared to the previous week, and the Omicron wave is said to have passed(146). Concerningly, global case numbers continue to rise rapidly(147) and many countries will continue to feel the pressure exerted by the wave of Omicron infections."

Comment

5. Vaccination/Waning immunity sections: please update these sections to include any new data on efficacy, and the recent data on the efficacy of the different booster jabs.

Response

We have updated these sections with new data. Table 2 has also been updated to include new data on vaccine effectiveness.

The waning immunity and boosters section now reads as:
"6.11 Waning immunity and boosters
Throughout the COVID-19 pandemic, emerging variants have threatened the effectiveness of vaccines (table 2). Simultaneously, waning immunity following vaccination questions how long vaccines remain effective, and highlights the importance of booster doses. Indeed, protection against SARS-CoV-2 following vaccination decreases over time, both in terms of antibody titres(188-190) and vaccine effectiveness(191-194). Cellular responses, such as T-cell immunity, may persist for longer periods, however(195, 196). With a gradual loss of protection from SARS-CoV-2 following COVID-19 vaccination, many countries are now rolling out booster programmes with the aim of raising levels of immunity.

Since booster programmes began, evidence that a booster vaccine dose enhances antibody and cellular responses has accumulated. Following a third dose of vaccine, neutralising antibody titres increase significantly(197-200) and, in some cases, to higher levels than after the primary two doses(197). Additionally, boosters have also been found to increase neutralising antibody titres against Beta, Gamma, Delta, and Omicron variants(198, 201, 202). T-cell response is also enhanced following a third dose(199, 203, 204). Together, enhancing neutralising antibody and cellular responses with a booster vaccine dose is likely to provide a greater level of protection than relying on immunity built through a primary regimen.

The antibody and cellular responses observed following booster vaccinations have been found to correlate with increased levels of protection against SAR-CoV-2 infetion and severe illness. On 30th July 2021, Israel was the first country to offer a third dose of BNT162b2 to certain groups. Subsequently, several studies have revealed that those who received a third vaccine dose were significantly less likely to be infected or have severe disease with SARS-CoV-2 compared to those who received two-doses(205-208). In those aged 60 or older, an observational study demonstrated that the rate of severe COVID-19 and death was lower in the boosted group by a factor of 17.9 and 14.7, respectively, compared to the non-boosted group(209). Booster doses of COVID-19 vaccine have been shown to be effective against infection with Delta(210, 211) and, to a lesser degree, Omicron variants(141, 142, 145, 211-213) despite the numerous mutations harboured by these variants. Overall, increasing evidence is pointing towards the benefits of booster doses of COVID-19 vaccines, therefore it is expected that booster programmes will continue to roll out across the globe. Based on current evidence, the CDC recommend that the time interval for receiving a booster following the primary regiment is five months for Pfizer/BioNTech BNT162b2 primary regimen, six months for Moderna mRNA-1273 primary regimen, and two months for Johnson & Johnson Ad26.COV2.S primary regimen(214). As the pandemic progresses and new variants emerge, variant-specific vaccines may require development, with pre-clinical studies demonstrating their efficacy(215) and pharmaceutical companies, such as Pfizer, advancing in variant-specific vaccine development(142). Policy makers should also consider when vaccine boosters will be given in the future and who will receive booster doses in the long-term."

Comment

6. Tables: please update the tables to include any new data.

Response

Thank you, the following sentences outline the updates that have been made to each table.

Table 1 has been updated to include the current VOC/VUI/VUM, as listed by WHO.

Table 2 has been updated to include new data on vaccine effectiveness.

Table 3 has been updated to include current vaccines that are approved in at least 1 county, that are not discussed in the main manuscript text.

Comment

7. Please include a section on **EMERGING TREATMENTS**: Please include a brief section on new techniques and advances that are currently being studied, cite the appropriate studies, and say when they will report.

Response

Thank you, we have now included this section with some discussion of recently approved drugs and those in development:

"7. Emerging Treatments

As more is learnt about the virus, the therapeutic strategy against COVID-19 devlops. There are currently over two thousand ongoing trials assessing certain treatment strategies for COVID-19(216). Recently, antivirals including molnupiravir (Lagevrio) and nirmatrelvir/ritonavir (Paxlovid) have been approved in the UK(217, 218), US(219, 220), and Europe(221, 222) for treating COVID-19 in certain risk groups. Similarly, sotrovimab (Xevudy), a monoclonal antibody treatment, has recently been approved for use in treating certain COVID-19 patients in the UK(223), US(224), and Europe(225). These drugs have been shown to be effective at preventing poor clinical outcomes, including death, in those vulnerable to severe COVID-19 infection. Other drug treatments, such as janus kinase inhibitors, corticosteroids, and anti-inflammatories have contrasting evidence to support their use, and therefore, the use of specific drugs is either recommended for or against by certain treatment and management guidelines, which are discussed below."

Comment

8. **GUIDELINES**: Please cite any relevant international guidelines and say how they differ, what their strengths and weaknesses are, and under what circumstances they are most appropriate. Please give preference to the most independent and recently updated guidelines.

Response

Thank you, we have now included this section to outline which treatment guidelines are available for COVID-19.

"8. Guidelines

The treatment and management of COVID-19 is a continually evolving topic, however, health authorities have published and continue to update guidelines and recommendations for treating COVID-19. The WHO living guildeline on COVID-19 and therapeutics is regularly updated, with the latest version, published on 14th January 2022 containing 14 recommendations on COVID-19 treatment(226). In the UK, the National Institute for Health and Care Excellence (NICE)(227) and Medicines and Healthcare products Regulatory Agency (MHRA)(228) provide updated guidelines on COVID-19 treatment, while in Europe, the ECDC regularly publishes several guidelines providing recommendations on a range of COVID-19 related topics(229). In the US, the National Institutes of Health (NIH)(230) and the CDC(231) provide guidance on COVID-19 treatment and management, with the CDC supplying guidelines for specific groups including, employers, schools, health departments, and governments."

Reviewer: 1

Comment

1. In the section "3. Viral transmission, clinical presentation, and genetic susceptibility of COVID-19", there could be a further briefing of the spectrum of the characteristic symptoms (clinical characteristics). It would also benefit by mentioning that the whole of the population would be susceptible to COVID-19 although there exist some subgroups more susceptible to develop poorer clinical outcomes.

Response

Thank you, we have added to this section to mention the broad spectrum of COVID-19 symptoms and have mentioned that although everyone is susceptible to covid-19, some groups are more susceptible to poorer outcomes:

"The clinical presentation of COVID-19 is non-specific, heterogeneous, and infection can result in a wide spectrum of symptoms. Following an incubation period of 4-14 days, symptoms develop ranging

from mild to severe disease and, in some cases, can result in death(12). The most common COVID-19 symptoms include fever, cough, dyspnoea, and fatigue(13, 14), while myalgia, gastrointestinal issues, cognitive deficits, and other symptoms are reported. Asymptomatic individuals can also test positive for COVID-19(15, 16). Although the entire population is susceptible to COVID-19 infection, some subgroups within the general population exist that are more susceptible to developing poorer clinical outcomes."

Comment

2. Also within the same section, the description for the gene loci associated with the risk of severe disease could be streamlined a bit since the contents did not seem to be aligned well in the current form. There could also be the introduction regarding the polygenetic risk score and the comorbidities (e.g., COPD) for predicting the susceptibility to COVID-19.

Response

Thank you for this comment. This section has been shortened in order to keep the focus firmly on the main topics of the article. We have also included a short introduction of polygenetic risk scores and how they may be used along with comorbidities to infer risk of COVID-19:

"The utilisation of polygenetic risk scores (PRS) may be useful in determining an individual's risk for developing severe disease caused by COVID-19(35). A PRS infers a person's risk of susceptibility to or development of a certain disease based on the total number of genomic variations they possess. Determining PRS with the inclusion of comorbidities, such as chronic obstructive pulmonary disease(36), or other aspects, such as coagulation factors(37), may improve the usefulness of PRS in determining a person's risk of severe COVID-19."

Comment

3. In the section "4. Virology of SARS-CoV-2", it would be better to summarize the duration that the SARS-CoV-2 could survive in the environment (e.g., metal surface, etc.).

Response

Towards the end of section "4. Virology of SARS-CoV-2", which now provides a useful description of how long the virus can survive in the environment, which is a contributing factor to its transmission:

"The SARS-CoV-2 virus may survive on surfaces or suspended in air droplets for varying periods of time. Indeed, on plastic, stainless steel, and glass surfaces, the half-life of the virus is around 5.3, 4.4, and 4.2 hours, respectively(7), with no difference seen between SARS-CoV-2 variants(8). Although SARS-CoV-2 can be detected on inanimate surfaces for hours and days, due to the evaporation of water droplets, the viruses' living environment, the concentration of the virus plummets rapidly(9). Protective measures, including using personal protective equipment (PPE), maintaining indoor ventilation, and disinfecting hands and surfaces, can effectively limit the spread of SARS-CoV-2(10)."

Comment

4. Perhaps it would merit if the conformational changes of the S protein that occur after binding with the host cell be described.

Response

Thank you. To address this comment, we have added a short description of the S protein structure and the conformational changes that occur:

"The subunits of the trimeric S complex are either in a closed (pre-fusion stage) or open (post-fusion stage) conformation(62), with one subunit always in an open conformation to allow for ACE2 recognition and binding(63). The RBD itself consists of five anti-parallel β-strands surrounded by several α-helices(64). From closed to open conformation, the RBD undergoes structural rearrangement whereby the globular head region rotates clockwise, which alters is elecropotential surface(64). Once positioned, numerous residues within the RBD form either hydrogen bonds or salt bridges with residues of the ACE2 receptor, allowing for tight binding(65), while the concave structure of the RBD allows for three distinct binding regions(64)."

Comment

5. Not sure why there should be the section "4.1 Other human coronaviruses" which seemed less relevant to the topic.

Response

Thank you, we agree that this section was less relevant and did not add much to the overall manuscript, therefore, this section has been removed.

Comment

6. In the section "5. Variants of SARS-CoV-2" perhaps it would not be necessary to address the abbreviations for VOI and VUM again since this has already been introduced well before.

Response

Thank you, we agree with this comment. As VOC/VOI/VUM have been defined previously in the introduction, it is not needed here. This repetition of definitions has been removed from section 5.

Comment

7. I am afraid that the authors should contemplate on what the focus of the VOC should be. Basic science or clinical themes? Most of the current efforts seemed to focus on the former rather than the latter. However, the impact of the variants on the subsequent waves of outbreaks globally would seem more important to the epidemiologist and clinicians. This is perhaps most relevant to the Delta strain.

Response

This is an important point and we have included the following section to stress the importance of the clinical themes, in addition to the basic science in regard to VOCs:
"The current method of identifying variants relies on the use of genomic testing such as whole genome sequencing, partial S-gene sequencing, or nucleic acid amplification technique (NAAT)-based assays(72). The aspects of different variants that most people experience, however, is the clinical symptoms they inflict. Certain variants induce a greater risk of severe disease and death, such as Alpha and Delta(73), while others are more likely to induce milder symptoms, such as Omicron(74, 75). Moreover, individual symptoms can differ between variants. For example, the Gamma variant is associated inflicting anosmia and dysgeusia(76), which is less commonly seen in Omicron infections. Moving forward, the clinical themes and symptoms associated with emerging variants should be elucidated rapidly in order for the public and healthcare professionals to rapidly identify possible cases of COVID-19."

Comment

8. The section "6. Vaccinations" seemed to be a pile-up of the evidence without a clear focus. I am afraid that not all identical weight should be given to the different vaccines. Moreover, the most

well-proven efficacy, safety, reactogenicity and adverse events should be summarized in a clearer way.

Response

We agree that this section had little focus and certain vaccines should have greater weight than others. We have attempted to address this by giving the major vaccines the majority of the weight and giving each vaccine section a clear structure: i) what the vaccine is ii) immunogenicity iii) reactogenicity iv) safety/adverse events v) mention that effectiveness can be seen in table 2. To save on words, effectiveness has not been fully outlined in the text, instead table 2 outlines studies that give estimations of effectiveness for each vaccine.
This section now reads as:

"6. Vaccinations
The COVID-19 pandemic prompted a rapid international search for safe and effective vaccines against the SARS-CoV-2 virus. In line with previous vaccine development, including for both SARS-CoV and MERS-CoV, the S protein was a key target for COVID-19 vaccine development(154). As of 24th January 2022, 33 approved vaccines are in use in 197 countries, with ten vaccines having gained emergency use listing approval from the WHO(4), (table 2). As of 25th January 2022 there are 194 vaccines in pre-clinical development and 140 in clinical development(155). Numerous studies have explored the effectiveness of approved vaccines, however, large variations in vaccine effectiveness are reported. This variability is likely due to several factors in the studies including, the country, date, and population size of the study, as well as the SARS-CoV-2 variants circulating during the study period. These factors, along with how the effectiveness is reported, mean that it is difficult to compare vaccines and fully understand how effective each vaccine is. Here, we review the COVID-19 vaccines in use around the world.

6.1 Pfizer/BioNtech - BNT162b2

The BNT162b2 vaccine (Comirnaty) is a lipid nanoparticle-formulated, nucleoside-modified mRNA vaccine encoding a modified SARS-CoV-2 S protein which was developed through a collaborative effort between Pfizer (New York, US) and BioNTech (Mainz, Germany)(156, 157). BNT162b2 gained WHO emergency use listing on 31st December 2020(158) and, as of 24th January 2022, has been approved for use in 136 countries(4). Following administration of BNT162b2, a Th1-biased response is observed, with tumour necrosis factor alpha (TNFα), interferon gamma (IFNγ), and interleukin-2 (IL-2) all elevated following vaccination, compared to placebo(159, 160). Highest neutralisation titres are found between seven and fourteen days following the second dose(161), while those previously infected with COVID-19 showed a four-fold increase in antibody binding and a 18-fold increase in neutralisation titres compared to previously uninfected individuals following two-doses(162). The BNT162b vaccine is well tolerated, with limited reactogenicity. Redness and swelling at injection site have been reported, however mild or moderate pain at the injection site is the most commonly reported reaction to vaccination(161). Fatigue, muscle pain, headache and chills are other commonly reported symptoms following BNT162b2 administration(163). The rate of systemic reactions after a second dose of BNT162b has been found to be 1.7 to 2 times higher than after a first dose, possibly suggesting an immunity-boosting effect(164). Many safety reports of this vaccine describe no serious adverse events(161, 164, 165), however, a large study found that BNT162b2 was associated with an increased risk of myocarditis, lymphadenopathy, appendicitis, and herpes zoster

infection(166). Although rare, allergic reaction or anaphylaxis has also been reported following administration of the BNT162b2 vaccine(163). Table 2 outlines clinical trial and real-world data for vaccine effectiveness.

6.2 Oxford-AtraZeneca – AZD1222

The AZD1222 vaccine (Vaxzevria) is a non-replicating vector of the chimpanzee adenovirus ChAdOx1, modified to encode the SARS-CoV-2 S protein(167). Developed through collaboration between the University of Oxford and AstraZeneca (Cambridge, UK), this vaccine was given WHO emergency use listing on 16th February 2021(158) and has been approved for use in 137 countries, as of 24th January 2022(4). The WHO has granted emergency use listing to two versions of this vaccine (AZD1222 and Covishield) in order to utilise Covishield as part of their worldwide COVAX initiate, which is being produced by the Serum Institute of India and AstraZeneca-SKBio (Republic of Korea)(168).

Following administration of AZD1222, significant antibody production, predominantly of IgG1 and IgG3 subclasses, and a Th-1 cell response, with increased expression of IFNγ and TNFα, is seen(122, 169). One dose of AZD1222 has been shown to produce a neutralising antibody response in 91% of participants, while a second dose resulted in 100% of participants producing neutralising antibodies(170). Mild and moderate itch, pain, redness, swelling, tenderness, and warmth are common local reactions, while chills, fatigue, fever, headache, muscle ache, and nausea are commonly reported systemic reactions following AZD1222 administration(170). Rare symptoms, including severe chest pain, nasal bleeding, and allergic reaction have been reported following AZD1222 administration(171). Table 2 outlines clinical trial and real-world data for vaccine effectiveness.

6.3 Johnson & Johnson - Ad26.COV.2.S

The Ad26.COV.2.S vaccine is a non-replicating adenovirus vector, modified to contain the SARS-CoV-2 S protein in a prefusion-stabilised conformation and requires a single dose(172). This vector was developed from the recombinant human adenovirus type 26 by the Janssen pharmaceutical company of Johnson & Johnson (New Brunswick, New Jersey, US)(172) and was listed for WHO emergency use listing on 12th March 2021(158). As of 24th January 2022, Ad26.COV.2.S has been approved for use in 106 countries(4).

The Ad26.COV.2.S vaccine induces the production of a variety of antibody subclasses, such as IgG, IgM and IgA, and promotes several non-neutralising antibody responses, including activation of CD4+ and CD8+ Th1-cells and production if IFNγ, IL-2, and TNFα(173, 174). Although neutralising antibody responses induced by Ad26.COV2.S are reduced against SARS-CoV-2 variants, non-neutralising antibody and T-cell responses have been found to be preserved against VOC(173), while a prior COVID-19 infection significantly increases levels of S protein-binding antibodies, antibody-dependent cellular cytotoxicity, and neutralising antibodies against VOCs including Beta and Delta(175). Ad26.COV.2.S is safe and well tolerated, with a large clinical trial demonstrating that headache, fatigue, and myalgia, are the most common systemic reactions, while injection-site pain is the most common local reaction following administration(172). Like other vaccines, Ad26.COV.2.S has veen associated with serious adverse events, such as allergic reactions and cerebral venous sinus thrombosis, however, these are rare(163, 176). Table 2 outlines clinical trial and real-world data for vaccine effectiveness.

6.4 Moderna – mRNA-1273

The mRNA-1273 vaccine (Spikevax) developed by Moderna (Massachusetts, US) is a lipid-nanoparticle-encapsulated mRNA vaccine expressing the SARS-CoV-2 S protein that has been prefusion-stabilised(177). This vaccine gained WHO emergency use listing on 30th April 2021(158), and as of 24th January 2022, has been approved for use in 85 countries(4).

The mRNA-1273 vaccine elicits a strong CD4+ Th-1 cell response, with TNFα, IFNγ, and IL-2 expression increased following administration(178-180), while neutralising antibody titres have been shown to significantly increase up until around 28 days following the second dose of the vaccine, and afterwards remain consistently high(181). Fatigue, muscle pain, headache, chills, joint pain, and injection-site pain/reaction are common adverse effects caused by the mRNA-1273 vaccine(163, 177), while serious adverse effects are often avoided(177, 181). Serious adverse events, including allergic reaction and anaphylaxis are rare, but not inconceivable following mRNA-1273 administration(163). Table 2 outlines clinical trial and real-world data for vaccine effectiveness.

6.5 Other WHO emergency use listed COVID-19 vaccines

In addition to the five COVID-19 vaccines described previously, five other vaccines have gained emergency use listing by the WHO. First, the Sinopharm BBIBP-CorV COVID-19 vaccine (Covilo) was developed by the Beijing Bio-Institute of Biological Products, a subsidiary of China National Biotec Group, and was given WHO emergency use listing on 7th May 2021(158). This vaccine is a 19nCoV-CDC-Tan-HB02 strain SARS-CoV-2 antigen that is produced in Vero cells, inactivated by β-propiolactone, and then purified and absorbed with aluminium hydroxide(182). Next, the CoronaVac vaccine, developed by Sinovac Biotech (Beijing, China), was listed for WHO emergency use on 1st June 2021(158). Like the BBIBP-CorV vaccine, this vaccine is a Vero cell-based, aluminium hydroxide-adjuvanted, β-propiolactone-inactivated vaccine, however, it is based on the SARS-CoV-2 CZ02 strain(183). Covaxin (BBV152) is a whole virion inactivated SARS-CoV-2 vaccine formula developed by Bharat Biotech International ltd (India)(184) which gained emergency use listing from the WHO On 3rd November 2021(185). Lastly, Covovax and its originator, Nuvaxovid (NVX-CoV2372), were both developed by Novavax (Maryland, United States) and the Coalition for Epidemic Preparedness Innovations (Oslo, Norway), and gained emergency use listing on 17st and 21th December 2021, respectively(186, 187). Both vaccines are manufactured using the same technology, and consist of a recombinant SARS-CoV-2 S protein nanoparticle administered with the adjuvant Matrix-M as a co-formulation(188). These vaccines produce similar immune responses to those already discussed. Studies assessing the efficacy of these vaccines are outlined in table 2.

6.10 Other approved vaccines

In addition to the vaccines that have received emergency use listing from the WHO, around the world, vaccines have been developed, tested and approved to combat COVID-19. As of 24th January 2022, 33 vaccines, including the ten described above, have been approved in at least one country(4). The remaining 23 approved vaccines are outlined in table 3."

Comment

9. Overall, I appreciate the section "6.8 Waning immunity and boosters" but perhaps it would also merit if the interval between the 2nd and 3rd vaccine could be outlined.

Response

Thank you, we have now added the following statement that outlines the recommended time interval between the 2nd and 3rd doses:

"Based on current evidence, the CDC recommend that the time interval for receiving a booster following the primary regiment is five months for Pfizer/BioNTech BNT162b2 primary regimen, six months for Moderna mRNA-1273 primary regimen, and two months for Johnson & Johnson Ad26.COV2.S primary regimen(216)."

Reviewer: 2

Major comments:

Comment

1. Although this is not a systematic review, selecting 227 articles from the enormous covid-19 literature, especially including bioRxiv and medRxiv, must involve many layers of judgment. It'd be important to include more details on this selection than currently-included two sentences.

Response

Thank you for this comment. As mentioned in the editor's comment 3, we have included more detail on the selection criteria that we used in the methods section, and more so in the supplementary file.

Comment

2. Dating: Tables 1 & 2, either in the table or legends need to clearly mark the data and definitions are as of [mm/dd/yyyy], as the authors acknowledged all these variant classification/vaccine data are dynamic.

Response

Thank you, the dynamic nature of this topic does require a time stamp like this. In the legend of table 1, we have now included that "information is correct as of 24th January 2021". While in table 2, we have added the dates which the studies took place to and from in order to give clarity on these data. Similarly we have included the date when information was correct from in table 3.

Comment

3. Large variations in vaccine effectiveness %: could these possibly be explained by the country/study date/variants of the publications that were listed? Table 2 made it evident that there were variable sample sizes and COVID-19 definition of VE against (and in some cases variants), but it remains unclear to the reader why there could be such large variations.

Response

We agree that the large variations in vaccine effectiveness reported by studies are confusing and required clarification. We have explained in section 5 why these variations may occur: *"Numerous studies have explored the effectiveness of approved vaccines, however, large variations in vaccine effectiveness are reported. This variability is likely due to several factors in the studies including, the country, date, and population size of the study, as well as the SARS-CoV-2 variants circulating during the study period. These factors, along with how the effectiveness is reported, mean that it is difficult to compare vaccines and fully understand how effective each vaccine is. Here, we review the COVID-19 vaccines in use around the world."*

Comment

4. Considerations for the future: The reviewer feels this is the weakest part of the review manuscript, making only vague/broad statements, not considering examples where covid-19 was controlled (ex. Taiwan, New Zealand). Even in countries with fluctuations, some key approaches have worked but are not discussed here. Ex. The rollout of rapid-testing and quarantine of positive cases, especially given asymptomatic individuals can also spread infections.) This part needs to be largely improved upon or toned down in the abstract.

Response

Thank you, we agree with this comment and therefore have re-written this section to include two main parts; what went wrong, and what went right when attempting to control COVID-19:

"9. Considerations for the future

Novel infectious diseases and pandemics are an unpredictable but inevitable aspect of nature and it is, therefore, important that we learn from past pandemics to prepare for future ones. Firstly, the COVID-19 pandemic has highlighted and amplified the existing inequalities within society(234), with non-white ethnicity, social disadvantage, and unemployment all risk factors for testing positive for COVID-19(235) and those most economically deprived found to be particularly vulnerable(236). These inequalities require addressing in order to be better prepared for similar situations in the future. Next, to progress through a pandemic we should be racing the pathogen, not each other. This statement becomes apparent when you consider the problems countries faced when seeking out PPE(237), and the vaccine inequity seen around the world(238), with developed countries often better placed to be able to purchase these items. Initiatives such as the WHO's COVAX programme are vital in order to protect those most vulnerable and reduce the global spread of disease. In October 2021, the UK government released a publication outlining where the policies implemented to reduce the impact of the COVID-19 pandemic failed, and the lessons learned from these failures (239). Here, it is clear that there is room for improvement, with the publication presenting conclusions and recommendations on how to enhance pandemic preparedness, lockdown and social distancing measures, testing and contact tracing, social care, and vaccines. In countries such as the UK, US, and much of Europe, where the COVID-19 death rate has been high, steps need to be taken and lessons need to be learnt in order to be better prepared for the next pandemic. The responsibility of improving pandemic response lies with policy makers, the medical/scientific community, and the public, and will ultimately require a collaborative approach.

Certain aspects of the response to the COVID-19 pandemic have been a triumph, however. One of the major victories was the rapid development and rollout of vaccines(240), which continue to be effective. The rollout of rapid testing and quarantine for positive cases was also important to at least disrupt the spread of the virus, especially given that asymptomatic individuals can contribute to the spread. Furthermore, the swift identification and sharing of knowledge of SARS-CoV-2 variants between countries should be applauded. Lessons can be learned from countries where COVID-19 was controlled. In Taiwan, managing the pandemic as directed by pre-COVID-19 pandemic plans prompted an immediate response; screening of all airline passengers arriving from Wuhan and high risk areas, restricting entry for non-Taiwanese citizens, 14-day quarantine period for contacts of confirmed cases or returning travellers, a ban on large gatherings, and widespread mask wearing were some of the quickly implemented management strategies(241). New Zealand implemented similarly effective restrictions, with the addition of a national lockdown(241). Many of the pandemic control components that kept case and death numbers low in Taiwan and New Zealand could be adopted by other countries in the future and may lead to greater outcomes in terms of protecting both health of individuals and the health and wellbeing of the country. Overall, there is much to be

learnt from the COVID-19 pandemic and, as we emerge from it, inspection of which policies failed, and which succeeded are imperative."

Minor comments:

Comment

1. Table 1 is a great summary of variants, if journal format allows, color-coding the mutations could allow people to quickly digest which variants share which mutations.

Response

Thank you, we agree that colour coding the mutations shared by different variants make it clearer to quickly digest the information, so have colour coded the mutations accordingly.

Comment

2. Figure 1, the texts in the figures (ex. D614G, ORF6, variant designations) could be enlarged

Response

Thank you, the text in figure 1 has been enlarged to make for easier reading.

Reviewer: 3

Comment

1. This review was not written in the systematic review format, which authors can use the statistical method to measurement the significant different between virology variant and vaccine aspects.

Response

Thank you for this comment. As this is not a systematic review in the strictest sense, we believe that this is difficult. We have aimed to explore the relationships between vaccines and circulating variants where possible, for example, where vaccine effectiveness against certain variants is stated in articles, we include it in table 2, while the dates that studies took place from and to are included and can be correlated with circulating variants.

Comment

2. The criteria of choosing and exclude scientific data / paper need to be explained to eliminated the potential bias.

Response

Thank you, as mentioned in previous responses, we have updated the methods section and included a supplementary file to explain our search and inclusion criteria.

Comment

3. Since, the severity of diseases did not depend on only viral genetic, host, and immune status, as well as significant risk factors, but also depend on medical treatment and duration of onset in each data set which are important confounding factors.

Response

Indeed, duration of disease and the treatment patients receive are important factors in determining the severity of disease patients endure, we have included the following statement to cover this:

"The duration of symptoms endured by COVID-19 patients, as well as the treatment they receive will also have profound influences on the severity of disease they experience and both the acute and long-term outcomes following recovery."

Comment

4. Most of review data are not suitable for publication in the modern scientific format but can be re-written with additional level of evidence based medicine.

Response

We believe that the review is written in a concise and methodical manner with all comments supported by published evidence and suitable data.

Comment

5. The basic knowledge and 3D structure of spike RBD and NTD molecule in each mutation and vaccine sequence antibody (MRNA)/ (VIRAL VECTORS) should be reviewed if authors want to determine the correlation of vaccine efficacy and variant of SARS-CoV-2. The authors can use the essential real world data of vaccine effectiveness to determine the response of vaccine across the variant in different time and place of epidemic.

Response

Thank you. Due to the limited word count available, it was not possible to explain the spike protein 3D structure changes caused by each mutation, however we have detailed the structure of the spike protein and where the mutations are located within the spike. We have indicated that mutations within the spike alter its 3D structure and influence immune escape:

Section 4:

"The subunits of the trimeric S complex are either in a closed (pre-fusion stage) or open (post-fusion stage) conformation(62), with one subunit always in an open conformation to allow for ACE2 recognition and binding(63). The RBD itself consists of five anti-parallel β-strands surrounded by several α-helices(64). From closed to open conformation, the RBD undergoes structural rearrangement whereby the globular head region rotates clockwise, which alters is elecropotential surface(64). Once positioned, numerous residues within the RBD form either hydrogen bonds or salt bridges with residues of the ACE2 receptor, allowing for tight binding(65), while the concave structure of the RBD allows for three distinct binding regions(64).

Section 5:

"Many of the mutations observed in SARS-CoV-2 variants are found within the RBD or the N-terminal domain of the S protein, which alters the three-dimensional structure of the S protein. Not only can these changes affect the transmission abilities of the virus, but can also allow it to better escape the immune response, including from neutralising antibodies either elicited through vaccine administration or natural infection."

Comment

6. The booster dose data should be reviewed in term of antibody response and T cell response.

Response

Thank you, we agree with this and we have now included some discussion of antibody and T-cell responses following booster dose:

"Since booster programmes began, evidence that a booster vaccine dose enhances antibody and cellular responses has accumulated. Following a third dose of vaccine, neutralising antibody titres increase significantly(199-202) and, in some cases, to higher levels than after the primary two doses(199). Additionally, boosters have also been found to increase neutralising antibody titres against Beta, Gamma, Delta, and Omicron variants(200, 203, 204). T-cell response is also enhanced following a third dose(201, 205, 206). Together, enhancing neutralising antibody and cellular responses with a booster vaccine dose is likely to provide a greater level of protection than relying on immunity built through a primary regimen."

Reviewer: 4

Comment

1) Introduction

- Line 22 - can you include the difference between VOI and VUM? e.g. in VUM evidence of phenotypic or epidemiological effect is currently unclear, and a name has not yet been assigned.

Response

Thank you, we agree that the differences between VOC, VUI and VUM should have been defined more clearly to include the difference between each. We have updated this as follows:

"The World Health Organisation (WHO) classify SARS-CoV-2 variants that increase transmissibility, disease severity or virulence, or decrease the effectiveness of public health measures, diagnostics, therapeutics or vaccines as variants of concern (VOC). Variants with genetic changes that are predicted to enhance the virulence and transmissibility of the virus which have been identified to cause community transmission in multiple countries posing a possible risk to global public health are defined as variants of interest (VOI). Lastly, the WHO defines variants with genetic changes that are suspected to affect virus characteristics and have currently unclear phenotypic or epidemiological effects as variants under monitoring (VUM). VUM are not typically assigned a name until they are upgraded to VOI or VOC. The full working definitions of VOC, VOI and VUM can be found on the WHO 'tracking SARS-CoV-2 variants' website: www.who.int/en/activities/tracking-SARS-CoV-2-variants/(3)."

Comment

2) Methods

- Including the specifics of how the searches were done would add clarity (maybe as a supplementary file), many of the terms which were searched for are not specific

Response

Thank you, clarity on the search terms and selection criteria was needed. We have included a supplementary file which includes the specific search terms that we used as well as the selection criteria that was implemented for different sections of the review.

Comment

3) Transmission

- Line 32 - maybe use "biological material" instead of "biological samples", presumably the virus doesn't normally spread via the samples themselves

Response

Thank you, this has been changed from "biological samples" to "biological material"

Comment

4) Virology
Page 6
line 8 typo - "interacting WITH host cell organelles"
line 25 - both halves of this sentence are talking about TMPRSS2 but it doesn't sound like it

Response

Thank you, these errors have been corrected:
"with" has now been inserted into "interacting WITH host cell organelles".

The TMPRSS2 sentence has been amended:

"Meanwhile, TMPRSS2, a host cell protease, facilitates fusion of the viral and host cell membranes(68), and may play a role in the spread of the virus in the airways(68)."

Comment

5) VOC
- You frequently refer to an increase in these variants, and state or imply that this is relative to the wild-type. Can you include a section at the start of 5 where you specify what that wild-type is? Is it clear that samples from a particular time period or geographic area are wild-type?

Response

Thank you. We agree that simply using 'wild-type' to discuss a SARS-CoV-2 strain is confusing. Firstly, we have changed this wording to refer to the initial strain that emerged from Wuhan as the 'primary strain, and have described what is meant by that at the end of section 5:
"Herein, we report studies that compare SARS-CoV-2 variants to the 'primary' virus strain. 'Primary strain' refers to the strain of the virus that first emerged in Wuhan, China at the end of 2019 and spread around the world in the first wave of infections, which is often also referred to as the Wuhan-Hu-1, B.1, or wild-type strain."

Comment

6) VOC - Alpha
line 22 typo "probable" not "probably"
line 48 typo "de-escalated"

Response

Thank you for highlighting these errors.
Due to re-wording of this section, "probably" has now been removed, while "de-escalated" has been amended.

Comment

7) 5.1.4 VOC – Delta
- p10 48 Transmissibility of Delta is 97% greater, or three times Alpha, Beta and Gamma?
- p10 54 Isn't replication rate a factor in transmissibility rather than an addition to it?
- p11 line 27 - when you talk about younger people, can you specify which age cutoff you are talking about?

Response

Thank you for identifying this.

The transmissibility sentence was worded poorly in the original manuscript, this has been amended to explain exactly what is meant:
"It was estimated that the reproduction number of the Delta variant is 97% greater than non-VOC/VOI and approximately three times that of the Alpha, Beta, and Gamma variants(110),"

We agree that replication rate is a factor in transmissibility, therefore we have amended this sentence:
"The fast replication rate of Delta likely contributes to its increased transmissibility compared to Alpha, Beta, and Gamma."

We also agree that it was unclear what "younger people" meant, we have amended the statement as follows:
"Lastly, a study in India found that the risk of death was around 1.8 times higher for Delta infections, while Delta also infected and induced symptoms in a greater proportion of younger people (0-19 years old), compared to the primary strain(131)."

Comment

8) Vaccination 6.1 Pfizer
line 15 - typo repeating "elicit a strong"

6.3 Johnson and Johnson
- Line 9 a bit unclear, is the point that there is a time lag of around 28 days before peak effectiveness? After second dose? And compared with how many days?

6.6 Sinovac
Line 6 - typo "alike" should be "like"

6.8 Boosters
Line 56 typo "On 30th July 2021" appears twice

Response

Thank you.
Repetition of "elicit a strong" has been corrected.
Due to re-wording of the manuscript, the statement commenting on the time lag of around 28 days before peak effectiveness has been removed.
"like" now replaces "alike" within the Sinovac section.
The second appearance of "On 30th July 2021" has been removed.

Comment

8 Conclusions

- Line 23 "Yet to be eradicated" - this is absolutely true; but this is unlikely to happen for decades if ever, and there are other more immediate unmet goals it might be better to mention, such as attaining high vaccination coverage globally, ensuring all health systems have the capacity to cope with seasonal waves.

Response

Thank you, we agree that "yet to be eradicated" is possibly a misleading statement. We have amended this part of the conclusion as follows:

"Although rollout of vaccines has been successful, we must aim to address unmet goals, such as attaining a high global vaccination coverage and ensuring that all healthcare systems have the capacity to cope with seasonal waves."

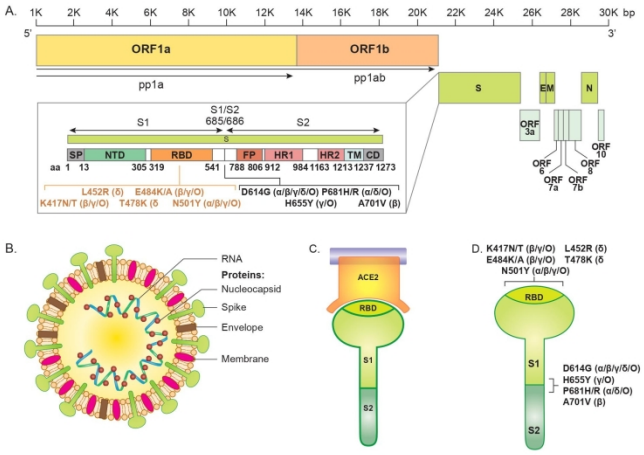

Figure 1: Genome and structure of SARS-CoV-2.

210x297mm (300 x 300 DPI)

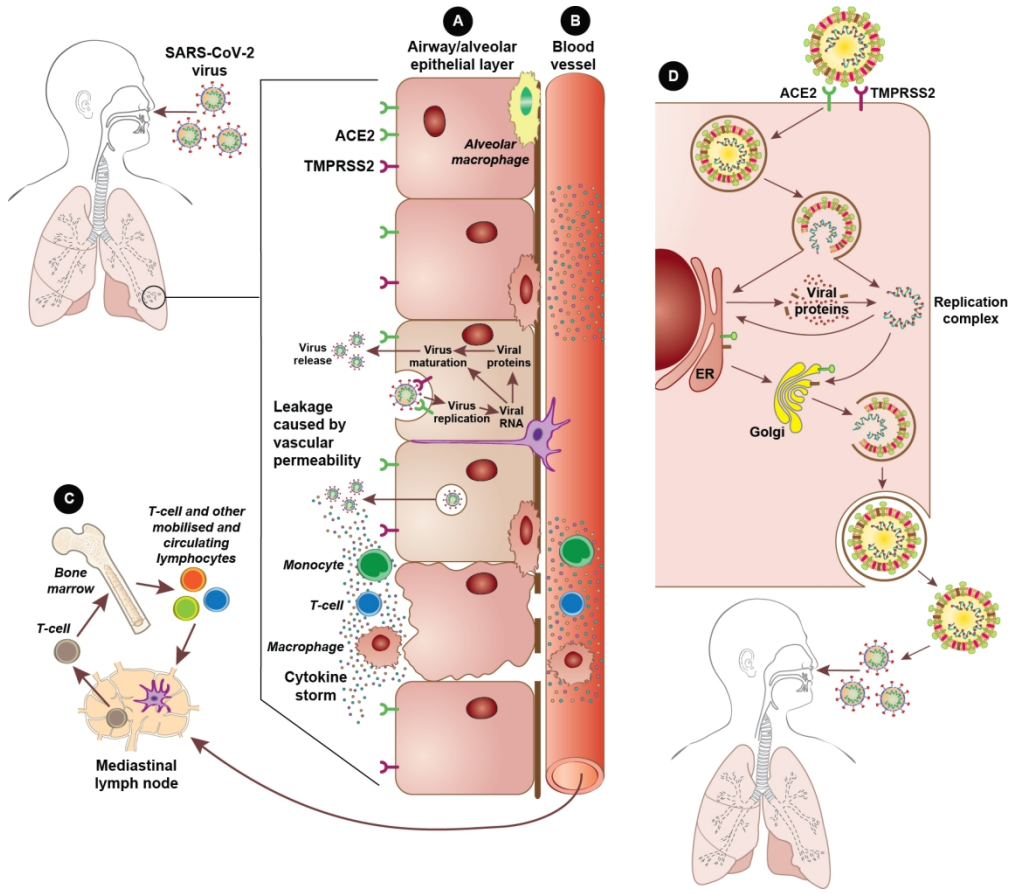

Figure 2: Viral entry and host response.

153x135mm (300 x 300 DPI)

Variants of concern			
WHO nomenclature or designation	**Pango Lineage**	**S protein mutations of interest**	**First detected samples ***
Alpha	B.1.1.7	N501Y D614G P681H	UK, Sept 2020
Beta	B.1.351	N501Y D614G E484K K417N A701V	South Africa, May 2020
Gamma	P.1	N501Y D614G E484K K417T H655Y	Brazil, Nov 2020
Delta	B.1.617.2	L452R D614G P681R T478K	India, Oct 2020
Omicron	B.1.1.529	N501Y D614G E484A P681H K417N H655Y A67V Δ69-70 T95I G142D Δ143-145 N211I Δ212 ins215EPE G339D S371L S373P S375F N440K G446S S477N T478K Q493R G496S Q498R Y505H T547K N679K N764K D796Y N856K Q954H N969K L981F	South Africa and Botswana, Nov 2021
Variants of Interest			
WHO nomenclature or designation	**Pango Lineage**	**S protein mutations of interest**	**First detected samples ***
Lambda	C.37	L452Q D614G F490S	Peru, Dec 2020
Mu	B.1.621	N501Y D614G P681H R346K E484K	Columbia, Jan 2021
Variants under monitoring			
Pango Lineage		**S protein mutations of interest**	**First detected samples ***
B.1.1.318		D614G P681H E484K	Multiple countries, Jan 2021
C.1.2		N501Y D614G E484K H655Y N679K Y449H	South Africa, May 2021
B.1.640		N501Y D614G P681H F490R N394S R346S Y449N 137–145del	Multiple countries, Sep 2021

Vaccine and vaccine type	Recommended dose and administration	Study ref.	Study type	Study date and location(s)	N	Vaccine effectiveness % (95% confidence interval) *		
						Against	One dose	Two doses
Pfizer/BioNtech (BNT162b2) – mRNA.	Two doses (30µg, 0.3ml each) intramuscularly (deltoid) with a recommended interval of 21-28 days between doses.	(156)	Randomised controlled trial	27/7/2020 to 14/11/2020 US, Argentina, Brazil, South Africa, Germany, and Turkey.	37,706	Symptomatic infection		95% (90.3–97.6%)
		(241)	Observational	20/12/2020 to 1/2/2021 Israel.	1,193,236	Documented infection	46% (40-51%)	92% (88-95%)
						Symptomatic infection	57% (50-63%)	94% (87-98%)
						Hospitalisation	74% (56-86%)	87% (55-100%)
						Severe disease	62% (39-80%)	92% (75-100%)
		(242)	Test-negative case-control	26/10/2020 to 16/5/2021 UK.	19,109	Infection with Alpha	47.5% (41.6–52.8%)	93.7% (91.6–95.3%)
						Infection with Delta	35.6% (22.7–46.4%)	88.0% (85.3–90.1%)
		(243)	Test-negative case-control	1/2/2021 to 31/3/2021 Qatar.	213,758	Infection with Beta		75.0% (70.5-78.9%)
						Infection with Alpha or Beta		97.4% (92.2-99.5%)
		(244)	Test-negative case-control	14/12/2020 to 19/4/2021 Canada.	324,033	Symptomatic infection	14-20 days: 48% (41-54%)	≥7 days: 91% (89-93%)
							≥14 days: 60% (57-64%)	
							35-41 days: 71% (63-78%)	
						Hospital admission or death	14-20 days: 62% (44-75%)	≥7 days: 98% (88-100%)
							≥14 days: 70% (60-77%)	
							≥35 days: 91% (73-97%)	
						[NOTE: Participants in this study received an mRNA vaccine (either BNT162b2 or mRNA-1273)]		
		(245)	Test-negative case-control	14/12/2020 to 3/8/2021 Canada.	682,071	Symptomatic infection - Alpha	≥14 days: 66% (95% CI: 64-68%)	≥7 days: 89% (86–91%)
						Symptomatic infection - Beta or Gamma variants	≥14 days: 60% (52-67%)	≥7 days: 84% (69–92%)
						Symptomatic infection - Delta	≥14 days: 56% (45-64%)	≥7 days: 87% (64–95%)
						Against hospitalisation or death - Alpha	≥14 days: 80% (78-82%)	≥7 days: 95% (92-97%)
						Against hospitalisation or death - Beta or Gamma	≥14 days: 77% (69-83%)	≥7 days: 95% (81-99%)
						Against hospitalisation or death - Delta	≥14 days: 78% (65-86%)	
		(246)	Retrospective case-control	January to July 2021 US.	119,463	Infection		≥14 days: 86% (81-90.6%)
						Hospitalisation		≥14 days: 85% (73-93%)
						Admission to an ICU		≥14 days: 87% (46-98.6%)
		(133)	Test-negative observational	1/4/2021 to 6/6/2021 Scotland.	400,827	Infection - Alpha		92% (90–93%)
						Infection - Delta		79% (75-82%)
		(247)			14,019	Hospitalisation - Alpha	83% (62-93%)	95% (78-99%)

			Test-negative case-control	12/4/2021 to 4/6/2021 England.		Hospitalisation - Delta	94% (46-99%)	96% (86-99%)
		(248)	Test-negative case-control	8/12/2020 to 19/2/2021. England.	156,930	Infection		10-13 days: 70% (59-78%)
								≥14 days: 89% (85-93%)
								28-34 days: 61% (51-69%)
		(249)	Test-negative case-control	4/4/2021 to 1/5/2021 Canada.	16,993	Infection	0-13 days: 14% (0-26%)	
							14-20 days: 43% (30-53%)	
							35-41 days: 75% (63-83%)	
						Infection		≥21 days: 65% (58-71%)
						Infection - non-VOC		72% (58-81%)
						Infection - Alpha		67% (57-75%)
						Infection - Gamma		61% (45-72%)
		(250)	Test-negative case-control	17/1/2021 to 5/6/2021 Canada.	5,8476	Infection	≥14 days: 70.3% (68.1-72.4%)	≥7 days: 85.5% (80.4-89.3%)
		(251)	Case-control	14/2/2021 to 3/5/2021 France.	67,760	Infection		≥7 days: 88% (81-92%)
						Infection - Alpha		≥7 days: 86% (81-90%)
						Infection - Beta/Gamma		≥7 days: 77% (63-86%)
		(252)	Test-negative case-control	23/3/2021 to 7/9/2021 Qatar.	1 dose: 906,078 2 doses: 877,354	Infection – Delta	65.5% (40.9-79.9%)	≥14 days: 59.6% (50.7-66.9%)
						Severe disease or death - Delta		97.3% (84.4-99.5%)
		(192)	Test-negative case-control	1/1/2021 to 5/9/2021 Qatar.	1 dose: 947,035 2 doses: 907,763	Symptomatic infection	0-13 days: -5.5% (-12.9-1.4%)	
							≥14 days: 47.9% (43.6-51.9%)	
							1 month: 81.5% (79.9-83.0%)	
							2 months: 72.5% (69.6-75.1%)	
							3 months: 70.6% (66.4-74.3%)	
							4 months: 57.0% (48.6-64.0%)	
							5 months: 12.0% (-6.1-27.1%)	
							6 months: 12.8% (-9.1-30.3%)	
							≥7 months: 27.8% (-1.4-48.7%)	
						Hospitalisation and death	0-13 days: 7.5% (−11.9-23.6%)	
							≥14 days: 65.0% (55.0-72.8%)	
							1 month: 95.9% (93.6-97.3%)	
							2 months: 96.3% (92.9-98.0%)	
							3 months: 93.4% (87.5-96.5%)	
							4 months: 80.8% (56.9-91.4%)	
							6 months: 81.8% (18.5-95.9%)	
							≥7 months: 44.1% (-86.5-83.3%)	
		(253)	Prospective cohort	7/12/2020 to 5/2/2021	23,324	Infection	≥21 days: 70% (55-85%)	≥7 days: 85% (74-96%)

				UK.				
		(254)	Observational	24/1/2021 to 3/4/2021 Israel.	186,109	Infection		≥7 days: 95.3% (94.9-95.7%)
						Asymptomatic infection		≥7 days: 91.5% (90.7-92.2%)
						Symptomatic infection		≥7 days: 97.0% (96.7-97.2%)
						Hospitalisation		≥7 days: 97.2% (96.8-97.5%)
						Severe or critical infection		≥7 days: 97.5% (97.1-97.8%)
						Death		≥7 days: 96.7% (96.0-97.3%)
		(255)	Observational	1/3/2021 to 1/8/2021 US.	10,428,783	Infection – Pre-Delta period		≥14 days: 74.2% (68.9-78.7%)
						Infection – Intermediate period		≥14 days: 66.5% (58.3-73.1%)
						Infection – Delta		≥14 days: 52.4% (48.0-56.4%)
		(256)	Observational	14/12/2020 to 14/8/2021 US.	Delta: 2,840 Pre-Delta: 7,012	Infection – Delta		14–119 days: 85% (68-93%)
								120–149 days: 81% (34-95%)
								≥150 days: 73% (49-86%)
						Infection – Pre-Delta		91% (81-96%)
					[NOTE only 65% of participants in this study received BNT162b2 (33% received mRNA-1273, and 2% received Ad26.COV2.S]			
		(257)	Observational	15/1/2021 to 16/4/2021 France.	378	Infection – Beta		≥7 days: 49% (14-69%)
						Severe disease		≥7 days: 86% (67-94%)
		(258)	Observational	1/12/2020 to 1/8/2021 UK.	384,543	Infection – Alpha	≥21 days: 59% (52-65%)	
						Infection – Delta	≥21 days: 57% (50-63%)	
						Infection – Alpha		0-13 days: 77% (66-84%)
								≥14 days: 78% (68-84%)
						Infection – Delta		0-13 days: 82% (75-87%)
								≥14 days: 80% (77-83%)
		(259)	Observational	April to May 2021. Canada	224	Infection		66.2% (2.3-88.3%)
						Symptomatic infection		25.6% (-157.8-78.5%)
		(260)	Retrospective cohort	27/12/2020 to 24/3/2021 Italy.	6,423	Infection	0-14 days: 47.3% (24.7-63.1%)	≥7 days: 95.1% (62.4-99.4%)
							14-21 days: 84.1% (39.7-95.8%)	
							≥21 days: 85.4% (-35.3-98.4%)	
						Symptomatic infection	0-14 days: 39.9% (9.1-60.3%)	≥7 days: 93.7% (50.8-99.2%)
							14-21 days: 83.3% (14.8-96.7%)	
							≥21 days: 65.9% (-171-95.7%)	
		(261)	Randomised controlled trial	27//7/2020 to 29/10/2020 US, Argentina, Brazil, South Africa, Germany, Turkey	44,165	Infection (without evidence of prior infection)		≥7 days: 91.3% (89-93.2%)
						Infection (with evidence of previous infection)		≥7 days: 91.1% (88.8-93.0%)
						Infection	<11 days: 18.2% (−26.1-47.3%)	<7 days: 91.5% (72.9-98.3%)
							≥11 days to second dose: 91.7% (79.6-97.4%)	≥7 days: 91.2% (88.9-93.0%)

								≥7 days to <2 months: 96.2% (93.3-98.1%)
								≥2 months to <4 months: 90.1% (86.6-92.9%)
								≥4 months: 83.7% (74.7-89.9%)
		(262)	Retrospective cohort	20/12/2020 to 25/2/2021 Israel.	6,710	Symptomatic Infection	7-21 days: 89% (83-94%)	≥7 days: 97% (94-99%)
								≥21 days: 98% (94-100%)
						Asymptomatic Infection	7-21 days: 36% (-51-69%)	≥7 days: 86% (69-93%)
								≥21 days: 94% (78-98%)
		(263)	Cohort	27/12/2020 to 28/2/2021 Sweden.	805,741	Infection	≥14 days: 42% (14-63%)	<7 days: 60% (27-81%)
								≥7 days: 86% (72-94%)
		(264)	Prospective cohort	27/12/2020 to 26/5/2021 Spain.	28,594	Infection – Nursing home residents	12 days: 20% (19.76-20.3%)	90.89% (90.84-90.95%
							40.28% (40.17-40.39)	
					26,238	Infection – Nursing home staff	12 days: 20.27% (19.8-20.73%)	85.02% (84.86-85.17%)
							26.49% (26.25-26.74%)	
					61,951	Infection – Healthcare workers	12 days: 15.44% (15.19-15.68%)	94% (93.92-94.1%)
							33.8% (33.66-33.92%)	
					28,594	Hospital admission - Nursing home residents	12 days: 67.59% (65.29-69.75%)	95.06% (94.73-95.38%)
							46.24% (45.62-46.86%)	
						Death - Nursing home residents	12 days: 43.95% (37.87-49.44%)	96.73% (96.43-96.99)
							51.71% (51.17-52.23%)	
		(265)	Cohort	27/12/2020 to 11/4/2021 Denmark.	864,096	Infection - Prioritised risk groups	0-14 days: -72% (-80- -64%)	0-7 days: 42% (33-50%)
							>14 days to second dose: 7% (-1-15%)	> 7 days: 82% (79-84%)
						COVID-19-related hospitalisation - Prioritised risk groups	0-14 days: 54% (44-62%)	0-7 days: 90% (80-95%)
							>14 days to second dose: 35% (18-49%)	>7 days: 93% (89-96%)
						COVID-19-related death - Prioritised risk groups	0-14 days: 76% (68-82%)	>7 days: 94% (90-96%)
							>14 to second dose days: 7% (-15-25%)	
		(266)	Case-control	27.1.2021 to 7/2/2021 Spain.	268	Infection	52.6% (95%CI: 1.1-77.3)	
		(267)	Observational	15/12/2020 to 3/2/2021 England.	170,226	Infection	21-27 days: 55.2% (40.8-66.8%)	
						Emergency hospital attendance	21-27 days: 57.8% (30.8-74.5%)	
						Hospitalisation	21-27 days: 50.1% (19.9-69.5%)	
		(268)	Cohort	27/12/2020 to 10/3/2021 Spain.	299,209	Infection (without evidence of prior infection)	0-14 days: 28.9% (26.9-31%)	
							15-21 days: 51.9% (50.7-53.1%)	
							22-28 days: 62.9% (61.9-64%)	
							≥29 days: 81.8% (81.0-82.7%)	
							0-14 days: 9.6% (-6.9-26.8%)	

						Infection (with evidence of prior infection)	15-21 days: 25.5% (15.1-36.6%)	
							22-28 days: 34.6% (25.7-44.1%)	
							≥29 days: 56.8% (47.1-67.7%)	
		(269)	Observational	1/12/2020 to 8/5/2021 UK.	383,812	Infection	8-20 days after either dose: 56% (51-61%)	
							≥21 days: 64% (59-68%)	≥21 days: 80% (74-84%)
					[NOTE: Both BNT162b2 and AZD1222 vaccines were included in this study]			
		(270)	Cohort	19/12/2020 to 14/3/2021 Israel.	9,347	Infection	4-10 days: 28% (-18-57%)	≥11 days: 65% (45-79%)
							≥11 days after first, ≤10 days after second: 55% (32-70%)	
						Symptomatic infection	4-10 days: 21% (-32-41%)	≥11 days: 90% (84-94%)
							≥11 days after first, ≤10 days after second: 80% (69-87%)	
		(271)	Prospective cohort	8/12/2020 to 15/3/2021 England.	10,412	Infection	0-6 days: 36% (-6-62%)	
							7-13 days: 17% (-28-46%)	
							14-20 days: 4% (-60-43%)	
							21-27 days: 8% (-59-47%)	
							28-34 days: 56% (19-76%)	
							35-48 days: 62% (23-81%)	
							≥49 days: 51% (-17-80%)	
					[NOTE: Both BNT162b2 and AZD1222 vaccines were included in this study]			
		(272)	Retrospective cohort	1/1/2021 to 31/3/2021 US.	44,498	Infection	>14 days after first, ≤14 days after second: 78.1% (71.1-82%)	
								>14 days: 96.8% (95.3-97.8%)
		(273)	Prospective cohort	14/12/2020 to 10/4/2021 US.	3,975	Infection	≥14 days after first, <14 days after second: 80% (60-90%)	
								≥14 days: 93% (78-98%)
		(274)	Randomised controlled trial	15/10/2020 to 12/1/2021 US.	2,260	Infection - Adolescents (12-15 years of age) - (without evidence of prior infection)		≥7 days: 100% (75.3-100%)
						Infection - Adolescents (12-15 years of age) - (with or without evidence of prior infection)		≥7 days: 100% (78.1-100%)
		(275)	Retrospective cohort	19/7/2021 to 13/11/2021 South Korea.	444,313	Infection – Adolescents (16-18 years of age)	≥14 days: 91.1% (89.6-92.5%)	≥14 days: 99.1% (98.5-99.5%)
		(276)	Prospective cohort	25/7/2021 to 4/12/2021 US.	243	Infection - Adolescents (12-17 years of age)		≥14 days: 92% (79-97%)
		(277)	Retrospective longitudinal cohort	21/12/2020 to 6/2/2021 Israel.	5,439,734 first dose, 5,112,516 second dose	Infection	14-20 days: 54.3% (50.6-57.8%)	8-14 days: 89.9% (88.6-91.1%)
						Symptomatic infection	14-20 days: 58.3% (54.7-61.6%)	8-14 days: 93.6% (92.7-94.3%)
						Hospitalisation	14-20 days: 74.5% (69.1-79%)	8-14 days: 93.8% (91.9-95.2%)
						Severe/Critical disease	14-20 days: 77.3% (71.2-82.1%)	8-14 days: 94.4% (92.6-95.8%)
						Death	14-20 days: 71.7% (64.1-77.7%)	8-14 days: 91.3% (87.4-94.0%)
						Infection		15-21 days: 96.8% (96.1-97.4%)

						Symptomatic infection		15-21 days: 98.1% (97.7-98.5%)
						Hospitalisation		15-21 days: 98% (97.1-98.6%)
						Severe/Critical disease		15-21 days: 98.6% (97.8-99.1%)
						Death		15-21 days: 97.7% (95.9-98.7%)
						Infection		22-28 days: 97.3% (96.7-97.8%)
						Symptomatic infection		22-28 days: 97.9% (97.4-98.3%)
						Hospitalisation		22-28 days: 99% (98.4-99.3%)
						Severe/Critical disease		22-28 days: 99.2% (98.6-99.5%)
						Death		22-28 days: 98.6% (97-99.3%)
		(278)	Test-negative case-control	January to March 2021 US.	1,843	Infection	≥14 days: 81.7% (74.3-86.9%)	≤2 days: 81.7% (74.3-86.9%)
								3-6 days: 81.7% (74.3-86.9%)
								≥7 days: 93.5% (86.5-96.9%)
					[NOTE: 76% of case-patients and 78% of controls received BNT162b2, remainder received mRNA-1273]			
		(279)	Prospective cohort	January to April 2021 Spain.	20,961	Infection	21% (3-36%)	65% (56-73%)
						Symptomatic infection	30% (10-45%)	82% (73-88%)
						Symptomatic infection – 18-59 years old	50% (12-72%)	85% (74-91%)
						Symptomatic infection - ≥60 years old	20% (−7-40%)	76% (55-87%)
						Hospitalisation	65% (25-83%)	94% (60-99%)
		(280)	Prospective cohort	8/10/2020 to 22/2/2021 Scotland.	409,588	Hospitalisation	0-6 days: 86% (81-90%)	
							7-13 days: 53% (45-59%)	
							14-20 days: 69% (62-75%)	
							21-27 days: 78% (71-83%)	
							28-34 days: 91% (85-94%)	
							35-41 days: 78% (69-85%)	
							≥42 days: 77% (68-83%)	
		(281)	Test-negative case-control	27/12/2020 to 30/6/2021 Belgium, Croatia, Czechia, France, Greece, Ireland, Luxembourg, Malta, Portugal, Spain.	1,893	Infection	≥14 days: 76% (61-86%)	≥14 days: 94% (88-97%)
		(282)	Prospective cohort	1/5/2021 to 3/9/2021 US.	8,690,825	Infection - 18-49 years old		≥14 days: 93.3% (92.2-94.4%)
						Infection - 50-64 years old		≥14 days: 95.0% (94.0-96.0%)
						Infection - ≤65 years old		≥14 days: 91.4% (90.0-92.8%)
						Hospitalisation - 18-49 years old		≥14 days: 96.1% (94.1-97.6%)
						Hospitalisation - 50-64 years old		≥14 days: 95.6% (94.2-96.7%)
						Hospitalisation - ≤65 years old		≥14 days: 94.8% (94.0-95.5%)
		(283)			1,222	Hospitalisation 12-18 years old	97% (86-100%)	≥14 days: 94% (90-96%)

			Test-negative case-control	1/7/2021 to 25/10/2021 US.		ICU admission – 12-18 years old		≥14 days: 98% (93-99%)
						Life support – 12-18 years old		≥14 days: 98% (92-100%)
		(284)	Test-negative case-control	1/7/2021 to 9/12/2021 US.	283	COVID-19 multisystem inflammatory syndrome – 12-18 years old		≥14 days: 92% (77-97%)
Oxford University/ AstraZeneca (AZD1222) - Non-replicating adenovirus viral vector (ChAdOx1).	Two doses (0.5ml each) intramuscularly (deltoid) with a recommended interval window of 8 to 12 weeks.	(242)	Test-negative case-control	26/10/2020 to 16/5/2021 UK.	19,109	Infection - Alpha	48.7% (45.2–51.9%)	74.5% (68.4–79.4%)
						Infection - Delta	30.0% (24.3–35.3%)	67.0% (61.3–71.8%)
		(245)	Test-negative case-control	14/12/2020 to 3/8/2021 Canada.	682,071	Symptomatic infection - Alpha	64% (60-68%)	
						Symptomatic infection – Beta or Gamma	48% (28-63%)	
						Symptomatic infection - Delta	67% (44-80%)	
						Hospitalisation or death - Alpha	85% (81-88%)	
						Hospitalisation or death – Bet or Gamma	83% (66-92%)	
						Hospitalisation or death - Delta	88% (60-96%)	
		(133)	Test-negative observational	1/4/2021 to 6/6/2021 Scotland.	462,755	Infection with Alpha variant		73% (66-78%)
						Infection with Delta variant		60% (53-66%)
		(285)	Randomised controlled trial	1/10/2020 to 14/1/2021 UK.	8,534	Symptomatic infection – Alpha		70.4% (43.6-84%%)
						Symptomatic infection – non-Alpha		81.5% (67.9-89.4%)
		(286)	Randomised controlled trial	28/8/2020 to 5/3/2021 US.	32,449	Symptomatic infection		79%
						Severe disease or hospitalisation		100%
		(247)	Test-negative case-control	12/4/2021 to 4/6/2021 England.	14,019	Hospitalisation – Alpha	76% (61-85%)	86% (53-96%)
						Hospitalisation – Delta	71% (51-83%)	92% (75-97%)
		(287)	Randomised controlled trial	23/4/2020 to 4/11/2020 UK, Brazil.	11,636	Infection		62.1% (41.0-75.7%)
		(288)	Randomised controlled trial	24/6/2020 to 9/11/2020 South Africa.	2,026	Symptomatic infection		21.9% (-49.9-59.8%)
						Symptomatic infection - Beta		10.4% (-76.8-54.8%)
		(248)	Test-negative case-control	8/12/2020 to 19/2/2021. England.	156,930	Symptomatic infection		28-34 days: 60% (41-73%)
								≥35 days: 73% (27-90%)
		(258)	Observational	1/12/2020 to 1/8/2021 UK.	384,543	Infection - Alpha	≥21 days: 63% (55–69%)	0-13 days: 72% (50-84%)
								≥14 days: 79% (56–90%)
						Infection Delta	≥21 days: 46% (35–55%)	0-13 days: 71% (64–77%)
								≥14 days: 67% (62–71%)
		(289)	Test-negative case-control	1/3/2021 to 31/5/2021 India	720	Infection	49% (17-68%)	54% (27-71%)
						Symptomatic infection	58% (28-75%)	64% (38-78%)
						Moderately severe disease	Any dosage >3 weeks ago: 95% (44-100%)	

		(269)	Observational	1/12/2020 to 8/5/2021 UK.	383,812	Infection	8-20 days after either dose: 56% (51-61%)	
							≥21 days: 64% (59-68%)	≥21 days: 80% (74-84%)
					[NOTE: Both BNT162b2 and AZD1222 vaccines were included in this study]			
		(290)	Randomised controlled trial	28/8/2020 to 15/1/2021 US, Chile, Peru.	32,451	Symptomatic infection		≥15 days: 74.0% (65.3-80.5%)
						Severe or critical infection		≥15 days: 100.0% (71.6-NE%)
						Emergency department visit		≥15 days: 94.8% (59.0-99.3%)
						Hospitalisation		≥15 days: 94.2% (53.3-99.3%)
						ICU admission		≥15 days: 100.0 (−1781.6-NE%)
		(291)	Clinical trial	23/6/2020 to 1/12/2020 Brazil.	9433	Infection – B.1.1.33		88.2 (5.4, 98.5)
						Infection – B.1.1.28		72.6% (46.4-86.0%)
						Infection – Zeta		68.7% (54.9-78.3%)
						Infection – Gamma		63.6% (−2.1-87.0%)
						Infection – Undetermined variant		56.6% (28.2-73.8%)
						Hospitalisation – Any variant		95% (61-99%)
		(292)	Meta-analysis	23/4/2020 to 6/12/2020 UK, Brazil, South Africa.	17,178	Asymptomatic infection		≥14 days: 22.2% (–9·9-45%)
						Symptomatic infection		≥14 days: 66.7% (57.4-74%)
						Asymptomatic infection - <6 weeks prime-boost interval (standard doses)		≥14 days: –11.8% (–189.5-56.8%)
						Asymptomatic infection - 6-8 weeks prime-boost interval (standard doses)		≥14 days: –74.2% (–330.3-29.5%)
						Asymptomatic infection – 9-11 weeks prime-boost interval (standard doses)		≥14 days: 39.9% (–62.3-77.8%)
						Asymptomatic infection - ≥12 weeks prime-boost interval (standard doses)		≥14 days: 22.8% (–63.3-63.5%)
						Symptomatic infection - <6 weeks prime-boost interval (standard doses)		≥14 days: 55.1% (33-69.9%)
						Symptomatic infection - 6-8 weeks prime-boost interval (standard doses)		≥14 days: 59.9% (32-76.4%)
						Symptomatic infection – 9-11 weeks prime-boost interval (standard doses)		≥14 days: 63.7% (28-81.7%)
						Symptomatic infection - ≥12 weeks prime-boost interval (standard doses)		≥14 days: 81.3% (60.3-91.2%)
		(293)	Cross-sectional observational	1/5/2021 to 31/5/2021 India.	583	Infection	<14 days: 15% (-68-57%)	<14 days: 66% (34-81%)
							≥14 days: 44% (7-66%)	≥14 days: 83% (73-89%)
						Hospitalisation	<14 days: 43% (-68-81%)	<14 days: 83% (17-96%)
							≥14 days: 76% (21-92%)	≥14 days: 88% (55-97%)
						ICU admission or death	<14 days: 62% (-27-89%)	<14 days: 93% (35-99%)
							≥14 days: 53% 9-29-83%)	≥14 days: 93% (64-99%)
					[NOTE: Participants either received Covaxin or Covishield (AZD1222)]			
		(279)	Prospective cohort	January to April 2021 Spain.	20,961	Infection	44% (31-54%)	
						Symptomatic infection	50% (37-61%)	
						Symptomatic infection – 18-59 years old	50% (34-62%)	

						Symptomatic infection - ≥60 years old	53% (19-72%)	
						Hospitalisation	92% (46-99%)	
		(294)	Retrospective cohort	1/6/2020 to 31/5/2021 India.	11,405	Infection (with evidence of prior infection)		≥14 days: 91.1% (84.1-94.9%)
						Infection (without evidence of prior infection)		≥14 days: 31.8% (23.5-39.1%)
					[NOTE: 5.77% of participants received Covaxin, 94.23% received Covishield (AZD1222)]			
		(280)	Prospective cohort	8/10/2020 to 22/2/2021 Scotland	409,588	Hospitalisation	0-6 days: 72% (66-77%)	
							7-13 days: 68% (61-73%)	
							14-20 days: 73% (66-79%)	
							21-27 days: 81% (72-87%)	
							28-34 days: 88% (75-94%)	
							35-41 days: 97% (63-100%)	
							≥42 days: 59% (–296-96%)	
		(295)	Cohort	17/1/2021 to 11/5/2021 Brazil.	313,328	Death	≥21 days: 94.4% (93.9-94.8%)	≥21 days: 99.8 (99.6-99.9%)
						Death – 75-79 years old	≥21 days: 88% (85.8-90%)	
						Death – 80-89 years old	≥21 days: 96.8% (96.5-97.2%)	
						Death - ≥90 years old	≥21 days: 99.2% (99.1-99.4%)	
		(296)	Retrospective cohort	18/1/2021 to 30/6/2021 Brazil.	60,577, 870	Infection	≥14 days: 34% (33.2-34.7%)	0-13 days: 56.9% (55.3-58.5%)
								≥14 days: 70% (68.6-71.3%)
						Hospitalisation	≥14 days: 52.2% (50.9-53.4%)	0-13 days: 69.6% (67.2-71.8%)
								≥14 days: 86.8% (85.2-88.2%)
						ICU admission	≥14 days: 54% (51.8-56%)	0-13 days: 69.2% (65-72.8%)
								≥14 days: 88.1% (85.4-90.3%)
						Death	≥14 days: 49.3% (47-51.5%)	0-13 days: 72.1% (69.1-74.9%)
								≥14 days: 90.2% (88.3-91.8%)
Johnson & Johnson (Ad26.COV2.S) - Recombinant, replication-incompetent adenovirus serotype 26 (Ad26) vector.	One dose (0.5ml) intramuscularly (deltoid).	(172)	Randomised controlled trial	21/9/2020 to 22/1/2021 Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, US.	39,321	Moderate to severe-critical infection	≥14 days: 66.9% (59.0-73.4%)	
							≥28 days: 66.1% (55.0-74.8%)	
						Severe-critical infection	≥14 days: 76.7% (54.6-89.1%)	
							≥28 days: 85.4% (54.2-96.9%)	
		(297)	Test-negative case-control	25/6/2021 to 30/9/2021 Brazil.	11,817	Symptomatic infection	14-27 days: 27.4% (8.7-42.7%)	
							≥28 days: 50.9% (35.5-63.0%)	
						Hospitalisation	14-27 days: 33.5% (-29.1-69.8%)	
							≥28 days: 72.9% (35.1-91.1%)	
						Admission to an ICU	14-27 days: 56.0% (-52.8-93.1%)	
							≥28 days: 92.5% (54.9-99.6%)	
							14-27 days: 65.2% (-74.7-98.1%)	

						Mechanical ventilation	≥28 days: 88.7% (17.9-99.5%)	
						Death	14-27 days: 48.9% (-92.3-92.5%)	
							≥28 days: 90.5% (31.5-99.6%)	
		(298)	Retrospective case-control	27/2/2021 to 14/4/2021 US.	126,572	Symptomatic infection	≥1 day: 50.6% (14.0-74.0%)	
							≥8 days: 65.5% (23.3-87.5%)	
							≥15 days: 76.7% (30.3-95.3%)	
		(299)	Test-negative case-control	1/7/2021 to 31/7/2021 US.	1,000	Symptomatic infection	51% (95% CI: -2-76%)	
		(256)	Observational	14/12/2020 to 14/8/2021 US.	Delta: 2,840 Pre-Delta: 7,012	Infection – Delta	14–119 days: 85% (68-93%)	
							120–149 days: 81% (34-95%)	
							≥150 days: 73% (49-86%)	
						Infection – Pre-Delta	91% (81-96%)	
					[NOTE: 2% of study participants received Ad26.COV2.S (65% received BNT162b2, and 33% received mRNA-1273)]			
		(300)	Cohort	March to July 2021 US.	1,914,670	Infection	79% (77-80%)	
						Hospitalisation	81% (79-84%)	
		(301)	Retrospective cohort	27/2/2021 to 22/7/2021 US.	97,787	Infection	≥1 day: 73.6% (65.9-79.9%)	
							≥8 days: 72.9% (64.2-79.9%)	
							≥15 days: 74.2% (64.9-81.6%)	
		(282)	Prospective cohort	1/5/2021 to 3/9/2021 US.	8,690,825	Infection - 18-49 years old		≥14 days: 89% (86.5-91.5%)
						Infection - 50-64 years old		≥14 days: 86.1% (82.5-89.6%)
						Infection - ≤65 years old		≥14 days: 80.8% (75.2-86.5%)
						Hospitalisation - 18-49 years old		≥14 days: 95.7% (91.1-98.3%)
						Hospitalisation - 50-64 years old		≥14 days: 87.5% (82.4-91.4%)
						Hospitalisation - ≤65 years old		≥14 days: 85.2% (81.1-88.6%)
Moderna (mRNA-1273) - mRNA	Two doses (100µg, 0.5ml each) intramuscularly (deltoid) with a recommended interval of 28 days between doses.	(245)	Test-negative case-control	14/12/2020 to 3/8/2021 Canada.	682,071	Symptomatic infection – Alpha	≥14 days: 83% (80-86%)	≥7 days: 92% (86-96%)
						Symptomatic infection – Beta or Gamma	≥14 days: 77% (63-86%)	
						Symptomatic infection – Delta	≥14 days: 72% (57-82%)	
						Hospitalisation - Alpha	≥14 days: 79% (74-83%)	≥7 days: 94% (89-97%)
						Hospitalisation – Beta or Gamma	≥14 days: 89% (73-95%)	
						Hospitalisation - Delta	≥14 days: 96% (72-99%)	
		(246)	Retrospective case-control	January to July 2021 US.	60,083	Infection		≥14 days: 86% (81-90.6%)
						Hospitalisation		≥14 days: 91.6% (81-97%)
						Admission to an ICU		≥14 days: 93.3% (57-99.8%)
		(250)	Test-negative case-control	17/1/2021 to 5/6/2021 Canada.	5,8476	Infection	≥14 days: 68.7% (59.5-75.9%)	≥7 days: 84.1% (34.9-96.1%)
		(252)	Test-negative case-control	23/3/2021 to 7/9/2021	1 dose: 490,828	Infection - Delta	≥14 days: 79.7% (60.8-89.5%)	≥14 days: 86.1% (78.0-91.3%)

				Qatar.	2 doses: 409,041			
		(255)	Observational	1/3/2021 to 1/8/2021 US.	10,428,783	Infection – Pre-Delta period		≥14 days: 74.7% (66.2-81.1%)
						Infection – Intermediate period		≥14 days: 70.4% (60.1-78.0%)
						Infection – Delta		≥14 days: 50.6% (45.0-55.7%)
		(256)	Observational	14/12/2020 to 14/8/2021 US.	Delta: 2,840 Pre-Delta: 7,012	Infection – Delta		14–119 days: 85% (68-93%)
								120–149 days: 81% (34-95%)
								≥150 days: 73% (49-86%)
						Infection – Pre-Delta		91% (81-96%)
					[NOTE: 33% of study participants received mRNA-1273 (2% received Ad26.COV2.S, and 65% received BNT162b2)]			
		(258)	Observational	1/12/2020 to 1/8/2021 UK.	384,543	Infection - Delta	75% (64-83%)	
		(259)	Observational	April to May 2021. Canada	124	Infection		52.5% (26.9-69.1%)
						Symptomatic infection		65.6% (33.8-82.1%)
						Severe infection		78.6% (47.9-91.2%)
		(272)	Retrospective cohort	1/1/2021 to 31/3/2021 US.	4,722	Infection	>14 days after first, ≤14 days after second: 91.2% (80.6-96.1%)	
								>14 days: 98.6% (90.1-99.8%)
		(273)	Prospective cohort	14/12/2020 to 10/4/2021 US.	3,975	Infection	≥14 days after first, <14 days after second: 83% (40-95%)	
								≥14 days: 82% (20-96%)
		(177)	Randomised controlled trial	27/7/2020 to 23/10/2020 US.	30,420	Infection		≥14 days: 94.1% (89.3-96.8%)
						Infection - ≥18 to <65 years of age		≥14 days: 95.6% (90.6-97.9%)
						Infection - ≥65 years of age		≥14 days: 86.4% (61.4-95.2%)
		(302)	Retrospective cohort	16/7/2021 to 15/8/2021 US.	827	Infection		≥14 days: 56.6% (42.0-67.5%)
						Symptomatic infection		≥14 days: 84.2% (56.4-94.3%)
		(303)	Retrospective cohort	22/12/2020 to 2/2/2021 US.	4,028	Infection	8-42 days: 77.5% (61.2-87%)	
							15-42 days: 95% (86-98.2%)	
		(304)	Test negative case-control	28/10/2020 to 10/5/2021 Qatar.	256,037	Infection – Alpha	0-6 days: 2.4% (0-21.7%)	0-6 days: 98.0% (94.7-99.5%)
							7-13 days: 0.0% (0.0-11.9%)	7-13 days: 99.2% (95.3-100.0%)
							14-20 days: 81.6% (73.1-87.8%)	
							21-27 days: 94.4% (89.1-97.5%)	
						Infection - Beta	0-6 days: 4.2% (0-15.1%)	0-6 days: 94.2% (92.1-95.9%)
							7-13 days: 0.0% (0.0-0.0%)	7-13 days: 96.4% (94.3-97.9%)
							14-20 days: 47.9% (39.5-55.2%)	
							21-27 days: 73.7% (67.6-78.8%)	
						Any severe, critical, or fatal infection	0-6 days: 18.7% (0-44.7%)	0-6 days: 100.0% (93.9-100.0%)
							7-13 days: 0.0% (0.0-10.1%)	7-13 days: 100.0% (86.9-100.0%)

							14-20 days: 70.3% (48.9-83.5%)	
							21-27 days: 92.1% (78.4-97.9%)	
		(305)	Retrospective cohort	27/4/2021 to 6/6/2021 US.	1,945	Symptomatic infection - Mesa County, US	(36% fully vaccinated) Crude vaccine effectiveness 78% (71-84%)	
						Symptomatic infection - Other Colorado counties, US	(44% fully vaccinated) Crude vaccine effectiveness 89% (88-91%)	
		(306)	Prospective cohort	18/12/2020 to 31/03/2021 US.	705,756	Infection		87.4% (85.6-89.1%
						Hospitalisation		95.8% (92.5-97.6%)
						Hospital death		97.9% (84.5-99.7%
		(307)	Test-negative case control	1/3/2021 to 27/7/2021 US.	8153 cases and matched controls.	Infection - Alpha	≥14 days: 90.1 (82.9 to 94.2)	≥14 days: 98.4 (96.9 to 99.1)
						Infection – Delta	≥14 days: 77.0% (60.7-86.5%)	≥14 days: 86.7% (84.3-88.7%)
						Infection – Epsilon	≥14 days: 76.3% (48.1-89.1%)	≥14 days: 97.6% (90.2-99.4%)
						Infection – Gamma	≥14 days: 74.2% (43.8-88.1%)	≥14 days: 95.5% (90.9-97.8%)
						Infection – Iota	≥14 days: 88.8% (0.7-98.7%)	≥14 days: 95.7% (81.7-99.0%)
						Infection – Mu	≥14 days: 45.8% (0.0-88.9%)	≥14 days: 90.4% (73.9-96.5%)
						Infection – Other	≥14 days: 84.3% (65.9-92.7%)	≥14 days: 96.4% (91.2-98.5%)
						Infection - Unidentified	≥14 days: 67.6% (57.1-75.6%)	≥14 days: 79.9% (76.9-82.5%)
		(278)	Test-negative case-control	January to March 2021 US.	1,843	Infection	≥14 days: 81.7% (74.3-86.9%)	≤2 days: 81.7% (74.3-86.9%)
								3-6 days: 81.7% (74.3-86.9%)
								≥7 days: 93.5% (86.5-96.9%)
						[NOTE: 24% of case-patients and 22% of controls received mRNA-1273, remainder received BNT162b2]		
		(282)	Prospective cohort	1/5/2021 to 3/9/2021 US.	8,690,825	Infection - 18-49 years old		≥14 days: 96.3% (95.4-97.2%)
						Infection - 50-64 years old		≥14 days: 97.3% (96.4-98.1%)
						Infection - ≤65 years old		≥14 days: 96.0% (95.1-96.9%)
						Hospitalisation - 18-49 years old		≥14 days: 96.6% (94.3-98.1%)
						Hospitalisation - 50-64 years old		≥14 days: 97.3% (95.9-98.2%)
						Hospitalisation - ≤65 years old		≥14 days: 97.1% (96.5-97.6%)
		(308)	Randomised controlled trial	27/7/2020 to 23/10/2020 US.	30,415	Asymptomatic infection		63.0% (56.6-68.5%)
						Symptomatic infection		93.2% (91.0-94.8%)
						Severe infection		98.2% (92.8-99.6%)
						Death		100.0% (NE-100.0%)
Sinopharm BBIBP-CorV - Aluminium-hydroxide-adjuvanted, inactivated whole virus vaccine	Two doses (0.5ml) intramuscularly (deltoid) with a recommended interval of 3 weeks between doses.	(309)	Test-negative case-control	18/5/2021 to 20/6/2021 China.	366	Infection	13.8% (-60.2-54.8%)	59.0% (16.0-81.6%)
						Moderately severe infection		70.2% (29.6-89.3%)
						[NOTE: 27.5% of study participants were vaccinated with Sinopharm BIBP (61.3% received CoronaVac)]		
		(310)	Retrospective cohort	May to June 2021 China.	10,813	Infection with Pneumonia – Delta	8.4% (-47.6-64.4%)	69.5% (42.8-96.3%)
						Severe/critical disease -Delta	100% (NA)	100% (NA)
		(311)	Retrospective cohort	9/2/2021 to 30/6/2021	606,772	Infection	≥14 days: 15·3 (12·7 to 17·8	≥14 days: 49·2 (47·9 to 50·4)
						COVID-19 mortality	≥14 days: 45.2% (28.8-57.8%)	≥14 days: 93.9% (90.9-95.9%)

				Peru.		Infection - ≥60 years old	≥14 days: 14.1% (5.2-22.2%)	≥14 days: 54.7% (50.7-58.3%)
						COVID-19 mortality - ≥60 years old	≥14 days: 25.5% (-10.2-49.7%)	≥14 days: 90.6% (83.8-94.5%)
		(312)	Randomised controlled trial	16/7/2020 to 20/12/2020 UAE, Bahrain.	40,382	Infection		≥14 days: 73.5% (60.6-82.2%)
						Symptomatic infection		≥14 days: 78.1% (64.8-86.3%)
						Severe infection		≥14 days: 100% (NA)
		(313)	Retrospective cohort	1/9/2020 to 1/5/2021 UAE.	176,640	Hospitalisation	-20% (-28.6-11.8%)	79.8% (78-81.4%)
						Critical care admission	3.7% (-12.8-18.1%)	92.2% (89.7-94.1%)
						Death	27.9% (-61-72.6%)	97.1% (83-99.9%)
		(314)	Observational	9/12/2020 to 17/7/2021 Bahrain.	569,054	Symptomatic infection		45.5%
						Hospitalisation		44.5%
						Hospitalisation - >50 years old		72%
						Death		63%
Sinovac-CoronaVac - Aluminium-hydroxide-adjuvanted, inactivated whole virus vaccine	Two doses (0.5ml) intramuscularly (deltoid) with a recommended interval window of 2 to 4 weeks.	(309)	Test-negative case-control	18/5/2021 to 20/6/2021 China.	366	Infection	13.8% (-60.2-54.8%)	59.0% (16.0-81.6%)
						Moderately severe infection		70.2% (29.6-89.3%)
					[NOTE: 61.3% of study participants were vaccinated with CoronaVac (27.5% recieved Sinopharm BIBP)]			
		(315)	Observational	2/2/2021 to 1/5/2021 Chile.	10,187, 720	Infection	17.2% (15.8–18.6%)	63.7% (62.8–64.6%)
						Hospitalisation	40.3% (37.6–42.8%)	86.5% (85.6–87.4%)
						Admission to an ICU	45.3% (41.2–49.2%)	90.2% (88.9–91.4%)
						Death	46.0% (40.7–50.8%)	86.7% (84.9–88.3%)
		(316)	Test-negative case-control	17/1/2021 to 29/4/2021 Brazil.	43,774	Symptomatic infection - Gamma	0-13 days: −0.8% (−9.4 to 7.2%)	0-13 days: 24.7% (14.7 to 33.4%)
							≥14 days: 12.5% (3.7 to 20.6%)	≥14 days: 46.8% (38.7 to 53.8%)
						Hospitalisation - Gamma	0-13 days: 6.6% (−4.3 to 16.3%)	0-13 days: 39.1% (28.0 to 48.5%)
							≥14 days: 16.9% (5.7 to 26.8%)	≥14 days: 55.5% (46.5 to 62.9%)
						Death - Gamma	0-13 days: 13.1% (−1.5 to 25.6%)	0-13 days: 48.9% (34.4 to 60.1%)
							≥14 days: 31.2% (17.6 to 42.5%)	≥14 days: 61.2% (48.9 to 70.5%)
		(317)	Test-negative case-control	19/1/2021 to 13/4/2021 Brazil.	53,153	Infection – Gamma	≥14 days: 49.4% 13.2-71.9%)	≥14 days: 37.1% (-53.3-74.2%)
						Infection	≥14 days: 35.1% (-6.6-60.5%)	37.9% (-46.4-73.6%)
		(115)	Prospective cohort	February to March 2021 Brazil.	20,187	Infection		≥14 days: 50.7% (33.3-62.5%)
								≥21 days: 51.8% (30-66.0%)
								≥28 days: 68.4% (51-80.8%)
								≥35 days: 73.8% (57-84.8%)
		(318)	Test-negative case-control	15/3/2021 to 3/10/2021 Brazil.	19,838	Symptomatic infection – Pregnant women	≥14 days: 5.02% (-18.22-23.69%)	≥14 days: 40.97% (27.07-52.22%)
						Severe infection – Pregnant women	≥14 days: 67.74% (20-87%)	≥14 days: 85.39% (59.44-94.80%)
		(319)			2,656	Symptomatic infection – Gamma	≥14 days: 49.6% (11.3-71.4%)	

			Test-negative case-control	19/1/2021 to 25/3/2021 Brazil.		Symptomatic infection	≥14 days: 35.1% (-6.6-60.5%)	
		(320)	Randomised controlled trial	14/9/2020 to 5/1/2021 Turkey.	10,029	Symptomatic infection	14-27 days: 46.4% (0.4-71.2%)	≥14 days: 83.5% (65.4-92.1%)
						Hospitalisation		≥14 days: 100% (20.4-100%)
		(321)	Randomised controlled trial	21/7/2020 to 16/12/2020 Brazil.	9,823	Infection	≤14 days: -3.3% (-4.8- -1.9%)	≥14 days: 50.7% (35.9-62%)
							14-28 days: 94.0% (55.1-99.2%)	
							≤28 days: 42.5% (32.9-50.7%)	
							≤42 days: 56.5% (49.6-62.5%)	
							≤56 days: 60.4% (56.5-63.9%)	
							≤70 days: 54.7% (53.2-56.1%)	
							≤84 days: 53.7% (52.7-54.7%)	
							≤98 days: 52.5% (51.9-53.1%)	
						Infection requiring medical assistance (hospitalisation)		≥14 days: 83.7% (58.0-93.7%)
						Moderate infection		≥14 days: 100% (56.4-100%)
						Severe infection or death		≥14 days: 100% (16.9-100%)
						Infection - <21 days between 2 doses		≥14 days: 49.1% (33-61.4%)
						Infection - ≥21 days between 2 doses		≥14 days: 62.3% (13.9-83.5%)
		(295)	Cohort	17/1/2021 to 11/5/2021 Brazil.	313,328	Death	≥21 days: 95.1% (94.7-95.5%)	≥21 days: 99.1% (98.9-99.3%)
						Death – 75-79 years old	≥21 days: 86.3% (84.7-87.7%)	
						Death – 80-89 years old	≥21 days: 97.6% (97.2-97.9%)	
						Death - ≥90 years old	≥21 days: 99.3% (99.1-99.5%)	
		(296)	Retrospective cohort	18/1/2021 to 30/6/2021 Brazil	60,577, 870	Infection	≥14 days: 16.4% (15.2-17.5%)	0-13 days: 40.3% (39.4-41.2%)
								≥14 days: 54.2% (53.4-55.0%)
						Hospitalisation	≥14 days: 26.6% (24.6-28.4%)	0-13 days: 57.3% (56.0-58.6%)
								≥14 days: 72.6% (71.6-73.6%)
						ICU admission	≥14 days: 28.1% (24.9-31.1%)	0-13 days: 58.1% (55.9-60.1%)
								≥14 days: 74.2% (72.6-75.7%)
						Death	≥14 days: 29.4% (26.7-32.0%)	0-13 days: 58.7% (56.9-60.4%)
								≥14 days: 74% (72.6-75.3%)
Bharat Biotech – Covaxin – whole virion inactivated virus vaccine	Two doses (0.5ml) intramuscularly (deltoid) with a recommended interval window of 28 days.	(322)	Randomised controlled trial	16/11/2020 to 7/1/2021 India.	25 798	Symptomatic infection		≥14 days: 77.8% (65.2-86.4%)
						Severe disease		≥14 days: 93.4% (57.1-99.8%)
						Symptomatic infection – 18-59 years old		≥14 days: 79.4% (66.0-88.2%)
						Symptomatic infection - ≥60 years old		≥14 days: 67.8% (8.0-90.0%)
						Symptomatic infection – participants with pre-existing chronic medical condition		≥14 days: 66.2% (33.8-84.0%)
						Asymptomatic infection		≥14 days: 63.6% (29.0-82.4%)

						Symptomatic or asymptomatic infection		≥14 days: 68.8% (46.7-82.5%)
		(323)	Test-negative case-control	15/4/2021 to 15/5/2021 India.	3,732	Symptomatic infection	<7 days: 40% (-21-71%)	<14 days: 27% (-35-61%)
							≥7 days: 1% (-30-25%)	≥14 days: 50% (33-62%)
							≥21 days: –1% (-51-33%)	≥28 days: 46% (22-62%)
								≥42 days: 57% (21-76%)
		(293)	Cross-sectional observational	1/5/2021 to 31/5/2021 India.	583	Infection	<14 days: 15% (-68-57%)	<14 days: 66% (34-81%)
							≥14 days: 44% (7-66%)	≥14 days: 83% (73-89%)
						Hospitalisation	<14 days: 43% (-68-81%)	<14 days: 83% (17-96%)
							≥14 days: 76% (21-92%)	≥14 days: 88% (55-97%)
						ICU admission or death	<14 days: 62% (-27-89%)	<14 days: 93% (35-99%)
							≥14 days: 53% 9-29-83%)	≥14 days: 93% (64-99%)
					[NOTE: Participants either received Covaxin or Covishield (AZD1222)]			
		(294)	Retrospective cohort	1/6/2020 to 31/5/2021 India.	11,405	Infection (with evidence of prior infection)		≥14 days: 91.1% (84.1-94.9%)
						Infection (without evidence of prior infection)		≥14 days: 31.8% (23.5-39.1%)
					[NOTE: 5.77% of participants received Covaxin, 94.23% received Covishield (AZD1222)]			
		(324)	Retrospective cohort	3/3/2020 to 18/6/2021 India.	15,244	Reinfection		86% (77-92%)
						Symptomatic reinfection		87% (76-93%)
						Asymptomatic reinfection		84% (47-95%)
Novavax – NVX-CoV2373 (Nuvaxovid) or Serum Institute of India – COVOVAX (Novavax formulation - recombinant SARS-CoV-2 S protein nanoparticle as a coformulation with the adjuvant Matrix-M	Two doses (0.5 ml) intramuscularly (deltoid) with a recommended interval of 3-4 weeks.	(325)	Randomised controlled trial	28/9/2020 to 28/10/2020 UK.	14,039	Infection		89.7% (80.2-94.6%)
						Infection – 18 to 64 years old		89.8% (79.7-95.5%)
						Infection – 65 to 84 years old		88.9% (20.2-99.7%)
						Infection – Alpha		86.3% (71.3-93.5%)
						Infection – Non-Alpha		96.4% (73.8-99.5%)
		(326)	Randomised controlled trial	27/12.2020 to 18/2/2021 US, Mexico.	29,949	Infection		≥7 days: 89.3% (81.6-93.8%)
						Infection – COVID-19 high risk group		≥7 days: 91.0% (83.6-95.0%)
		(327)	Randomised controlled trial	28/9/2020 to 28/10/2020 UK.	15,139	Infection		89.8% (79.7-95.5%)
						Infection – 18-64 years old		87.5% (–0.2-98.4%)
		(328)	Randomised controlled trial	17/7/2020 to 25/11/2020 South Africa.	2,684	Symptomatic infection		≥7 days: 49.4% (6.1-72.8%)
						Symptomatic infection – Beta		≥7 days: 51.0% (-0.6-76.2%)

Vaccine type	Vaccine	Company	Countries approved for use in	Clinical trials
Inactivated virus	**KoviVac**	Chumakov Center (Moscow, Russia)	***3 countries:*** Belarus, Cambodia, Russian Federation	Phase 1: 502 (Russian Federation). Phase 2: 502 (Russian Federation). 622 (Russian Federation).
	QazVac	Kazakhstan Research Institute for Biological Safety Problems (RIBSP) (Kazakhstan)	***2 countries:*** Kazakhstan, Kyrgyzstan	Phase 1: NCT04530357 (Kazakhstan). Phase 2: NCT04530357 (Kazakhstan). Phase 3: NCT04691908 (Kazakhstan).
	KCONVAC	Minhai Biotechnology Co. (Beijing, China)	***2 countries:*** China, Indonesia	Phase 1: NCT05003479 (China). ChiCTR2000038804, NCT04758273 (China). Phase 2: ChiCTR2000039462, NCT04756323 (China). NCT05003466 (China). Phase 3: NCT04852705
	COVIran Barekat	Shifa Pharmed Industrial Co. (Tehran, Iran)	***1 country:*** Iran	Phase 1: IRCT20201202049567N1 (Iran). IRCT20201202049567N2 (Iran). IRCT20171122037571N3 (Iran). Phase 2: IRCT20201202049567N3 (Iran). IRCT20171122037571N3 (Iran). Phase 3: IRCT20201202049567N3 (Iran).
	Inactivated (Vero Cells)	Sinopharm (Wuhan, China)	***2 countries:*** China, Philippines	Phase 1: ChiCTR2000031809 (China) Phase 2: NCT04885764 (Egypt). ChiCTR2000031809 (China). Phase 3: NCT04885764 (Egypt). ChiCTR2000034780 (United Arab Emirates). NCT04612972 (Peru). NCT04510207 (Bahrain, Egypt, Jordan, United Arab Emirates). ChiCTR2000039000 (Morocco).
	Turkovac	Health Institutes of Turkey (Istanbul, Turkey)	***1 country:*** Turkey	Phase 1: NCT04691947 (Turkey). Phase 2: NCT04824391 (Turkey). NCT04979949 (Turkey). NCT05035238 (Turkey). Phase 3: NCT04942405 (Turkey). NCT05077176 (Turkey).
	FAKHRAVAC (MIVAC)	Organization of Defensive Innovation and Research (Tehran, Iran)	***1 country:*** Iran	Phase 1: IRCT20210206050259N1 (Iran). Phase 2: IRCT20210206050259N2 (Iran). Phase 3: IRCT20210206050259N3 (Iran).
Non-replicating viral vector	**Convidecia**	CanSino (Tianjin, China)	***10 countries:*** Argentina, Chile, China, Ecuador, Hungary, Indonesia, Malaysia, Mexico, Pakistan, Republic of Moldova	Phase 1: NCT05043259 (China). ChiCTR2000030906, NCT04313127 (China). NCT04568811 (China). NCT04840992 (China). Phase 2: NCT05043259 (China). NCT05162482 (Pakistan). NCT04840992 (China). ChiCTR2000031781, NCT04341389 (China). NCT04566770 (China). NCT05005156 (Argentina). Phase 3: NCT05169008 (Chile, Mexico). NCT04526990 (Argentina, Chile, Mexico, Pakistan, Russian Federation). NCT04540419 (Russian Federation).
	Sputnik Light	Gamaleya Research Institute of Epidemiology and	***24 countries:*** Angola, Argentina, Armenia, Bahrain, Belarus, Cambodia, Egypt, Iran, Kazakhstan,	Phase 1: NCT04713488 (Russian Federation). Phase 2: NCT04713488 (Russian Federation).

		Microbiology (Moscow, Russia)	Kyrgyzstan, Lao People's Democratic Republic, Mauritius, Mongolia, Nicaragua, Philippines, Republic of the Congo, Russian Federation, San Marino, Tunisia, Turkmenistan, United Arab Emirates, United Republic of Tanzania, Venezuela, West Bank	NCT05027672 (Argentina). Phase 3: NCT04741061 (Russian Federation).
	Sputnik V	Gamaleya Research Institute of Epidemiology and Microbiology (Moscow, Russia)	***74 countries:*** Albania, Algeria, Angola, Antigua and Barbuda, Argentina, Armenia, Azerbaijan, Bahrain, Bangladesh, Belarus, Bolivia, Bosnia and Herzegovina, Brazil, Cambodia, Cameroon, Chile, Djibouti, Ecuador, Egypt, Gabon, Ghana, Guatemala, Guinea, Guyana, Honduras, Hungary, India, Indonesia, Iran, Iraq, Jordan, Kazakhstan, Kenya, Kyrgyzstan, Lao People's Democratic Republic, Lebanon, Libya, Maldives, Mali, Mauritius, Mexico, Mongolia, Montenegro, Morocco, Myanmar, Namibia, Nepal, Nicaragua, Nigeria, North Macedonia, Oman, Pakistan, Panama, Paraguay, Philippines, Republic of Moldova, Republic of the Congo, Russian Federation, Rwanda, Saint Vincent and the Grenadines, San Marino, Serbia, Seychelles, Sri Lanka, Syrian Arab Republic, Tunisia, Turkey, Turkmenistan, United Arab Emirates, Uzbekistan, Venezuela, Vietnam, West Bank, Zimbabwe	Phase 1: NCT04760730 (United Arab Emirates). NCT04684446 (Belarus, Russian Federation). NCT04436471, 241 (Russian Federation). NCT04437875 (Russian Federation). Phase 2: NCT05027672 (Argentina). NCT04988048 (Argentina). NCT04954092 (Russian Federation). NCT04962906 (Argentina). NCT04983537 (Argentina). NCT04760730 (United Arab Emirates). NCT04684446 (Belarus, Russian Federation). NCT04686773 (Azerbaijan). NCT04436471, 241 (Russian Federation). NCT04437875 (Russian Federation). NCT04587219 (Russian Federation). NCT04640233 (India). Phase 3: NCT04564716 (Belarus). NCT04530396 (Russian Federation). NCT04642339 (Venezuela). NCT04656613 (United Arab Emirates). NCT04954092 (Russian Federation). NCT04640233 (India).
RNA	**TAK-919 (Moderna formulation)**	Takeda (Tokyo, Japan)	***1 country:*** Japan	Phase 1: NCT04677660 (Japan). Phase 2: NCT04677660 (Japan).
DNA	**ZyCoV-D**	Zydus Cadila (Ahmedabad, India)	***1 country:*** India	Phase 1: CTRI/2020/07/026352 (India). CTRI/2021/03/032051 (India). Phase 2: CTRI/2020/07/026352 (India). CTRI/2021/03/032051 (India). Phase 3: CTRI/2021/01/030416 (India).
Protein subunit	**ZF2001**	Anhui Zhifei Longcom (Hefei, China)	***3 countries:*** China, Indonesia, Uzbekistan	Phase 1: NCT04445194 (China). NCT04636333 (China). NCT04550351, ChiCTR2000035691 (China). NCT04961359 (China). Phase 2: NCT04466085 (China). NCT05109598 (China). NCT04813562 (China). Phase 3: NCT05091411 (China). NCT05128643 (China). NCT05107375 (China). ChiCTR2000040153, NCT04646590 (China, Ecuador, Indonesia, Pakistan, Uzbekistan). ChiCTR2100050849 (China).
	Abdala	Center for Genetic Engineering and Biotechnology (CIGB) (Havana, Cuba)	***6 countries:*** Cuba, Mexico, Nicaragua, Saint Vincent and the Grenadines, Venezuela, Vietnam	Phase 1: RPCEC00000345 (Cuba). RPCEC00000346 (Cuba). Phase 2: RPCEC00000345 (Cuba) RPCEC00000346 (Cuba).

				Phase 3: RPCEC00000359 (Cuba).
	EpiVacCorona	FBRI (Koltsovo, Russia)	***4 countries:*** Cambodia, Russian Federation, Turkmenistan, Venezuela	Phase 1: NCT04527575 (Russian Federation). Phase 2: NCT04527575 (Russian Federation). Phase 3: NCT04780035 (Russian Federation). NCT05021016 (Russian Federation)
	Aurora-CoV	FBRI (Koltsovo, Russia)	***1 country:*** Russian Federation	Phase 1: 197 (Russian Federation). Phase 2: 197 (Russian Federation).
	MVC-COV1901	Medigen Biotechnology Corp. (Taipei City, Taiwan)	***2 countries:*** Somaliland, Taiwan	Phase 1: NCT05132855 (Taiwan). NCT04487210 (Taiwan). Phase 2: NCT05132855 (Taiwan). NCT04695652 (Taiwan, Vietnam). NCT04822025 (Taiwan). NCT04951388 (Taiwan). NCT05038618 (Taiwan). NCT05048849 (Taiwan). NCT05054621 (Taiwan). Phase 3: NCT05011526 (Paraguay)
	SpikoGen	Vaxine/CinnaGen Co. (Iran)	***1 country:*** Iran	Phase 1: NCT04453852 (Australia). Phase 2: IRCT20150303021315N23 (Iran). NCT04944368, IRCT20150303021315N23 (Iran). NCT05148871 (Australia). Phase 3: NCT05005559, IRCT20150303021315N24 (Iran). NCT05148871 (Australia). NCT05175625, IRCT20150303021315N26 (Iran).
	Corbevax	Biological E Limited (Telangana, India)	***1 country:*** India	Phase 1: CTRI/2020/11/029032 (India). Phase 2: CTRI/2020/11/029032 (India). CTRI/2021/06/034014 (India). CTRI/2021/10/037066 (India). Phase 3: CTRI/2021/06/034014 (India). CTRI/2021/08/036074 (India). CTRI/2021/10/037066 (India).
	Soberana 02	Instituto Finlay de Vacunas Cuba (Havana, Cuba)	***4 countries:*** Cuba, Iran, Nicaragua, Venezuela	Phase 1: IFV/COR/06 (Cuba). Phase 2: IFV/COR/08 (Cuba). Phase 3: IFV/COR/09 (Cuba).
	Soberana Plus	Instituto Finlay de Vacunas Cuba (Havana, Cuba)	***1 country:*** Cuba	Phase 1: IFV/COR/15 (Cuba). IFV/COR/05 (Cuba). Phase 2: IFV/COR/11 (Cuba). IFV/COR/15 (Cuba). Phase 3: IFV/COR/09 (Cuba).
	Razi Cov Pars	Razi Vaccine and Serum Research Institute (Karaj, Iran)	***1 country:*** Iran	Phase 1: IRCT20201214049709N1 (Iran). Phase 2: IRCT20201214049709N2 (Iran). Phase 3: IRCT20201214049709N3 (Iran).
	Recombinant SARS-CoV-2 Vaccine (CHO Cell)	National Vaccine and Serum Institute (Beijing, China)	***1 country:*** United Arab Emirates	Phase 1: NCT04869592 (China). Phase 2: NCT04869592 (China) Phase 3: NCT05069129 (United Arab Emirates)

Supplementary file 1:

1a: Specific database search terms:

"transmission", "host cell entry", "clinical presentation", "symptoms", "risk factors", "genetic risk", "coronavirus", "structure", "genetics", "replication", open reading frame", "structural proteins", "accessory proteins", "spike", "receptor binding domain", "mutation", "variant of concern", "variant of interest", "alpha", "beta", "gamma", "delta", "omicron", "lambda", "mu", "pfizer", "BNT162b2", "oxford-AtraZeneca", "AZD1222", "ChAdOx1", "johnson and johnson", "janssen", "Ad26.COV.2.S", "moderna", "mrna-1273", "sinopharm", "BBIBP-CorV", "sinovac", "CoronaVac", "bharat biotech", "Covaxin", "BBV152", "Novavax", " Coalition for Epidemic Preparedness Innovations", "Covovax", "Nuvaxovid", "NVX-CoV2372", "immunogenicity" "antibody", "neutralisation", "reactogenicity", "safety", "adverse events", "effectiveness", "efficacy", "immunity", "booster", "treatment", "therapy", "guideline", "recommendations".

1b: Selection of studies (inclusion/exclusion criteria):

Virology studies – preference was given to studies directly examining/discussing SARS-CoV-2, however, useful papers that explored the structure, genetics, and virology of coronaviruses in general were considered.

Variant studies – in general, large epidemiological studies that explored the prevalence and risk of certain outcomes (e.g. hospitalisation, death, etc.) with COVID-19 infection for certain variants were included. Authors aimed to include studies from multiple countries.

Vaccine studies – Studies with human derived data (e.g. blood sera, phase 1/2 trials) were of greatest interest when collating information on immunogenicity, reactogenicity, and safety. Large randomised controlled trials, test-negative case-control, and observational studies were of selected when exploring vaccine efficacy. Review articles summarising effectiveness studies were excluded, unless a meta-analysis was performed.

Variants of concern			
WHO nomenclature or designation	**Pango Lineage**	**S protein mutations of interest**	**First detected samples ***
Alpha	B.1.1.7	N501Y D614G P681H	UK, Sept 2020
Beta	B.1.351	N501Y D614G E484K K417N A701V	South Africa, May 2020
Gamma	P.1	N501Y D614G E484K K417T H655Y	Brazil, Nov 2020
Delta	B.1.617.2	L452R D614G P681R T478K	India, Oct 2020
Omicron	B.1.1.529	N501Y D614G E484A P681H K417N H655Y A67V Δ69-70 T95I G142D Δ143-145 N211I Δ212 ins215EPE G339D S371L S373P S375F N440K G446S S477N T478K Q493R G496S Q498R Y505H T547K N679K N764K D796Y N856K Q954H N969K L981F	South Africa and Botswana, Nov 2021
Variants of Interest			
WHO nomenclature or designation	**Pango Lineage**	**S protein mutations of interest**	**First detected samples ***
Lambda	C.37	L452Q D614G F490S	Peru, Dec 2020
Mu	B.1.621	N501Y D614G P681H R346K E484K	Columbia, Jan 2021
Variants under monitoring			
Pango Lineage		**S protein mutations of interest**	**First detected samples ***
B.1.1.318		D614G P681H E484K	Multiple countries, Jan 2021
C.1.2		N501Y D614G E484K H655Y N679K Y449H	South Africa, May 2021
B.1.640		N501Y D614G P681H F490R N394S R346S Y449N 137–145del	Multiple countries, Sep 2021

Vaccine and vaccine type	Recommended dose and administration	Study ref.	Study type	Study date and location(s)	N	Vaccine effectiveness % (95% confidence interval) *		
						Against	One dose	Two doses
Pfizer/BioNtech (BNT162b2) – mRNA.	Two doses (30µg, 0.3ml each) intramuscularly (deltoid) with a recommended interval of 21-28 days between doses.	(156)	Randomised controlled trial	27/7/2020 to 14/11/2020 US, Argentina, Brazil, South Africa, Germany, and Turkey.	37,706	Symptomatic infection		95% (90.3–97.6%)
		(241)	Observational	20/12/2020 to 1/2/2021 Israel.	1,193,236	Documented infection	46% (40-51%)	92% (88-95%)
						Symptomatic infection	57% (50-63%)	94% (87-98%)
						Hospitalisation	74% (56-86%)	87% (55-100%)
						Severe disease	62% (39-80%)	92% (75-100%)
		(242)	Test-negative case-control	26/10/2020 to 16/5/2021 UK.	19,109	Infection with Alpha	47.5% (41.6–52.8%)	93.7% (91.6–95.3%)
						Infection with Delta	35.6% (22.7–46.4%)	88.0% (85.3–90.1%)
		(243)	Test-negative case-control	1/2/2021 to 31/3/2021 Qatar.	213,758	Infection with Beta		75.0% (70.5-78.9%)
						Infection with Alpha or Beta		97.4% (92.2-99.5%)
		(244)	Test-negative case-control	14/12/2020 to 19/4/2021 Canada.	324,033	Symptomatic infection	14-20 days: 48% (41-54%)	≥7 days: 91% (89-93%)
							≥14 days: 60% (57-64%)	
							35-41 days: 71% (63-78%)	
						Hospital admission or death	14-20 days: 62% (44-75%)	≥7 days: 98% (88-100%)
							≥14 days: 70% (60-77%)	
							≥35 days: 91% (73-97%)	
						[NOTE: Participants in this study received an mRNA vaccine (either BNT162b2 or mRNA-1273)]		
		(245)	Test-negative case-control	14/12/2020 to 3/8/2021 Canada.	682,071	Symptomatic infection - Alpha	≥14 days: 66% (95% CI: 64-68%)	≥7 days: 89% (86–91%)
						Symptomatic infection - Beta or Gamma variants	≥14 days: 60% (52-67%)	≥7 days: 84% (69–92%)
						Symptomatic infection - Delta	≥14 days: 56% (45-64%)	≥7 days: 87% (64–95%)
						Against hospitalisation or death - Alpha	≥14 days: 80% (78-82%)	≥7 days: 95% (92-97%)
						Against hospitalisation or death - Beta or Gamma	≥14 days: 77% (69-83%)	≥7 days: 95% (81-99%)
						Against hospitalisation or death - Delta	≥14 days: 78% (65-86%)	
		(246)	Retrospective case-control	January to July 2021 US.	119,463	Infection		≥14 days: 86% (81-90.6%)
						Hospitalisation		≥14 days: 85% (73-93%)
						Admission to an ICU		≥14 days: 87% (46-98.6%)
		(133)	Test-negative observational	1/4/2021 to 6/6/2021 Scotland.	400,827	Infection - Alpha		92% (90–93%)
						Infection - Delta		79% (75-82%)
		(247)	Test-negative	12/4/2021 to	14,019	Hospitalisation - Alpha	83% (62-93%)	95% (78-99%)

			case-control	4/6/2021 England.		Hospitalisation - Delta	94% (46-99%)	96% (86-99%)
		(248)	Test-negative case-control	8/12/2020 to 19/2/2021. England.	156,930	Infection		10-13 days: 70% (59-78%)
								≥14 days: 89% (85-93%)
								28-34 days: 61% (51-69%)
		(249)	Test-negative case-control	4/4/2021 to 1/5/2021 Canada.	16,993	Infection	0-13 days: 14% (0-26%)	
							14-20 days: 43% (30-53%)	
							35-41 days: 75% (63-83%)	
						Infection		≥21 days: 65% (58-71%)
						Infection - non-VOC		72% (58-81%)
						Infection - Alpha		67% (57-75%)
						Infection - Gamma		61% (45-72%)
		(250)	Test-negative case-control	17/1/2021 to 5/6/2021 Canada.	5,8476	Infection	≥14 days: 70.3% (68.1-72.4%)	≥7 days: 85.5% (80.4-89.3%)
		(251)	Case-control	14/2/2021 to 3/5/2021 France.	67,760	Infection		≥7 days: 88% (81-92%)
						Infection - Alpha		≥7 days: 86% (81-90%)
						Infection - Beta/Gamma		≥7 days: 77% (63-86%)
		(252)	Test-negative case-control	23/3/2021 to 7/9/2021 Qatar.	1 dose: 906,078 2 doses: 877,354	Infection – Delta	65.5% (40.9-79.9%)	≥14 days: 59.6% (50.7-66.9%)
						Severe disease or death - Delta		97.3% (84.4-99.5%)
		(192)	Test-negative case-control	1/1/2021 to 5/9/2021 Qatar.	1 dose: 947,035 2 doses: 907,763	Symptomatic infection	0-13 days: -5.5% (-12.9-1.4%)	
							≥14 days: 47.9% (43.6-51.9%)	
							1 month: 81.5% (79.9-83.0%)	
							2 months: 72.5% (69.6-75.1%)	
							3 months: 70.6% (66.4-74.3%)	
							4 months: 57.0% (48.6-64.0%)	
							5 months: 12.0% (-6.1-27.1%)	
							6 months: 12.8% (-9.1-30.3%)	
							≥7 months: 27.8% (-1.4-48.7%)	
						Hospitalisation and death	0-13 days: 7.5% (−11.9-23.6%)	
							≥14 days: 65.0% (55.0-72.8%)	
							1 month: 95.9% (93.6-97.3%)	
							2 months: 96.3% (92.9-98.0%)	
							3 months: 93.4% (87.5-96.5%)	
							4 months: 80.8% (56.9-91.4%)	
							6 months: 81.8% (18.5-95.9%)	
							≥7 months: 44.1% (-86.5-83.3%)	
		(253)	Prospective cohort	7/12/2020 to 5/2/2021 UK.	23,324	Infection	≥21 days: 70% (55-85%)	≥7 days: 85% (74-96%)

		(254)	Observational	24/1/2021 to 3/4/2021 Israel.	186,109	Infection		≥7 days: 95.3% (94.9-95.7%)
						Asymptomatic infection		≥7 days: 91.5% (90.7-92.2%)
						Symptomatic infection		≥7 days: 97.0% (96.7-97.2%)
						Hospitalisation		≥7 days: 97.2% (96.8-97.5%)
						Severe or critical infection		≥7 days: 97.5% (97.1-97.8%)
						Death		≥7 days: 96.7% (96.0-97.3%)
		(255)	Observational	1/3/2021 to 1/8/2021 US.	10,428,783	Infection – Pre-Delta period		≥14 days: 74.2% (68.9-78.7%)
						Infection – Intermediate period		≥14 days: 66.5% (58.3-73.1%)
						Infection – Delta		≥14 days: 52.4% (48.0-56.4%)
		(256)	Observational	14/12/2020 to 14/8/2021 US.	Delta: 2,840 Pre-Delta: 7,012	Infection – Delta		14–119 days: 85% (68-93%)
								120–149 days: 81% (34-95%)
								≥150 days: 73% (49-86%)
						Infection – Pre-Delta		91% (81-96%)
					[NOTE only 65% of participants in this study received BNT162b2 (33% received mRNA-1273, and 2% received Ad26.COV2.S]			
		(257)	Observational	15/1/2021 to 16/4/2021 France.	378	Infection – Beta		≥7 days: 49% (14-69%)
						Severe disease		≥7 days: 86% (67-94%)
		(258)	Observational	1/12/2020 to 1/8/2021 UK.	384,543	Infection – Alpha	≥21 days: 59% (52-65%)	
						Infection – Delta	≥21 days: 57% (50-63%)	
						Infection – Alpha		0-13 days: 77% (66-84%)
								≥14 days: 78% (68-84%)
						Infection – Delta		0-13 days: 82% (75-87%)
								≥14 days: 80% (77-83%)
		(259)	Observational	April to May 2021. Canada	224	Infection		66.2% (2.3-88.3%)
						Symptomatic infection		25.6% (-157.8-78.5%)
		(260)	Retrospective cohort	27/12/2020 to 24/3/2021 Italy.	6,423	Infection	0-14 days: 47.3% (24.7-63.1%)	≥7 days: 95.1% (62.4-99.4%)
							14-21 days: 84.1% (39.7-95.8%)	
							≥21 days: 85.4% (-35.3-98.4%)	
						Symptomatic infection	0-14 days: 39.9% (9.1-60.3%)	≥7 days: 93.7% (50.8-99.2%)
							14-21 days: 83.3% (14.8-96.7%)	
							≥21 days: 65.9% (-171-95.7%)	
		(261)	Randomised controlled trial	27//7/2020 to 29/10/2020 US, Argentina, Brazil, South Africa, Germany, Turkey	44,165	Infection (without evidence of prior infection)		≥7 days: 91.3% (89-93.2%)
						Infection (with evidence of previous infection)		≥7 days: 91.1% (88.8-93.0%)
						Infection	<11 days: 18.2% (−26.1-47.3%)	<7 days: 91.5% (72.9-98.3%)
							≥11 days to second dose: 91.7% (79.6-97.4%)	≥7 days: 91.2% (88.9-93.0%)
								≥7 days to <2 months: 96.2% (93.3-98.1%)

								≥2 months to <4 months: 90.1% (86.6-92.9%)
								≥4 months: 83.7% (74.7-89.9%)
		(262)	Retrospective cohort	20/12/2020 to 25/2/2021 Israel.	6,710	Symptomatic Infection	7-21 days: 89% (83-94%)	≥7 days: 97% (94-99%)
								≥21 days: 98% (94-100%)
						Asymptomatic Infection	7-21 days: 36% (-51-69%)	≥7 days: 86% (69-93%)
								≥21 days: 94% (78-98%)
		(263)	Cohort	27/12/2020 to 28/2/2021 Sweden.	805,741	Infection	≥14 days: 42% (14-63%)	<7 days: 60% (27-81%)
								≥7 days: 86% (72-94%)
		(264)	Prospective cohort	27/12/2020 to 26/5/2021 Spain.	28,594	Infection – Nursing home residents	12 days: 20% (19.76-20.3%)	90.89% (90.84-90.95%
							40.28% (40.17-40.39)	
					26,238	Infection – Nursing home staff	12 days: 20.27% (19.8-20.73%)	85.02% (84.86-85.17%)
							26.49% (26.25-26.74%)	
					61,951	Infection – Healthcare workers	12 days: 15.44% (15.19-15.68%)	94% (93.92-94.1%)
							33.8% (33.66-33.92%)	
					28,594	Hospital admission - Nursing home residents	12 days: 67.59% (65.29-69.75%)	95.06% (94.73-95.38%)
							46.24% (45.62-46.86%)	
						Death - Nursing home residents	12 days: 43.95% (37.87-49.44%)	96.73% (96.43-96.99)
							51.71% (51.17-52.23%)	
		(265)	Cohort	27/12/2020 to 11/4/2021 Denmark.	864,096	Infection - Prioritised risk groups	0-14 days: -72% (-80- -64%)	0-7 days: 42% (33-50%)
							>14 days to second dose: 7% (-1-15%)	> 7 days: 82% (79-84%)
						COVID-19-related hospitalisation - Prioritised risk groups	0-14 days: 54% (44-62%)	0-7 days: 90% (80-95%)
							>14 days to second dose: 35% (18-49%)	>7 days: 93% (89-96%)
						COVID-19-related death - Prioritised risk groups	0-14 days: 76% (68-82%)	>7 days: 94% (90-96%)
							>14 to second dose days: 7% (-15-25%)	
		(266)	Case-control	27.1.2021 to 7/2/2021 Spain.	268	Infection	52.6% (95%CI: 1.1-77.3)	
		(267)	Observational	15/12/2020 to 3/2/2021 England.	170,226	Infection	21-27 days: 55.2% (40.8-66.8%)	
						Emergency hospital attendance	21-27 days: 57.8% (30.8-74.5%)	
						Hospitalisation	21-27 days: 50.1% (19.9-69.5%)	
		(268)	Cohort	27/12/2020 to 10/3/2021 Spain.	299,209	Infection (without evidence of prior infection)	0-14 days: 28.9% (26.9-31%)	
							15-21 days: 51.9% (50.7-53.1%)	
							22-28 days: 62.9% (61.9-64%)	
							≥29 days: 81.8% (81.0-82.7%)	
						Infection (with evidence of prior	0-14 days: 9.6% (-6.9-26.8%)	
							15-21 days: 25.5% (15.1-36.6%)	
							22-28 days: 34.6% (25.7-44.1%)	

						infection)	≥29 days: 56.8% (47.1-67.7%)	
		(269)	Observational	1/12/2020 to 8/5/2021 UK.	383,812	Infection	8-20 days after either dose: 56% (51-61%)	
							≥21 days: 64% (59-68%)	≥21 days: 80% (74-84%)
						[NOTE: Both BNT162b2 and AZD1222 vaccines were included in this study]		
		(270)	Cohort	19/12/2020 to 14/3/2021 Israel.	9,347	Infection	4-10 days: 28% (-18-57%)	≥11 days: 65% (45-79%)
							≥11 days after first, ≤10 days after second: 55% (32-70%)	
						Symptomatic infection	4-10 days: 21% (-32-41%)	≥11 days: 90% (84-94%)
							≥11 days after first, ≤10 days after second: 80% (69-87%)	
		(271)	Prospective cohort	8/12/2020 to 15/3/2021 England.	10,412	Infection	0-6 days: 36% (-6-62%)	
							7-13 days: 17% (-28-46%)	
							14-20 days: 4% (-60-43%)	
							21-27 days: 8% (-59-47%)	
							28-34 days: 56% (19-76%)	
							35-48 days: 62% (23-81%)	
							≥49 days: 51% (-17-80%)	
						[NOTE: Both BNT162b2 and AZD1222 vaccines were included in this study]		
		(272)	Retrospective cohort	1/1/2021 to 31/3/2021 US.	44,498	Infection	>14 days after first, ≤14 days after second: 78.1% (71.1-82%)	
								>14 days: 96.8% (95.3-97.8%)
		(273)	Prospective cohort	14/12/2020 to 10/4/2021 US.	3,975	Infection	≥14 days after first, <14 days after second: 80% (60-90%)	
								≥14 days: 93% (78-98%)
		(274)	Randomised controlled trial	15/10/2020 to 12/1/2021 US.	2,260	Infection - Adolescents (12-15 years of age) - (without evidence of prior infection)		≥7 days: 100% (75.3-100%)
						Infection - Adolescents (12-15 years of age) - (with or without evidence of prior infection)		≥7 days: 100% (78.1-100%)
		(275)	Retrospective cohort	19/7/2021 to 13/11/2021 South Korea.	444,313	Infection – Adolescents (16-18 years of age)	≥14 days: 91.1% (89.6-92.5%)	≥14 days: 99.1% (98.5-99.5%)
		(276)	Prospective cohort	25/7/2021 to 4/12/2021 US.	243	Infection - Adolescents (12-17 years of age)		≥14 days: 92% (79-97%)
		(277)	Retrospective longitudinal cohort	21/12/2020 to 6/2/2021 Israel.	5,439,734 first dose, 5,112,516 second dose	Infection	14-20 days: 54.3% (50.6-57.8%)	8-14 days: 89.9% (88.6-91.1%)
						Symptomatic infection	14-20 days: 58.3% (54.7-61.6%)	8-14 days: 93.6% (92.7-94.3%)
						Hospitalisation	14-20 days: 74.5% (69.1-79%)	8-14 days: 93.8% (91.9-95.2%)
						Severe/Critical disease	14-20 days: 77.3% (71.2-82.1%)	8-14 days: 94.4% (92.6-95.8%)
						Death	14-20 days: 71.7% (64.1-77.7%)	8-14 days: 91.3% (87.4-94.0%)
						Infection		15-21 days: 96.8% (96.1-97.4%)
						Symptomatic infection		15-21 days: 98.1% (97.7-98.5%)
						Hospitalisation		15-21 days: 98% (97.1-98.6%)

						Severe/Critical disease		15-21 days: 98.6% (97.8-99.1%)
						Death		15-21 days: 97.7% (95.9-98.7%)
						Infection		22-28 days: 97.3% (96.7-97.8%)
						Symptomatic infection		22-28 days: 97.9% (97.4-98.3%)
						Hospitalisation		22-28 days: 99% (98.4-99.3%)
						Severe/Critical disease		22-28 days: 99.2% (98.6-99.5%)
						Death		22-28 days: 98.6% (97-99.3%)
		(278)	Test-negative case-control	January to March 2021 US.	1,843	Infection	≥14 days: 81.7% (74.3-86.9%)	≤2 days: 81.7% (74.3-86.9%)
								3-6 days: 81.7% (74.3-86.9%)
								≥7 days: 93.5% (86.5-96.9%)
					[NOTE: 76% of case-patients and 78% of controls received BNT162b2, remainder received mRNA-1273]			
		(279)	Prospective cohort	January to April 2021 Spain.	20,961	Infection	21% (3-36%)	65% (56-73%)
						Symptomatic infection	30% (10-45%)	82% (73-88%)
						Symptomatic infection – 18-59 years old	50% (12-72%)	85% (74-91%)
						Symptomatic infection - ≥60 years old	20% (−7-40%)	76% (55-87%)
						Hospitalisation	65% (25-83%)	94% (60-99%)
		(280)	Prospective cohort	8/10/2020 to 22/2/2021 Scotland.	409,588	Hospitalisation	0-6 days: 86% (81-90%)	
							7-13 days: 53% (45-59%)	
							14-20 days: 69% (62-75%)	
							21-27 days: 78% (71-83%)	
							28-34 days: 91% (85-94%)	
							35-41 days: 78% (69-85%)	
							≥42 days: 77% (68-83%)	
		(281)	Test-negative case-control	27/12/2020 to 30/6/2021 Belgium, Croatia, Czechia, France, Greece, Ireland, Luxembourg, Malta, Portugal, Spain.	1,893	Infection	≥14 days: 76% (61-86%)	≥14 days: 94% (88-97%)
		(282)	Prospective cohort	1/5/2021 to 3/9/2021 US.	8,690,825	Infection - 18-49 years old		≥14 days: 93.3% (92.2-94.4%)
						Infection - 50-64 years old		≥14 days: 95.0% (94.0-96.0%)
						Infection - ≤65 years old		≥14 days: 91.4% (90.0-92.8%)
						Hospitalisation - 18-49 years old		≥14 days: 96.1% (94.1-97.6%)
						Hospitalisation - 50-64 years old		≥14 days: 95.6% (94.2-96.7%)
						Hospitalisation - ≤65 years old		≥14 days: 94.8% (94.0-95.5%)
		(283)	Test-negative case-control	1/7/2021 to 25/10/2021 US.	1,222	Hospitalisation 12-18 years old	97% (86-100%)	≥14 days: 94% (90-96%)
						ICU admission – 12-18 years old		≥14 days: 98% (93-99%)
						Life support – 12-18 years old		≥14 days: 98% (92-100%)

		(284)	Test-negative case-control	1/7/2021 to 9/12/2021 US.	283	COVID-19 multisystem inflammatory syndrome – 12-18 years old		≥14 days: 92% (77-97%)
Oxford University/ AstraZeneca (AZD1222) - Non-replicating adenovirus viral vector (ChAdOx1).	Two doses (0.5ml each) intramuscularly (deltoid) with a recommended interval window of 8 to 12 weeks.	(242)	Test-negative case-control	26/10/2020 to 16/5/2021 UK.	19,109	Infection - Alpha	48.7% (45.2–51.9%)	74.5% (68.4–79.4%)
						Infection - Delta	30.0% (24.3–35.3%)	67.0% (61.3–71.8%)
		(245)	Test-negative case-control	14/12/2020 to 3/8/2021 Canada.	682,071	Symptomatic infection - Alpha	64% (60-68%)	
						Symptomatic infection – Beta or Gamma	48% (28-63%)	
						Symptomatic infection - Delta	67% (44-80%)	
						Hospitalisation or death - Alpha	85% (81-88%)	
						Hospitalisation or death – Bet or Gamma	83% (66-92%)	
						Hospitalisation or death - Delta	88% (60-96%)	
		(133)	Test-negative observational	1/4/2021 to 6/6/2021 Scotland.	462,755	Infection with Alpha variant		73% (66-78%)
						Infection with Delta variant		60% (53-66%)
		(285)	Randomised controlled trial	1/10/2020 to 14/1/2021 UK.	8,534	Symptomatic infection – Alpha		70.4% (43.6-84%%)
						Symptomatic infection – non-Alpha		81.5% (67.9-89.4%)
		(286)	Randomised controlled trial	28/8/2020 to 5/3/2021 US.	32,449	Symptomatic infection		79%
						Severe disease or hospitalisation		100%
		(247)	Test-negative case-control	12/4/2021 to 4/6/2021 England.	14,019	Hospitalisation – Alpha	76% (61-85%)	86% (53-96%)
						Hospitalisation – Delta	71% (51-83%)	92% (75-97%)
		(287)	Randomised controlled trial	23/4/2020 to 4/11/2020 UK, Brazil.	11,636	Infection		62.1% (41.0-75.7%)
		(288)	Randomised controlled trial	24/6/2020 to 9/11/2020 South Africa.	2,026	Symptomatic infection		21.9% (-49.9-59.8%)
						Symptomatic infection - Beta		10.4% (-76.8-54.8%)
		(248)	Test-negative case-control	8/12/2020 to 19/2/2021. England.	156,930	Symptomatic infection		28-34 days: 60% (41-73%)
								≥35 days: 73% (27-90%)
		(258)	Observational	1/12/2020 to 1/8/2021 UK.	384,543	Infection - Alpha	≥21 days: 63% (55–69%)	0-13 days: 72% (50-84%)
								≥14 days: 79% (56–90%)
						Infection Delta	≥21 days: 46% (35–55%)	0-13 days: 71% (64–77%)
								≥14 days: 67% (62–71%)
		(289)	Test-negative case-control	1/3/2021 to 31/5/2021 India	720	Infection	49% (17-68%)	54% (27-71%)
						Symptomatic infection	58% (28-75%)	64% (38-78%)
						Moderately severe disease	Any dosage >3 weeks ago: 95% (44-100%)	
		(269)	Observational	1/12/2020 to 8/5/2021 UK.	383,812	Infection	8-20 days after either dose: 56% (51-61%)	
							≥21 days: 64% (59-68%)	≥21 days: 80% (74-84%)
					[NOTE: Both BNT162b2 and AZD1222 vaccines were included in this study]			

		(290)	Randomised controlled trial	28/8/2020 to 15/1/2021 US, Chile, Peru.	32,451	Symptomatic infection		≥15 days: 74.0% (65.3-80.5%)
						Severe or critical infection		≥15 days: 100.0% (71.6-NE%)
						Emergency department visit		≥15 days: 94.8% (59.0-99.3%)
						Hospitalisation		≥15 days: 94.2% (53.3-99.3%)
						ICU admission		≥15 days: 100.0 (−1781.6-NE%)
		(291)	Clinical trial	23/6/2020 to 1/12/2020 Brazil.	9433	Infection – B.1.1.33		88.2 (5.4, 98.5)
						Infection – B.1.1.28		72.6% (46.4-86.0%)
						Infection – Zeta		68.7% (54.9-78.3%)
						Infection – Gamma		63.6% (−2.1-87.0%)
						Infection – Undetermined variant		56.6% (28.2-73.8%)
						Hospitalisation – Any variant		95% (61-99%)
		(292)	Meta-analysis	23/4/2020 to 6/12/2020 UK, Brazil, South Africa.	17,178	Asymptomatic infection		≥14 days: 22.2% (–9·9-45%)
						Symptomatic infection		≥14 days: 66.7% (57.4-74%)
						Asymptomatic infection - <6 weeks prime-boost interval (standard doses)		≥14 days: –11.8% (–189.5-56.8%)
						Asymptomatic infection - 6-8 weeks prime-boost interval (standard doses)		≥14 days: –74.2% (–330.3-29.5%)
						Asymptomatic infection – 9-11 weeks prime-boost interval (standard doses)		≥14 days: 39.9% (–62.3-77.8%)
						Asymptomatic infection - ≥12 weeks prime-boost interval (standard doses)		≥14 days: 22.8% (–63.3-63.5%)
						Symptomatic infection - <6 weeks prime-boost interval (standard doses)		≥14 days: 55.1% (33-69.9%)
						Symptomatic infection - 6-8 weeks prime-boost interval (standard doses)		≥14 days: 59.9% (32-76.4%)
						Symptomatic infection – 9-11 weeks prime-boost interval (standard doses)		≥14 days: 63.7% (28-81.7%)
						Symptomatic infection - ≥12 weeks prime-boost interval (standard doses)		≥14 days: 81.3% (60.3-91.2%)
		(293)	Cross-sectional observational	1/5/2021 to 31/5/2021 India.	583	Infection	<14 days: 15% (-68-57%)	<14 days: 66% (34-81%)
							≥14 days: 44% (7-66%)	≥14 days: 83% (73-89%)
						Hospitalisation	<14 days: 43% (-68-81%)	<14 days: 83% (17-96%)
							≥14 days: 76% (21-92%)	≥14 days: 88% (55-97%)
						ICU admission or death	<14 days: 62% (-27-89%)	<14 days: 93% (35-99%)
							≥14 days: 53% 9-29-83%)	≥14 days: 93% (64-99%)
					[NOTE: Participants either received Covaxin or Covishield (AZD1222)]			
		(279)	Prospective cohort	January to April 2021 Spain.	20,961	Infection	44% (31-54%)	
						Symptomatic infection	50% (37-61%)	
						Symptomatic infection – 18-59 years old	50% (34-62%)	
						Symptomatic infection - ≥60 years old	53% (19-72%)	
						Hospitalisation	92% (46-99%)	

		(294)	Retrospective cohort	1/6/2020 to 31/5/2021 India.	11,405	Infection (with evidence of prior infection)		≥14 days: 91.1% (84.1-94.9%)
						Infection (without evidence of prior infection)		≥14 days: 31.8% (23.5-39.1%)
					[NOTE: 5.77% of participants received Covaxin, 94.23% received Covishield (AZD1222)]			
		(280)	Prospective cohort	8/10/2020 to 22/2/2021 Scotland	409,588	Hospitalisation	0-6 days: 72% (66-77%)	
							7-13 days: 68% (61-73%)	
							14-20 days: 73% (66-79%)	
							21-27 days: 81% (72-87%)	
							28-34 days: 88% (75-94%)	
							35-41 days: 97% (63-100%)	
							≥42 days: 59% (–296-96%)	
		(295)	Cohort	17/1/2021 to 11/5/2021 Brazil.	313,328	Death	≥21 days: 94.4% (93.9-94.8%)	≥21 days: 99.8 (99.6-99.9%)
						Death – 75-79 years old	≥21 days: 88% (85.8-90%)	
						Death – 80-89 years old	≥21 days: 96.8% (96.5-97.2%)	
						Death - ≥90 years old	≥21 days: 99.2% (99.1-99.4%)	
		(296)	Retrospective cohort	18/1/2021 to 30/6/2021 Brazil.	60,577, 870	Infection	≥14 days: 34% (33.2-34.7%)	0-13 days: 56.9% (55.3-58.5%)
								≥14 days: 70% (68.6-71.3%)
						Hospitalisation	≥14 days: 52.2% (50.9-53.4%)	0-13 days: 69.6% (67.2-71.8%)
								≥14 days: 86.8% (85.2-88.2%)
						ICU admission	≥14 days: 54% (51.8-56%)	0-13 days: 69.2% (65-72.8%)
								≥14 days: 88.1% (85.4-90.3%)
						Death	≥14 days: 49.3% (47-51.5%)	0-13 days: 72.1% (69.1-74.9%)
								≥14 days: 90.2% (88.3-91.8%)
Johnson & Johnson (Ad26.COV2.S) - Recombinant, replication-incompetent adenovirus serotype 26 (Ad26) vector.	One dose (0.5ml) intramuscularly (deltoid).	(172)	Randomised controlled trial	21/9/2020 to 22/1/2021 Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, US.	39,321	Moderate to severe-critical infection	≥14 days: 66.9% (59.0-73.4%)	
							≥28 days: 66.1% (55.0-74.8%)	
						Severe-critical infection	≥14 days: 76.7% (54.6-89.1%)	
							≥28 days: 85.4% (54.2-96.9%)	
		(297)	Test-negative case-control	25/6/2021 to 30/9/2021 Brazil.	11,817	Symptomatic infection	14-27 days: 27.4% (8.7-42.7%)	
							≥28 days: 50.9% (35.5-63.0%)	
						Hospitalisation	14-27 days: 33.5% (-29.1-69.8%)	
							≥28 days: 72.9% (35.1-91.1%)	
						Admission to an ICU	14-27 days: 56.0% (-52.8-93.1%)	
							≥28 days: 92.5% (54.9-99.6%)	
						Mechanical ventilation	14-27 days: 65.2% (-74.7-98.1%)	
							≥28 days: 88.7% (17.9-99.5%)	
							14-27 days: 48.9% (-92.3-92.5%)	

						Death	≥28 days: 90.5% (31.5-99.6%)	
		(298)	Retrospective case-control	27/2/2021 to 14/4/2021 US.	126,572	Symptomatic infection	≥1 day: 50.6% (14.0-74.0%)	
							≥8 days: 65.5% (23.3-87.5%)	
							≥15 days: 76.7% (30.3-95.3%)	
		(299)	Test-negative case-control	1/7/2021 to 31/7/2021 US.	1,000	Symptomatic infection	51% (95% CI: -2-76%)	
		(256)	Observational	14/12/2020 to 14/8/2021 US.	Delta: 2,840 Pre-Delta: 7,012	Infection – Delta	14–119 days: 85% (68-93%)	
							120–149 days: 81% (34-95%)	
							≥150 days: 73% (49-86%)	
						Infection – Pre-Delta	91% (81-96%)	
					[NOTE: 2% of study participants received Ad26.COV2.S (65% received BNT162b2, and 33% received mRNA-1273)]			
		(300)	Cohort	March to July 2021 US.	1,914,670	Infection	79% (77-80%)	
						Hospitalisation	81% (79-84%)	
		(301)	Retrospective cohort	27/2/2021 to 22/7/2021 US.	97,787	Infection	≥1 day: 73.6% (65.9-79.9%)	
							≥8 days: 72.9% (64.2-79.9%)	
							≥15 days: 74.2% (64.9-81.6%)	
		(282)	Prospective cohort	1/5/2021 to 3/9/2021 US.	8,690,825	Infection - 18-49 years old		≥14 days: 89% (86.5-91.5%)
						Infection - 50-64 years old		≥14 days: 86.1% (82.5-89.6%)
						Infection - ≤65 years old		≥14 days: 80.8% (75.2-86.5%)
						Hospitalisation - 18-49 years old		≥14 days: 95.7% (91.1-98.3%)
						Hospitalisation - 50-64 years old		≥14 days: 87.5% (82.4-91.4%)
						Hospitalisation - ≤65 years old		≥14 days: 85.2% (81.1-88.6%)
Moderna (mRNA-1273) - mRNA	Two doses (100µg, 0.5ml each) intramuscularly (deltoid) with a recommended interval of 28 days between doses.	(245)	Test-negative case-control	14/12/2020 to 3/8/2021 Canada.	682,071	Symptomatic infection – Alpha	≥14 days: 83% (80-86%)	≥7 days: 92% (86-96%)
						Symptomatic infection – Beta or Gamma	≥14 days: 77% (63-86%)	
						Symptomatic infection – Delta	≥14 days: 72% (57-82%)	
						Hospitalisation - Alpha	≥14 days: 79% (74-83%)	≥7 days: 94% (89-97%)
						Hospitalisation – Beta or Gamma	≥14 days: 89% (73-95%)	
						Hospitalisation - Delta	≥14 days: 96% (72-99%)	
		(246)	Retrospective case-control	January to July 2021 US.	60,083	Infection		≥14 days: 86% (81-90.6%)
						Hospitalisation		≥14 days: 91.6% (81-97%)
						Admission to an ICU		≥14 days: 93.3% (57-99.8%)
		(250)	Test-negative case-control	17/1/2021 to 5/6/2021 Canada.	5,8476	Infection	≥14 days: 68.7% (59.5-75.9%)	≥7 days: 84.1% (34.9-96.1%)
		(252)	Test-negative case-control	23/3/2021 to 7/9/2021 Qatar.	1 dose: 490,828 2 doses: 409,041	Infection - Delta	≥14 days: 79.7% (60.8-89.5%)	≥14 days: 86.1% (78.0-91.3%)
		(255)	Observational	1/3/2021 to	10,428,	Infection – Pre-Delta period		≥14 days: 74.7% (66.2-81.1%)

				1/8/2021 US.	783	Infection – Intermediate period		≥14 days: 70.4% (60.1-78.0%)
						Infection – Delta		≥14 days: 50.6% (45.0-55.7%)
		(256)	Observational	14/12/2020 to 14/8/2021 US.	Delta: 2,840 Pre-Delta: 7,012	Infection – Delta		14–119 days: 85% (68-93%)
								120–149 days: 81% (34-95%)
								≥150 days: 73% (49-86%)
						Infection – Pre-Delta		91% (81-96%)
					[NOTE: 33% of study participants received mRNA-1273 (2% received Ad26.COV2.S, and 65% received BNT162b2)]			
		(258)	Observational	1/12/2020 to 1/8/2021 UK.	384,543	Infection - Delta	75% (64-83%)	
		(259)	Observational	April to May 2021. Canada	124	Infection		52.5% (26.9-69.1%)
						Symptomatic infection		65.6% (33.8-82.1%)
						Severe infection		78.6% (47.9-91.2%)
		(272)	Retrospective cohort	1/1/2021 to 31/3/2021 US.	4,722	Infection	>14 days after first, ≤14 days after second: 91.2% (80.6-96.1%)	
								>14 days: 98.6% (90.1-99.8%)
		(273)	Prospective cohort	14/12/2020 to 10/4/2021 US.	3,975	Infection	≥14 days after first, <14 days after second: 83% (40-95%)	
								≥14 days: 82% (20-96%)
		(177)	Randomised controlled trial	27/7/2020 to 23/10/2020 US.	30,420	Infection		≥14 days: 94.1% (89.3-96.8%)
						Infection - ≥18 to <65 years of age		≥14 days: 95.6% (90.6-97.9%)
						Infection - ≥65 years of age		≥14 days: 86.4% (61.4-95.2%)
		(302)	Retrospective cohort	16/7/2021 to 15/8/2021 US.	827	Infection		≥14 days: 56.6% (42.0-67.5%)
						Symptomatic infection		≥14 days: 84.2% (56.4-94.3%)
		(303)	Retrospective cohort	22/12/2020 to 2/2/2021 US.	4,028	Infection	8-42 days: 77.5% (61.2-87%)	
							15-42 days: 95% (86-98.2%)	
		(304)	Test negative case-control	28/10/2020 to 10/5/2021 Qatar.	256,037	Infection – Alpha	0-6 days: 2.4% (0-21.7%)	0-6 days: 98.0% (94.7-99.5%)
							7-13 days: 0.0% (0.0-11.9%)	7-13 days: 99.2% (95.3-100.0%)
							14-20 days: 81.6% (73.1-87.8%)	
							21-27 days: 94.4% (89.1-97.5%)	
						Infection - Beta	0-6 days: 4.2% (0-15.1%)	0-6 days: 94.2% (92.1-95.9%)
							7-13 days: 0.0% (0.0-0.0%)	7-13 days: 96.4% (94.3-97.9%)
							14-20 days: 47.9% (39.5-55.2%)	
							21-27 days: 73.7% (67.6-78.8%)	
						Any severe, critical, or fatal infection	0-6 days: 18.7% (0-44.7%)	0-6 days: 100.0% (93.9-100.0%)
							7-13 days: 0.0% (0.0-10.1%)	7-13 days: 100.0% (86.9-100.0%)
							14-20 days: 70.3% (48.9-83.5%)	
							21-27 days: 92.1% (78.4-97.9%)	
		(305)	Retrospective	27/4/2021 to	1,945	Symptomatic infection - Mesa	(36% fully vaccinated) Crude vaccine effectiveness 78% (71-84%)	

			cohort	6/6/2021 US.		County, US		
						Symptomatic infection - Other Colorado counties, US	(44% fully vaccinated) Crude vaccine effectiveness 89% (88-91%)	
		(306)	Prospective cohort	18/12/2020 to 31/03/2021 US.	705,756	Infection		87.4% (85.6-89.1%
						Hospitalisation		95.8% (92.5-97.6%)
						Hospital death		97.9% (84.5-99.7%
		(307)	Test-negative case control	1/3/2021 to 27/7/2021 US.	8153 cases and matched controls.	Infection - Alpha	≥14 days: 90.1 (82.9 to 94.2)	≥14 days: 98.4 (96.9 to 99.1)
						Infection – Delta	≥14 days: 77.0% (60.7-86.5%)	≥14 days: 86.7% (84.3-88.7%)
						Infection – Epsilon	≥14 days: 76.3% (48.1-89.1%)	≥14 days: 97.6% (90.2-99.4%)
						Infection – Gamma	≥14 days: 74.2% (43.8-88.1%)	≥14 days: 95.5% (90.9-97.8%)
						Infection – Iota	≥14 days: 88.8% (0.7-98.7%)	≥14 days: 95.7% (81.7-99.0%)
						Infection – Mu	≥14 days: 45.8% (0.0-88.9%)	≥14 days: 90.4% (73.9-96.5%)
						Infection – Other	≥14 days: 84.3% (65.9-92.7%)	≥14 days: 96.4% (91.2-98.5%)
						Infection - Unidentified	≥14 days: 67.6% (57.1-75.6%)	≥14 days: 79.9% (76.9-82.5%)
		(278)	Test-negative case-control	January to March 2021 US.	1,843	Infection	≥14 days: 81.7% (74.3-86.9%)	≤2 days: 81.7% (74.3-86.9%)
								3-6 days: 81.7% (74.3-86.9%)
								≥7 days: 93.5% (86.5-96.9%)
						[NOTE: 24% of case-patients and 22% of controls received mRNA-1273, remainder received BNT162b2]		
		(282)	Prospective cohort	1/5/2021 to 3/9/2021 US.	8,690,825	Infection - 18-49 years old		≥14 days: 96.3% (95.4-97.2%)
						Infection - 50-64 years old		≥14 days: 97.3% (96.4-98.1%)
						Infection - ≤65 years old		≥14 days: 96.0% (95.1-96.9%)
						Hospitalisation - 18-49 years old		≥14 days: 96.6% (94.3-98.1%)
						Hospitalisation - 50-64 years old		≥14 days: 97.3% (95.9-98.2%)
						Hospitalisation - ≤65 years old		≥14 days: 97.1% (96.5-97.6%)
		(308)	Randomised controlled trial	27/7/2020 to 23/10/2020 US.	30,415	Asymptomatic infection		63.0% (56.6-68.5%)
						Symptomatic infection		93.2% (91.0-94.8%)
						Severe infection		98.2% (92.8-99.6%)
						Death		100.0% (NE-100.0%)
Sinopharm BBIBP-CorV - Aluminium-hydroxide-adjuvanted, inactivated whole virus vaccine	Two doses (0.5ml) intramuscularly (deltoid) with a recommended interval of 3 weeks between doses.	(309)	Test-negative case-control	18/5/2021 to 20/6/2021 China.	366	Infection	13.8% (-60.2-54.8%)	59.0% (16.0-81.6%)
						Moderately severe infection		70.2% (29.6-89.3%)
						[NOTE: 27.5% of study participants were vaccinated with Sinopharm BIBP (61.3% received CoronaVac)]		
		(310)	Retrospective cohort	May to June 2021 China.	10,813	Infection with Pneumonia – Delta	8.4% (-47.6-64.4%)	69.5% (42.8-96.3%)
						Severe/critical disease -Delta	100% (NA)	100% (NA)
		(311)	Retrospective cohort	9/2/2021 to 30/6/2021 Peru.	606,772	Infection	≥14 days: 15·3 (12·7 to 17·8	≥14 days: 49·2 (47·9 to 50·4)
						COVID-19 mortality	≥14 days: 45.2% (28.8-57.8%)	≥14 days: 93.9% (90.9-95.9%)
						Infection - ≥60 years old	≥14 days: 14.1% (5.2-22.2%)	≥14 days: 54.7% (50.7-58.3%)
						COVID-19 mortality - ≥60 years old	≥14 days: 25.5% (-10.2-49.7%)	≥14 days: 90.6% (83.8-94.5%)
		(312)	Randomised	16/7/2020 to	40,382	Infection		≥14 days: 73.5% (60.6-82.2%)

			controlled trial	20/12/2020 UAE, Bahrain.		Symptomatic infection		≥14 days: 78.1% (64.8-86.3%)
						Severe infection		≥14 days: 100% (NA)
		(313)	Retrospective cohort	1/9/2020 to 1/5/2021 UAE.	176,640	Hospitalisation	-20% (-28.6-11.8%)	79.8% (78-81.4%)
						Critical care admission	3.7% (-12.8-18.1%)	92.2% (89.7-94.1%)
						Death	27.9% (-61-72.6%)	97.1% (83-99.9%)
		(314)	Observational	9/12/2020 to 17/7/2021 Bahrain.	569,054	Symptomatic infection		45.5%
						Hospitalisation		44.5%
						Hospitalisation - >50 years old		72%
						Death		63%
Sinovac-CoronaVac - Aluminium-hydroxide-adjuvanted, inactivated whole virus vaccine	Two doses (0.5ml) intramuscularly (deltoid) with a recommended interval window of 2 to 4 weeks.	(309)	Test-negative case-control	18/5/2021 to 20/6/2021 China.	366	Infection	13.8% (-60.2-54.8%)	59.0% (16.0-81.6%)
						Moderately severe infection		70.2% (29.6-89.3%)
						[NOTE: 61.3% of study participants were vaccinated with CoronaVac (27.5% recieved Sinopharm BIBP)]		
		(315)	Observational	2/2/2021 to 1/5/2021 Chile.	10,187, 720	Infection	17.2% (15.8–18.6%)	63.7% (62.8–64.6%)
						Hospitalisation	40.3% (37.6–42.8%)	86.5% (85.6–87.4%)
						Admission to an ICU	45.3% (41.2–49.2%)	90.2% (88.9–91.4%)
						Death	46.0% (40.7–50.8%)	86.7% (84.9–88.3%)
		(316)	Test-negative case-control	17/1/2021 to 29/4/2021 Brazil.	43,774	Symptomatic infection - Gamma	0-13 days: −0.8% (−9.4 to 7.2%)	0-13 days: 24.7% (14.7 to 33.4%)
							≥14 days: 12.5% (3.7 to 20.6%)	≥14 days: 46.8% (38.7 to 53.8%)
						Hospitalisation - Gamma	0-13 days: 6.6% (−4.3 to 16.3%)	0-13 days: 39.1% (28.0 to 48.5%)
							≥14 days: 16.9% (5.7 to 26.8%)	≥14 days: 55.5% (46.5 to 62.9%)
						Death - Gamma	0-13 days: 13.1% (−1.5 to 25.6%)	0-13 days: 48.9% (34.4 to 60.1%)
							≥14 days: 31.2% (17.6 to 42.5%)	≥14 days: 61.2% (48.9 to 70.5%)
		(317)	Test-negative case-control	19/1/2021 to 13/4/2021 Brazil.	53,153	Infection – Gamma	≥14 days: 49.4% 13.2-71.9%)	≥14 days: 37.1% (-53.3-74.2%)
						Infection	≥14 days: 35.1% (-6.6-60.5%)	37.9% (-46.4-73.6%)
		(115)	Prospective cohort	February to March 2021 Brazil.	20,187	Infection		≥14 days: 50.7% (33.3-62.5%)
								≥21 days: 51.8% (30-66.0%)
								≥28 days: 68.4% (51-80.8%)
								≥35 days: 73.8% (57-84.8%)
		(318)	Test-negative case-control	15/3/2021 to 3/10/2021 Brazil.	19,838	Symptomatic infection – Pregnant women	≥14 days: 5.02% (-18.22-23.69%)	≥14 days: 40.97% (27.07-52.22%)
						Severe infection – Pregnant women	≥14 days: 67.74% (20-87%)	≥14 days: 85.39% (59.44-94.80%)
		(319)	Test-negative case-control	19/1/2021 to 25/3/2021 Brazil.	2,656	Symptomatic infection – Gamma	≥14 days: 49.6% (11.3-71.4%)	
						Symptomatic infection	≥14 days: 35.1% (-6.6-60.5%)	
		(320)	Randomised controlled	14/9/2020 to 5/1/2021	10,029	Symptomatic infection	14-27 days: 46.4% (0.4-71.2%)	≥14 days: 83.5% (65.4-92.1%)
						Hospitalisation		≥14 days: 100% (20.4-100%)

			trial	Turkey.				
		(321)	Randomised controlled trial	21/7/2020 to 16/12/2020 Brazil.	9,823	Infection	≤14 days: -3.3% (-4.8- -1.9%)	≥14 days: 50.7% (35.9-62%)
							14-28 days: 94.0% (55.1-99.2%)	
							≤28 days: 42.5% (32.9-50.7%)	
							≤42 days: 56.5% (49.6-62.5%)	
							≤56 days: 60.4% (56.5-63.9%)	
							≤70 days: 54.7% (53.2-56.1%)	
							≤84 days: 53.7% (52.7-54.7%)	
							≤98 days: 52.5% (51.9-53.1%)	
						Infection requiring medical assistance (hospitalisation)		≥14 days: 83.7% (58.0-93.7%)
						Moderate infection		≥14 days: 100% (56.4-100%)
						Severe infection or death		≥14 days: 100% (16.9-100%)
						Infection - <21 days between 2 doses		≥14 days: 49.1% (33-61.4%)
						Infection - ≥21 days between 2 doses		≥14 days: 62.3% (13.9-83.5%)
		(295)	Cohort	17/1/2021 to 11/5/2021 Brazil.	313,328	Death	≥21 days: 95.1% (94.7-95.5%)	≥21 days: 99.1% (98.9-99.3%)
						Death – 75-79 years old	≥21 days: 86.3% (84.7-87.7%)	
						Death – 80-89 years old	≥21 days: 97.6% (97.2-97.9%)	
						Death - ≥90 years old	≥21 days: 99.3% (99.1-99.5%)	
		(296)	Retrospective cohort	18/1/2021 to 30/6/2021 Brazil	60,577, 870	Infection	≥14 days: 16.4% (15.2-17.5%)	0-13 days: 40.3% (39.4-41.2%)
								≥14 days: 54.2% (53.4-55.0%)
						Hospitalisation	≥14 days: 26.6% (24.6-28.4%)	0-13 days: 57.3% (56.0-58.6%)
								≥14 days: 72.6% (71.6-73.6%)
						ICU admission	≥14 days: 28.1% (24.9-31.1%)	0-13 days: 58.1% (55.9-60.1%)
								≥14 days: 74.2% (72.6-75.7%)
						Death	≥14 days: 29.4% (26.7-32.0%)	0-13 days: 58.7% (56.9-60.4%)
								≥14 days: 74% (72.6-75.3%)
Bharat Biotech – Covaxin – whole virion inactivated virus vaccine	Two doses (0.5ml) intramuscularly (deltoid) with a recommended interval window of 28 days.	(322)	Randomised controlled trial	16/11/2020 to 7/1/2021 India.	25 798	Symptomatic infection		≥14 days: 77.8% (65.2-86.4%)
						Severe disease		≥14 days: 93.4% (57.1-99.8%)
						Symptomatic infection – 18-59 years old		≥14 days: 79.4% (66.0-88.2%)
						Symptomatic infection - ≥60 years old		≥14 days: 67.8% (8.0-90.0%)
						Symptomatic infection – participants with pre-existing chronic medical condition		≥14 days: 66.2% (33.8-84.0%)
						Asymptomatic infection		≥14 days: 63.6% (29.0-82.4%)
						Symptomatic or asymptomatic infection		≥14 days: 68.8% (46.7-82.5%)
		(323)	Test-negative case-control	15/4/2021 to 15/5/2021 India.	3,732	Symptomatic infection	<7 days: 40% (-21-71%)	<14 days: 27% (-35-61%)
							≥7 days: 1% (-30-25%)	≥14 days: 50% (33-62%)
							≥21 days: –1% (-51-33%)	≥28 days: 46% (22-62%)
								≥42 days: 57% (21-76%)

		(293)	Cross-sectional observational	1/5/2021 to 31/5/2021 India.	583	Infection	<14 days: 15% (-68-57%)	<14 days: 66% (34-81%)
							≥14 days: 44% (7-66%)	≥14 days: 83% (73-89%)
						Hospitalisation	<14 days: 43% (-68-81%)	<14 days: 83% (17-96%)
							≥14 days: 76% (21-92%)	≥14 days: 88% (55-97%)
						ICU admission or death	<14 days: 62% (-27-89%)	<14 days: 93% (35-99%)
							≥14 days: 53% 9-29-83%)	≥14 days: 93% (64-99%)
					[NOTE: Participants either received Covaxin or Covishield (AZD1222)]			
		(294)	Retrospective cohort	1/6/2020 to 31/5/2021 India.	11,405	Infection (with evidence of prior infection)		≥14 days: 91.1% (84.1-94.9%)
						Infection (without evidence of prior infection)		≥14 days: 31.8% (23.5-39.1%)
					[NOTE: 5.77% of participants received Covaxin, 94.23% received Covishield (AZD1222)]			
		(324)	Retrospective cohort	3/3/2020 to 18/6/2021 India.	15,244	Reinfection		86% (77-92%)
						Symptomatic reinfection		87% (76-93%)
						Asymptomatic reinfection		84% (47-95%)
Novavax – NVX-CoV2373 (Nuvaxovid) or Serum Institute of India – COVOVAX (Novavax formulation - recombinant SARS-CoV-2 S protein nanoparticle as a coformulation with the adjuvant Matrix-M	Two doses (0.5 ml) intramuscularly (deltoid) with a recommended interval of 3-4 weeks.	(325)	Randomised controlled trial	28/9/2020 to 28/10/2020 UK.	14,039	Infection		89.7% (80.2-94.6%)
						Infection – 18 to 64 years old		89.8% (79.7-95.5%)
						Infection – 65 to 84 years old		88.9% (20.2-99.7%)
						Infection – Alpha		86.3% (71.3-93.5%)
						Infection – Non-Alpha		96.4% (73.8-99.5%)
		(326)	Randomised controlled trial	27/12.2020 to 18/2/2021 US, Mexico.	29,949	Infection		≥7 days: 89.3% (81.6-93.8%)
						Infection – COVID-19 high risk group		≥7 days: 91.0% (83.6-95.0%)
		(327)	Randomised controlled trial	28/9/2020 to 28/10/2020 UK.	15,139	Infection		89.8% (79.7-95.5%)
						Infection – 18-64 years old		87.5% (–0.2-98.4%)
		(328)	Randomised controlled trial	17/7/2020 to 25/11/2020 South Africa.	2,684	Symptomatic infection		≥7 days: 49.4% (6.1-72.8%)
						Symptomatic infection – Beta		≥7 days: 51.0% (-0.6-76.2%)

Vaccine type	Vaccine	Company	Countries approved for use in	Clinical trials
Inactivated virus	**KoviVac**	Chumakov Center (Moscow, Russia)	***3 countries:*** Belarus, Cambodia, Russian Federation	Phase 1: 502 (Russian Federation). Phase 2: 502 (Russian Federation). 622 (Russian Federation).
	QazVac	Kazakhstan Research Institute for Biological Safety Problems (RIBSP) (Kazakhstan)	***2 countries:*** Kazakhstan, Kyrgyzstan	Phase 1: NCT04530357 (Kazakhstan). Phase 2: NCT04530357 (Kazakhstan). Phase 3: NCT04691908 (Kazakhstan).
	KCONVAC	Minhai Biotechnology Co. (Beijing, China)	***2 countries:*** China, Indonesia	Phase 1: NCT05003479 (China). ChiCTR2000038804, NCT04758273 (China). Phase 2: ChiCTR2000039462, NCT04756323 (China). NCT05003466 (China). Phase 3: NCT04852705
	COVIran Barekat	Shifa Pharmed Industrial Co. (Tehran, Iran)	***1 country:*** Iran	Phase 1: IRCT20201202049567N1 (Iran). IRCT20201202049567N2 (Iran). IRCT20171122037571N3 (Iran). Phase 2: IRCT20201202049567N3 (Iran). IRCT20171122037571N3 (Iran). Phase 3: IRCT20201202049567N3 (Iran).
	Inactivated (Vero Cells)	Sinopharm (Wuhan, China)	***2 countries:*** China, Philippines	Phase 1: ChiCTR2000031809 (China) Phase 2: NCT04885764 (Egypt). ChiCTR2000031809 (China). Phase 3: NCT04885764 (Egypt). ChiCTR2000034780 (United Arab Emirates). NCT04612972 (Peru). NCT04510207 (Bahrain, Egypt, Jordan, United Arab Emirates). ChiCTR2000039000 (Morocco).
	Turkovac	Health Institutes of Turkey (Istanbul, Turkey)	***1 country:*** Turkey	Phase 1: NCT04691947 (Turkey). Phase 2: NCT04824391 (Turkey). NCT04979949 (Turkey). NCT05035238 (Turkey). Phase 3: NCT04942405 (Turkey). NCT05077176 (Turkey).
	FAKHRAVAC (MIVAC)	Organization of Defensive Innovation and Research (Tehran, Iran)	***1 country:*** Iran	Phase 1: IRCT20210206050259N1 (Iran). Phase 2: IRCT20210206050259N2 (Iran). Phase 3: IRCT20210206050259N3 (Iran).
Non-replicating viral vector	**Convidecia**	CanSino (Tianjin, China)	***10 countries:*** Argentina, Chile, China, Ecuador, Hungary, Indonesia, Malaysia, Mexico, Pakistan, Republic of Moldova	Phase 1: NCT05043259 (China). ChiCTR2000030906, NCT04313127 (China). NCT04568811 (China). NCT04840992 (China). Phase 2: NCT05043259 (China). NCT05162482 (Pakistan). NCT04840992 (China). ChiCTR2000031781, NCT04341389 (China). NCT04566770 (China). NCT05005156 (Argentina). Phase 3: NCT05169008 (Chile, Mexico). NCT04526990 (Argentina, Chile, Mexico, Pakistan, Russian Federation). NCT04540419 (Russian Federation).
	Sputnik Light	Gamaleya Research Institute of Epidemiology and	***24 countries:*** Angola, Argentina, Armenia, Bahrain, Belarus, Cambodia, Egypt, Iran, Kazakhstan,	Phase 1: NCT04713488 (Russian Federation). Phase 2: NCT04713488 (Russian Federation).

		Microbiology (Moscow, Russia)	Kyrgyzstan, Lao People's Democratic Republic, Mauritius, Mongolia, Nicaragua, Philippines, Republic of the Congo, Russian Federation, San Marino, Tunisia, Turkmenistan, United Arab Emirates, United Republic of Tanzania, Venezuela, West Bank	NCT05027672 (Argentina). Phase 3: NCT04741061 (Russian Federation).
	Sputnik V	Gamaleya Research Institute of Epidemiology and Microbiology (Moscow, Russia)	***74 countries:*** Albania, Algeria, Angola, Antigua and Barbuda, Argentina, Armenia, Azerbaijan, Bahrain, Bangladesh, Belarus, Bolivia, Bosnia and Herzegovina, Brazil, Cambodia, Cameroon, Chile, Djibouti, Ecuador, Egypt, Gabon, Ghana, Guatemala, Guinea, Guyana, Honduras, Hungary, India, Indonesia, Iran, Iraq, Jordan, Kazakhstan, Kenya, Kyrgyzstan, Lao People's Democratic Republic, Lebanon, Libya, Maldives, Mali, Mauritius, Mexico, Mongolia, Montenegro, Morocco, Myanmar, Namibia, Nepal, Nicaragua, Nigeria, North Macedonia, Oman, Pakistan, Panama, Paraguay, Philippines, Republic of Moldova, Republic of the Congo, Russian Federation, Rwanda, Saint Vincent and the Grenadines, San Marino, Serbia, Seychelles, Sri Lanka, Syrian Arab Republic, Tunisia, Turkey, Turkmenistan, United Arab Emirates, Uzbekistan, Venezuela, Vietnam, West Bank, Zimbabwe	Phase 1: NCT04760730 (United Arab Emirates). NCT04684446 (Belarus, Russian Federation). NCT04436471, 241 (Russian Federation). NCT04437875 (Russian Federation). Phase 2: NCT05027672 (Argentina). NCT04988048 (Argentina). NCT04954092 (Russian Federation). NCT04962906 (Argentina). NCT04983537 (Argentina). NCT04760730 (United Arab Emirates). NCT04684446 (Belarus, Russian Federation). NCT04686773 (Azerbaijan). NCT04436471, 241 (Russian Federation). NCT04437875 (Russian Federation). NCT04587219 (Russian Federation). NCT04640233 (India). Phase 3: NCT04564716 (Belarus). NCT04530396 (Russian Federation). NCT04642339 (Venezuela). NCT04656613 (United Arab Emirates). NCT04954092 (Russian Federation). NCT04640233 (India).
RNA	**TAK-919 (Moderna formulation)**	Takeda (Tokyo, Japan)	***1 country:*** Japan	Phase 1: NCT04677660 (Japan). Phase 2: NCT04677660 (Japan).
DNA	**ZyCoV-D**	Zydus Cadila (Ahmedabad, India)	***1 country:*** India	Phase 1: CTRI/2020/07/026352 (India). CTRI/2021/03/032051 (India). Phase 2: CTRI/2020/07/026352 (India). CTRI/2021/03/032051 (India). Phase 3: CTRI/2021/01/030416 (India).
Protein subunit	**ZF2001**	Anhui Zhifei Longcom (Hefei, China)	***3 countries:*** China, Indonesia, Uzbekistan	Phase 1: NCT04445194 (China). NCT04636333 (China). NCT04550351, ChiCTR2000035691 (China). NCT04961359 (China). Phase 2: NCT04466085 (China). NCT05109598 (China). NCT04813562 (China). Phase 3: NCT05091411 (China). NCT05128643 (China). NCT05107375 (China). ChiCTR2000040153, NCT04646590 (China, Ecuador, Indonesia, Pakistan, Uzbekistan). ChiCTR2100050849 (China).
	Abdala	Center for Genetic Engineering and Biotechnology (CIGB) (Havana, Cuba)	***6 countries:*** Cuba, Mexico, Nicaragua, Saint Vincent and the Grenadines, Venezuela, Vietnam	Phase 1: RPCEC00000345 (Cuba). RPCEC00000346 (Cuba). Phase 2: RPCEC00000345 (Cuba) RPCEC00000346 (Cuba).

				Phase 3: RPCEC00000359 (Cuba).
	EpiVacCorona	FBRI (Koltsovo, Russia)	***4 countries:*** Cambodia, Russian Federation, Turkmenistan, Venezuela	Phase 1: NCT04527575 (Russian Federation). Phase 2: NCT04527575 (Russian Federation). Phase 3: NCT04780035 (Russian Federation). NCT05021016 (Russian Federation)
	Aurora-CoV	FBRI (Koltsovo, Russia)	***1 country:*** Russian Federation	Phase 1: 197 (Russian Federation). Phase 2: 197 (Russian Federation).
	MVC-COV1901	Medigen Biotechnology Corp. (Taipei City, Taiwan)	***2 countries:*** Somaliland, Taiwan	Phase 1: NCT05132855 (Taiwan). NCT04487210 (Taiwan). Phase 2: NCT05132855 (Taiwan). NCT04695652 (Taiwan, Vietnam). NCT04822025 (Taiwan). NCT04951388 (Taiwan). NCT05038618 (Taiwan). NCT05048849 (Taiwan). NCT05054621 (Taiwan). Phase 3: NCT05011526 (Paraguay)
	SpikoGen	Vaxine/CinnaGen Co. (Iran)	***1 country:*** Iran	Phase 1: NCT04453852 (Australia). Phase 2: IRCT20150303021315N23 (Iran). NCT04944368, IRCT20150303021315N23 (Iran). NCT05148871 (Australia). Phase 3: NCT05005559, IRCT20150303021315N24 (Iran). NCT05148871 (Australia). NCT05175625, IRCT20150303021315N26 (Iran).
	Corbevax	Biological E Limited (Telangana, India)	***1 country:*** India	Phase 1: CTRI/2020/11/029032 (India). Phase 2: CTRI/2020/11/029032 (India). CTRI/2021/06/034014 (India). CTRI/2021/10/037066 (India). Phase 3: CTRI/2021/06/034014 (India). CTRI/2021/08/036074 (India). CTRI/2021/10/037066 (India).
	Soberana 02	Instituto Finlay de Vacunas Cuba (Havana, Cuba)	***4 countries:*** Cuba, Iran, Nicaragua, Venezuela	Phase 1: IFV/COR/06 (Cuba). Phase 2: IFV/COR/08 (Cuba). Phase 3: IFV/COR/09 (Cuba).
	Soberana Plus	Instituto Finlay de Vacunas Cuba (Havana, Cuba)	***1 country:*** Cuba	Phase 1: IFV/COR/15 (Cuba). IFV/COR/05 (Cuba). Phase 2: IFV/COR/11 (Cuba). IFV/COR/15 (Cuba). Phase 3: IFV/COR/09 (Cuba).
	Razi Cov Pars	Razi Vaccine and Serum Research Institute (Karaj, Iran)	***1 country:*** Iran	Phase 1: IRCT20201214049709N1 (Iran). Phase 2: IRCT20201214049709N2 (Iran). Phase 3: IRCT20201214049709N3 (Iran).
	Recombinant SARS-CoV-2 Vaccine (CHO Cell)	National Vaccine and Serum Institute (Beijing, China)	***1 country:*** United Arab Emirates	Phase 1: NCT04869592 (China). Phase 2: NCT04869592 (China) Phase 3: NCT05069129 (United Arab Emirates)