PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	COVID-19: Virology, variants, and vaccines
AUTHORS	Edison, Paul; Young, Megan; Crook, Harry; Scott, Janet

VERSION 1 - REVIEW

REVIEWER	**Reviewer 1: Guan, Wei-jie** Guangzhou Institute of Respiratory Disease, No conflict of interest
REVIEW RETURNED	03-Nov-2021

GENERAL COMMENTS	Young and colleagues performed a narrative review pertaining to the virology, variants and vaccine treatment for COVID-19. Most of the contents are up to date and might have clinical relevance to inform our practice. I have a number of comments for the authors to consider with: - 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. - Also within the same section, the description for the gene loci associated with the risk of severe disease could be streamlned 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. - 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.). - Perhaps it would merit if the conformational changes of the S protein that occur after binding with the host cell be described. - Not sure why there should be the section "4.1 Other human coronaviruses" which seemed less relevant to the topic. - 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. - 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. - 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. - 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.

REVIEWER	**Reviewer 3: Kongsaengdao, Subsai** Rajavithi Hospital, Medicine, No competing interests
REVIEW RETURNED	12-Nov-2021

GENERAL COMMENTS	This review was not written in the systematic review format, which authors can use the statistical method to measument the significant different between virology variant and vaccine aspects. The criteria of choosing andexclude scientific data / paper need to be.explained to eliminated the potential bias. Since, the severity of diseases did not depend on only viral genetic, host, and immune status,as well.as significant riskfactors, but also depend on medical treatment and duration of onset in each data set which are important confounding factors. Most of review data are not.suitable for publication inthe modern scientific format but can be.re-written with additional level.of evidence bass.medicine. The basic knowledge and 3D structure of spike RBD andNTD molecule ineachmutation and vaccine sequence antibody (MRNA)/ (VIRAL VECTORS) should be reviewed if authors want to determine the.correlation ofvaccine efficacy and variant of SAR-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. The booster dose data should be reviewed interm of antibody response and T cell response.

REVIEWER	**Reviewer 4: Shirreff, George** Institut Pasteur, Epidemiology and Modelling of Bacterial Resistance, No competing interests
REVIEW RETURNED	24-Nov-2021

GENERAL COMMENTS	I have some suggestions/comments that I thought I would share, most are typos. 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. 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 3 - Transmission Line 32 - maybe use "biological material" instead of "biological samples", presumably the virus doesn't normally spread via the samples themselves 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 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? 5 VOC - Alpha line 22 typo "probable" not "probably" line 48 typo "de-escalated" 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? 6 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 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.

REVIEWER	**Reviewer 2: Huang, Kuan-lin** Icahn School of Medicine at Mount Sinai, Department of Genetics and Genomic Sciences, No competing interests
REVIEW RETURNED	09-Nov-2021

GENERAL COMMENTS	Young, Crook et al. contributed here a review on 3Vs in COVID-19, virology, variants, and vaccines. They summarized here a total of 227 articles from published literature and bioRxiv and medRxiv, based on the quality of the articles. In general, the manuscript is well-written, and the basics of the topic were presented clearly. Major Comments: 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. 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. 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. 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. Minor comments: 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. 2. Figure 1, the texts in the figures (ex. D614G, ORF6, variant designations) could be enlarged

VERSION 1 – AUTHOR RESPONSE

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.”