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Diagnostic Microbiology and Infectious Disease 98 (2020) 115094

Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

Review

Clinical, molecular, and epidemiological characterization of the SARS-CoV-2 virus and the Coronavirus Disease 2019 (COVID-19), a comprehensive literature review

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ARTICLE INFO

Article history:
Received 14 April 2020
Received in revised form 21 May 2020
Accepted 22 May 2020
Available online 30 May 2020

Keywords:
COVID-19
Coronavirus
SARS-CoV-2
Review
Pandemic

ABSTRACT

Coronaviruses are an extensive family of viruses that can cause disease in both animals and humans. The current classification of coronaviruses recognizes 39 species in 27 subgenera that belong to the family Coronaviridae. From those, at least 7 coronaviruses are known to cause respiratory infections in humans. Four of these viruses can cause common cold-like symptoms. Those that infect animals can evolve and become infectious to humans. Three recent examples of these viral jumps include SARS CoV, MERS-CoV and SARS CoV-2 virus. They are responsible for causing severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and the most recently discovered coronavirus disease during 2019 (COVID-19).

COVID-19, a respiratory disease caused by the SARS-CoV-2 virus, was declared a pandemic by the World Health Organization (WHO) on 11 March 2020. The rapid spread of the disease has taken the scientific and medical community by surprise. Latest figures from 20 May 2020 show more than 5 million people had been infected with the virus, causing more than 330,000 deaths in over 210 countries worldwide.

The large amount of information received daily relating to COVID-19 is so abundant and dynamic that medical staff, health authorities, academics and the media are not able to keep up with this new pandemic.

In order to offer a clear insight of the extensive literature available, we have conducted a comprehensive literature review of the SARS CoV-2 Virus and the Coronavirus Diseases 2019 (COVID-19).

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Abbreviations: ACE2, angiotensin-converting enzyme-2; ARDS, acute respiratory distress syndrome; CDCC, The Center for Disease Control in China; COVID-19, Coronavirus disease 2019; ELISA, enzyme-linked immunosorbent assay; GISAID, Global Initiative on Sharing All Influenza Data; INF, interferon; ISGs, IFN-stimulated genes; MERS, Middle East respiratory syndrome; MHC-I, major histocompatibility complex I; ORF, open reading frames; PDB, Protein Data Bank archive; pDCs, plasmacytoid dendritic cells; RCSB, Research Collaboratory for Structural Bioinformatics; RNA, ribonucleic acid; RdRp, RNA-dependent RNA polymerase; RBD, receptor-binding domain; SARS-CoV-2, severe acute respiratory syndrome Coronavirus 2; SARS, severe acute respiratory syndrome; TCGA, The Cancer Genome Atlas; TLRs, endosomal toll-like receptors; WHO, World Health Organization.

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https://doi.org/10.1016/j.diagmicrobio.2020.115094
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Contents

1. Background

The new COVID-19 disease is caused by a Novel Coronavirus (SARS-CoV2) probably originated in Wuhan, China. In mid-December 2019, the Wuhan health authorities detected few cases of an atypical pneumonia that eventually was discovered to be caused by a novel coronavirus. It probably jumped from an animal reservoir to a human during the first week of November 2019(Shanker, 2020).

Subsequent investigations discovered that the etiological agent was a RNA virus related to the same family of Coronavirus that caused the Severe Acute Respiratory Syndrome (SARS) and to Respiratory Syndrome of Middle East (MERS) pandemic during 2003 and 2012 respectively (Lu et al., 2020).

The specific origin of this new pandemic is not totally understood. At the beginning of the outbreak it was believed that a viral jump occurred between a wild animal and a human being in one of the most populated *wet market* in Wuhan, China during the November 2019. Further investigations were focused around identifying which animals were responsible for these new zoonotic diseases Although it still remains unclear which animal is the intermediary host, it is well-known that bats are the main reservoirs for these types of virus and they probably emerged in one of the local wild-animal farms (Giri et al., 2020; Lorusso et al., 2020).

1.1. Chronology of the pandemic

The Center for Disease Control in China (CDCC) reported that during the last week of December 2019, the first cases of an atypical pneumonia were seen in Wuhan, the capital of Central China's Hubei province. Days later, after the first cases were reported, the Chinese health authorities decided to close the Huanan's "wet market" after some research suggested this place as the probable initial source of contagion (Rothan and Byrareddy, 2020).

During the first week of January, China's authorities announced that the new atypical pneumonia was not caused by either the SARS or the MERS Coronavirus, but a new variant of the Coronaviriade family, a newly discovered virus called SARS-CoV2 (Rothan and Byrareddy, 2020).

On January 11, the first SARS CoV-2 related death was reported and 1 day later, a group of Chinese researchers revealed the genome of the virus implicated in the Wuhan pneumonia outbreak.

From the initial case reported in China, the SARS-CoV-2 virus spread worldwide. At the beginning of the outbreak it started to move through Asia but only days later the first suspicious cases were reported in Europe and North America. On March 11, the World Health Organization (WHO) declared this disease a worldwide distributed pandemic. Since the first case and using the latest figures from April the 14, 2020, more than 2 million people had been infected with the virus, causing more than 120,000 deaths in over 210 countries worldwide (Dong et al., 2020a).

1.2. Epidemiology trends for COVID-19

Reviewing the data collected from the WHO-Coronavirus Disease (COVID-2019) situation reports, the Center for Systems Science and Engineering (CSSE) from Johns Hopkins University and the Worldometers databases, the latest figures from 20 May2020 show more than 5,090,118 people had been infected with the virus from over 210 countries, with more than 333,000 deaths worldwide. There have also been roughly 2,546,198 recovered cases.

The epidemiological dynamics of COVID-19 has changed dramatically over the course of months. At the beginning of the outbreak, the most affected continent was Asia, with China being the most affected country worldwide, however, nowadays, the Americas, driven mainly by the USA and Brazil, have converted the region in the most affected on the planet (Simbana-Rivera et al., 2020). It is important to emphasize that mortality has an important variability among each of the countries, for instance, South Korea has very low mortality rates, showing a very efficient testing strategy and an excellent response to the emergency, while other countries with less testing capacities, weaker health systems and overall poorer responses to the virus, report higher attack, mortality and case fatality rates (Ortiz-Prado et al., 2020).

The transmission of COVID-19 is by droplets expelled when speaking or sneezing within a 2-meter distance, or by being in contact with exposed surfaces. Fifty percent of transmissions occur secondary to exposure to an asymptomatic people. In-fact one sign of infection of COIVD-19 is a symptom of anosmia (see below) in asymptomatic patients without nasal obstruction. Additionally, patient can transmit the infection up to 2 weeks after having recovered from symptoms of the disease. Transmission through fecal-oral stool is reported to be unlikely. Perinatal transmission has not been detected.

The basic reproduction number (R naught also known as R_0) is a measure that quantifies the epidemic potential of a pathogen. This number is defined as the average number of persons an infected person can spread the virus. Based on standard epidemics, having R_0 greater than 1 could lead to potential spread of diseases. The basic reproduction rate of SARS-CoV-2 ranges between 2.4 and 3.3, numbers that vary in relationship with mobility, containment measures, susceptibility, population at risk among other parameters. In this sense, each infected person would therefore infect 2 or 3 other people (Peiris et al., 2004; Zhu et al., 2020).

The incubation period of COVID-19 typically ranges from 2 to 14 days (98% of patients), with an average of 5 days, although there have been cases with incubations periods of up to 24 days. Typically, the time from infection onset to development of severe disease [including hypoxia] is one week.

COVID-19 generally causes flu-like symptoms, such as fever (80-90%), non-productive cough (50%) and lethargy (20-40%) although in some patients', diarrhea may precede these symptoms.

In specific patient groups, particularly the elderly and those with chronic health conditions, symptoms may progress into pneumonia, with tightness-chest pain and fatigue. After a week, it can lead to difficulty breathing, with approximately 20% of patients requiring hospital treatment. COVID-19 infection rarely seems to cause a runny nose, sneezing, or sore throat [these symptoms have been seen in approximately 5% of patients]. In China, reportedly 80.9% of COVID-19 infections are mild [with flu-like symptoms] and recover at home without hospital intervention. Spain has a much lower figure of home recovery without hospital admission (70%). Recovery from the onset of symptoms in mild cases is approximately 2 weeks and, with severe or critical illness, 3–6 weeks.

China had much lower percentages of the population that was tested and developed complex disease (including pneumonia) compared to Spain (13.8% vs. to 23% respectively).

Again, China had fewer critical patients than Spain (4.7% compared to 7% in Spain). Critical complications include respiratory failure, septic shock, and multiorgan damage.

It is important to understand that these figures depend on the percentage of the population screened, if repeat tests were included and the demographics of those tested. In average, the population age in Spain is 13 years older than that in China (Fig. 1).

In relation to radiographic detection, computed tomography is much more sensitive (86%) than the chest plate (59%) to identify those with COVID-19. Typically, radiographic features include ground glass patterned images, sometimes in patches, without frequently observing interstitial pattern.

Internationally, it is recognized that relatively few cases are seen in children and generally cases are more benign than in adults.

The risk of death increases as you get older. Mortality in the Chinese series of studies is <0.5% in patients younger than 50 years, 2% (50–59 years), 4% (60–69 years), 8% (70–79 years) and 16% (>80 years). The international average mortality is 3%, although there is a difference between countries depending on the average age, the ascending curve, the method used to register COVID-19, and the health services, especially ICU units. In Spain at the time of writing mortality is 67% in patients over 80 years, 20% in those aged between 70 and 79 years and 8% between 60 and 69 years. It is important to note that if identification of cases was universal across all the population, these figures may vary considerably. It is vital that reliable, comparable data is available internationally, to facilitate comparison of mortality data in Italy, Spain and other countries such as Germany or the USA (Fig. 2).

In addition to age, a further comorbidity that is potentially associated with severe illness associated with COVID-19 is hypertension (high blood pressure). One study found that 40% of seriously ill patients had hypertension. Other comorbidities potentially associated with poor outcome include such as diabetes, obesity, and cardiovascular and lung disease. This prevalence of hypertension has led to associating the possibility of treatment with ACE inhibitors or ARA2 and the severity of COVID-19, which we discuss below.

1.3. Structure and genome of the SARS-CoV-2 virion

The family *Coronaviridae* is a large group of viruses infecting animals and humans. There are 7 types of human coronaviruses that are primarily respiratory pathogens: 229E, NL63, OC43, KHU1, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), and Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). MERS-CoV, SARS-CoV and SARS-CoV-2 belong to genus *Betacoronavirus* and all have high mutation rates that result in viral genetic diversity, plasticity, and adaptability to invade a wide range of hosts (Walls et al., 2020).

Like other coronaviruses, SARS-CoV-2 is an enveloped virus with roughly spherical or moderately pleomorphic virions of approximately 60 to 140 nm in diameter (Fig. 3a) (Yan et al., 2020).

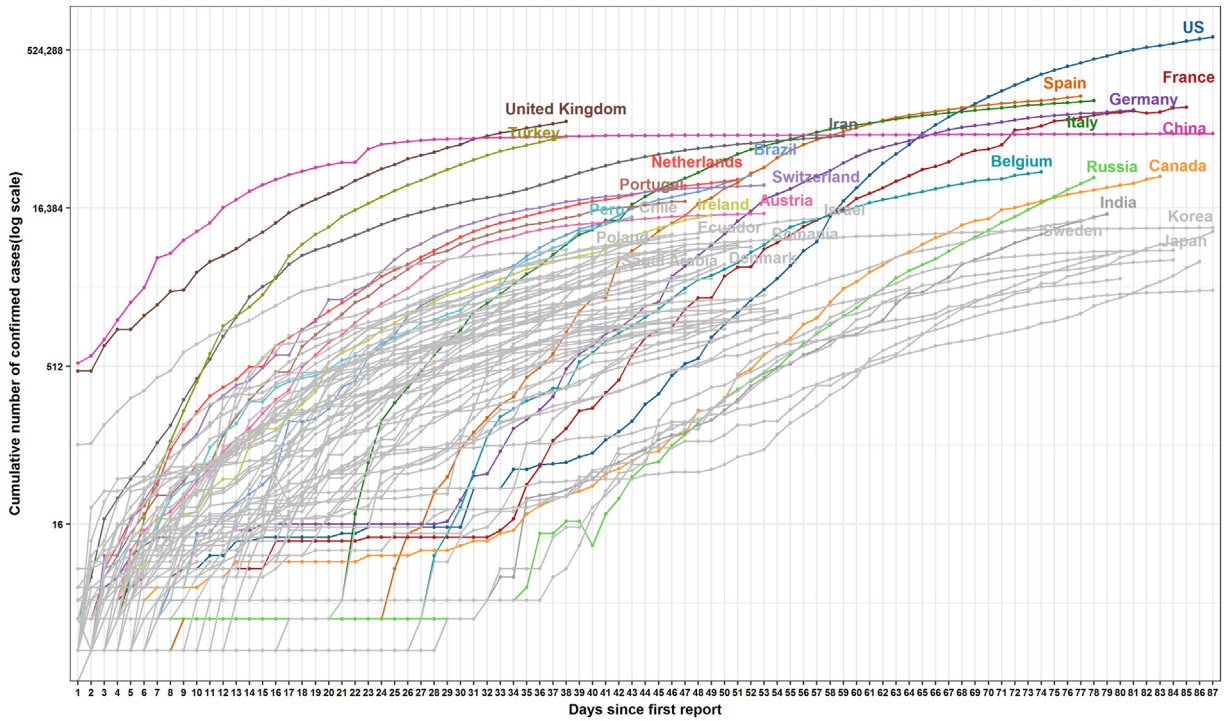

Fig. 1. Cumulative number of confirmed cases in the world from their first reporting day to day 87.

The viral membrane contains the spike (S) glycoprotein that forms the peplomers on the virion surface, giving the virus its "corona" – or crown-like morphology in the electron microscope. The membrane (M) glycoprotein and the envelope (E) protein provide the ring structure. Within the virion interior lies a helical nucleocapsid comprised of the nucleocapsid (N) protein complexed with a single positive-strand RNA genome of about 30 kb in length (Gralinski and Menachery, 2020).

The first genome of SARS-CoV-2 named Wuhan-Hu-1 (NCBI reference sequence NC_045512) was isolated and sequenced in China in January 2020 (Gralinski and Menachery, 2020; Yan et al., 2020). The SARS-CoV-2 genome has similarities to other viruses: approximately 96% similarity to the bat coronavirus BatCoV RaTH13; an estimated 80% similarity with SARS-CoV (Gralinski and Menachery, 2020), and an estimated 50% identity with MERS-CoV (Wu et al., 2020a; Wu et al., 2020b). SARS-

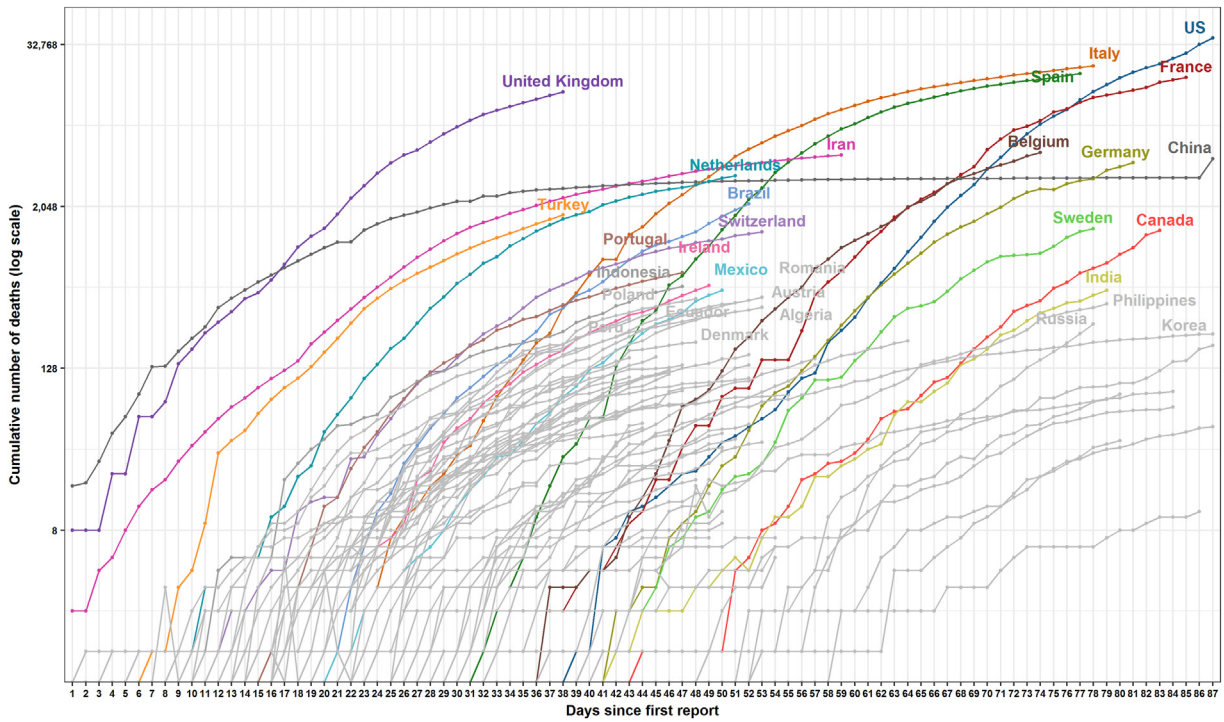

Fig. 2. Cumulative number of confirmed deaths in the world from their first reporting day to day 87.

CoV-2 has a positive-sense single-stranded RNA genome. It is approximately 30,000 bases in length and comprises of a 5′ terminal cap structure and a 3′ poly A tail. According to Wu et al. (Elbe and Buckland-Merrett, 2017), this Novel Coronavirus (IVDC-HB-01/2019 strain) has 14 open reading frames (ORFs) encoding 29 proteins. The 5′ terminus of the genome contains the ORF1ab and ORF1a genes. ORF1ab is the largest gene and encodes the pp1ab protein that contains 15 non-structural proteins named nsps (nsp1-nsp10 and nsp12-nsp16). ORF1a encodes the pp1a protein and also has 10 nsps (nsp1-nsp10) (Elbe and Buckland-Merrett, 2017). The 3′ terminus of the genome contains 4 structural proteins: spike (S) glycoprotein; envelope (E) protein; membrane (M) glycoprotein and nucleocapsid (N) phosphoprotein. It also contains 8 accessory proteins (3a, 3b, p6, 7a, 7b, 8b, 9b and ORF14) (Shu and McCauley, 2017) (Fig. 3b).

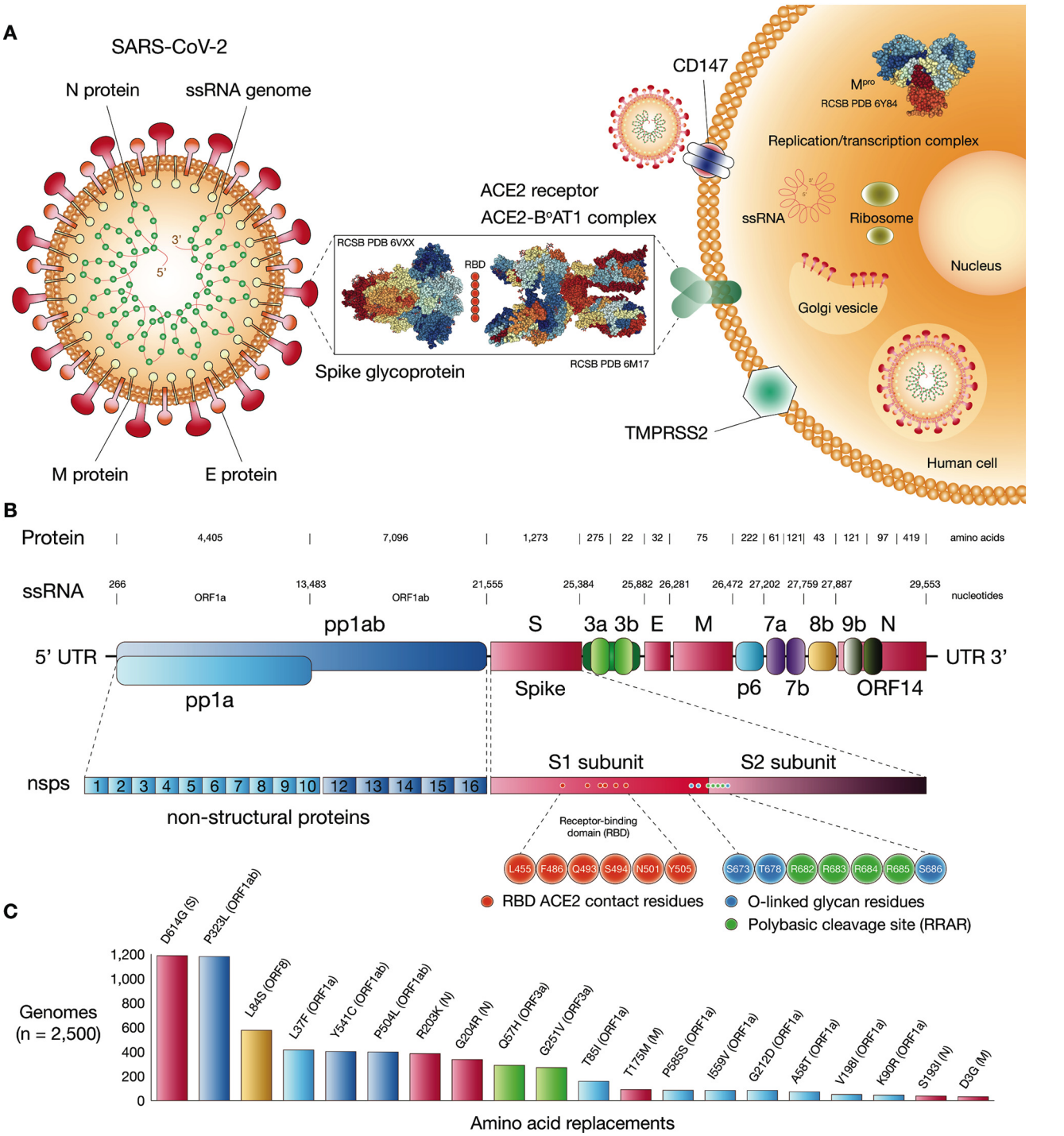

Fig. 3. Overall structure and mechanism of infection of SARS-CoV-2. A) Structure and mechanism of infection of the novel coronavirus into human cells through the spike glycoprotein, the ACE2 receptor protein, and the CD147 receptor. The structure of the spike glycoprotein was taken from RCSB PDB 6VXX according to Walls et al. (Zhang et al., 2020a); the structure of the ACE2-BoAT1 complex was taken from RCSB PDB 6M17 according to Yan et al. (Zhou et al., 2020a); lastly, the structure of the main protease (Mpro) was taken from RCSB PDB 6Y84 according to Zhang et al. (Lu et al., 2020). B) Genomic structure and proteins encoded by SARS-CoV-2. C) Genomic structure and proteins encoded by SARS-CoV-2. D) Most frequent amino acid replacements in genomes analyzed worldwide.

The global scientific community from 58 countries have united to study this novel coronavirus by sequencing and submitting 12,059 SARS-CoV-2 genomes to the Global Initiative on Sharing All Influenza Data (GISAID) (https://www.gisaid.org/) between December 2019 and April 2020 (Kirchdoerfer et al., 2016; Yuan et al., 2017). SARS-CoV-2 has accumulated mutations in its RNA genome as the outbreak progresses.

From the 12,509 viral genomes of SARS-CoV-2 sequences analyzed to date in the outbreak, the CoV-GLUE project (http://cov-glue.cvr.gla.ac.uk/#/home) has identified 5,033 amino acid replacements where 952 mutations were found in nsp3 (ORF1a) corresponding to the papain-like protease (PL^{pro})/transmembrane domain 1, 687 were found in the S glycoprotein; 457 were found in nsp2 (ORF1a); 334 were found in the N phosphoprotein; 310 were found in nsp12 (ORF1ab) corresponding to the RNA-dependent RNA polymerase (RdRp); 253 were found in nsp14 (ORF1ab) corresponding to the 3′-5′ exonuclease; 200 were found in nsp4 (ORF1a) corresponding to the transmembrane domain 2; 222 were found in nsp13 (ORF1ab) corresponding to the Zinc-binding domain / helicase domain; 261 were found in nsp15 (ORF1ab) corresponding to the endoRNAse; 228 were found in ORF3a, 153 were found in nsp16 (ORF1ab) corresponding to the 2′-O-ribose methyltransferase; 123 were found in nsp6 (ORF1a) corresponding to the putative transmembrane domain; 116 were found in ORF7a; 107 were found in nsp5 (ORF1a) corresponding to the 3C-like proteinase; 116 were found in nsp1 (ORF1a); 95 were found in the M glycoprotein; 103 were found in ORF8; 48 were found in nsp10 (ORF1a) and ORF6; 35 were found in ORF10; 68 were found in nsp8 corresponding to the putative primase; 45 were found in the E protein; 43 were found in nsp9 corresponding to the ssRNA-binding domain; 32 were found in nsp7; 40 were found in ORF7b; and 9 were found in nsp11. The most prevalent amino acid replacements were D614G (S glycoprotein) in 6,855 sequences, P323L (RdRp) in 6,819 sequences, Q57H (ORF3a) in 2,666 sequences, T85I (nsp2) in 2,184 sequences, and R203K (N phosphoprotein) in 1,944 sequences (Fig. 3c and Supplementary Table 2).

1.4. SARS-CoV-2 replication cycle

As an intracellular obligate microorganism, the coronavirus exploits the host cell machinery for its own replication and spread. Since virus–host interactions form the basis of diseases, knowledge about their interplay is of great importance, particularly when identifying key targets for antivirals.

SARS-CoV-2 entry into host cells is mediated by the transmembrane S glycoprotein that forms homotrimers protruding from the viral surface (Fig. 3a) (Zhang et al., 2020a). Coronavirus S protein consists of 2 functional subunits: S1 subunit, where the receptor-binding domain (RBD) is found and is responsible for binding host cell surface receptors and S2 subunit, which mediates subsequent fusion between the viral and host cellular membranes (Li et al., 2003a; Hoffmann et al., 2020a).

SARS-CoV-2 RBD directly binds to the peptide domain of angiotensin-covering enzyme 2 (ACE2), which is also the cellular receptor for the SARS-CoV (Wan et al., 2020; Zhang et al., 2020a; Zhou et al., 2020a; Wu et al., 2020c). RBD is the most variable part of SARS-CoV-2 genome (Andersen et al., 2020; Gralinski and Menachery, 2020). Six RBD amino acids (L455, F486, Q493, S494, N501 and Y505) are involved in the binding to ACE2 receptors (Donoghue et al., 2000), and 5 of these 6 residues differ between SARS-CoV and SARS-CoV-2 (Liu et al., 2011) (Fig. 3a and b).

ACE2 is a type I membrane protein that participates in the maturation of angiotensin, a peptide hormone that controls vasoconstriction and blood pressure (Kuba et al., 2005). In the respiratory tract, ACE2 is widely expressed on the epithelial cells of alveoli, trachea, bronchi, bronchial serous glands (Xu et al., 2020a), and alveolar monocytes and macrophages (Forrest et al., 2014). Xu *et al*. reported the (Hoffmann et al., 2020b) RNA-seq profiling data of 13 organs with para-carcinoma normal tissues from The Cancer Genome Atlas (TCGA; https://www.cancer.gov/tcga) and 14 organs with normal tissue from FANTOM5 CAGE (https://fantom.gsc.riken.jp/). These were used to validate the expression of the human cell receptor ACE2 in the virus and may indicate the potential infection routes of SARS-CoV-2 (Coutard et al., 2020). Interestingly, the ACE2 receptor is expressed more in oral cavity than lung. This potentially could indicate that susceptibility and infectivity of SARS-CoV-2 is greater from oral mucosa surfaces (Hoffmann et al., 2020b).

Following the binding of the RBD in the S1 subunit to the receptor ACE2, SARS-CoV-2 S protein is cleaved by the cell surface-associated transmembrane protease serine 2 TMPRSS2, which activates S2 domain for membrane fusion between the viral and cell membrane (de Wilde et al., 2018). A functional polybasic (furin) cleavage site was found at the S1-S2 boundary through the insertion of 12 nucleotides (Liu et al., 2011; Lim et al., 2016; Zhang et al., 2020a). The S673, T678 and S686 residues of O-linked glycans flank the cleavage site and are unique in SARS-CoV-2 (Liu et al., 2011).

In addition to the S glycoprotein–ACE2 receptor complex, Wang et al. reported an alternative route where SARS-CoV-2 invades host cell through the S glycoprotein – CD147 complex. These findings were validated using co-immunoprecipitation, ELISA, and *in vitro* antiviral tests with meplazumab. This anti-CD147 humanized antibody significantly inhibited the viruses from invading host cells (https://doi.org/10.1101/2020.03.14.988345; Paper: SARS-CoV-2 invades host cells via a novel route: CD147-spike protein).

Like SARS-CoV and other coronaviruses, SARS-CoV-2 likely enters target cells through receptor-mediated endocytosis, where fusion of the virus envelops the endosome membranes and leads to the release of the viral nucleocapsid into the cytosol of the infected cell (Knoops et al., 2008).

Following the release and uncoating of viral RNA to the cytoplasm, coronavirus replication starts with the translation of ORF1a and ORF1b into polyproteins pp1a and pp1ab via a frameshifting mechanism (Fig. 4) (Weiss and Navas-Martin, 2005). Subsequently, polyproteins pp1a and pp1ab are processed by internal viral proteases, including the main protease M^{pro}, a potential drug target whose crystal structure was recently determined for SARS-CoV-2 (Lu et al., 2020). Polyprotein cleavage yields 15 mature replicase proteins, which assemble into a replication-transcription complex that engages in negative-strand RNA synthesis. Both full-length and multiple subgenomic negative-strand RNAs are produced. The former serves as template for new full-length genomic RNAs and the latter template the synthesis of the subgenomic mRNAs required to express the structural and accessory protein genes residing in the 3′-proximal quarter of the genome (Knoops et al., 2008). Coronavirus RNA replication occurs on a virus-induced reticulovesicular network of modified endoplasmic reticulum (ER) membranes (Neuman et al., 2011).

The assembly of virions is quickly ensued with the accumulation of new genomic RNA and structural components. The N protein complexes with genome RNA, forming helical structures. Then, the transmembrane M protein, localized to the intracellular membranes of the ER – Golgi intermediate compartment (ERGIC), interacts with the other viral structural proteins (S, E, and N proteins) to allow the budding of virions (Chen et al., 2020a; Huang et al., 2020a). Following assembly and budding, virions are transported in vesicles and eventually released by exocytosis.

1.5. SARS CoV-2 and human immune responses

Normal immune responses against the majority of viruses involve a rapid containment phase mediated by innate immunity components and – if necessary – a delayed, yet more sophisticated adaptive immunity phase that should be able to eradicate the pathogen and –hopefully – generate long-lasting immunological memory. The former includes antiviral Type I interferons (IFNs), and macrophage and neutrophil activation that leads to pro-inflammatory cytokine production and NK cells. On the other hand, anti-viral adaptive immune responses involve a virus-tailored coordinated attack by antigen specific CD8+ cytotoxic T cells (CTLs), the Th1 subset of CD4+ T helper cells that orchestrates

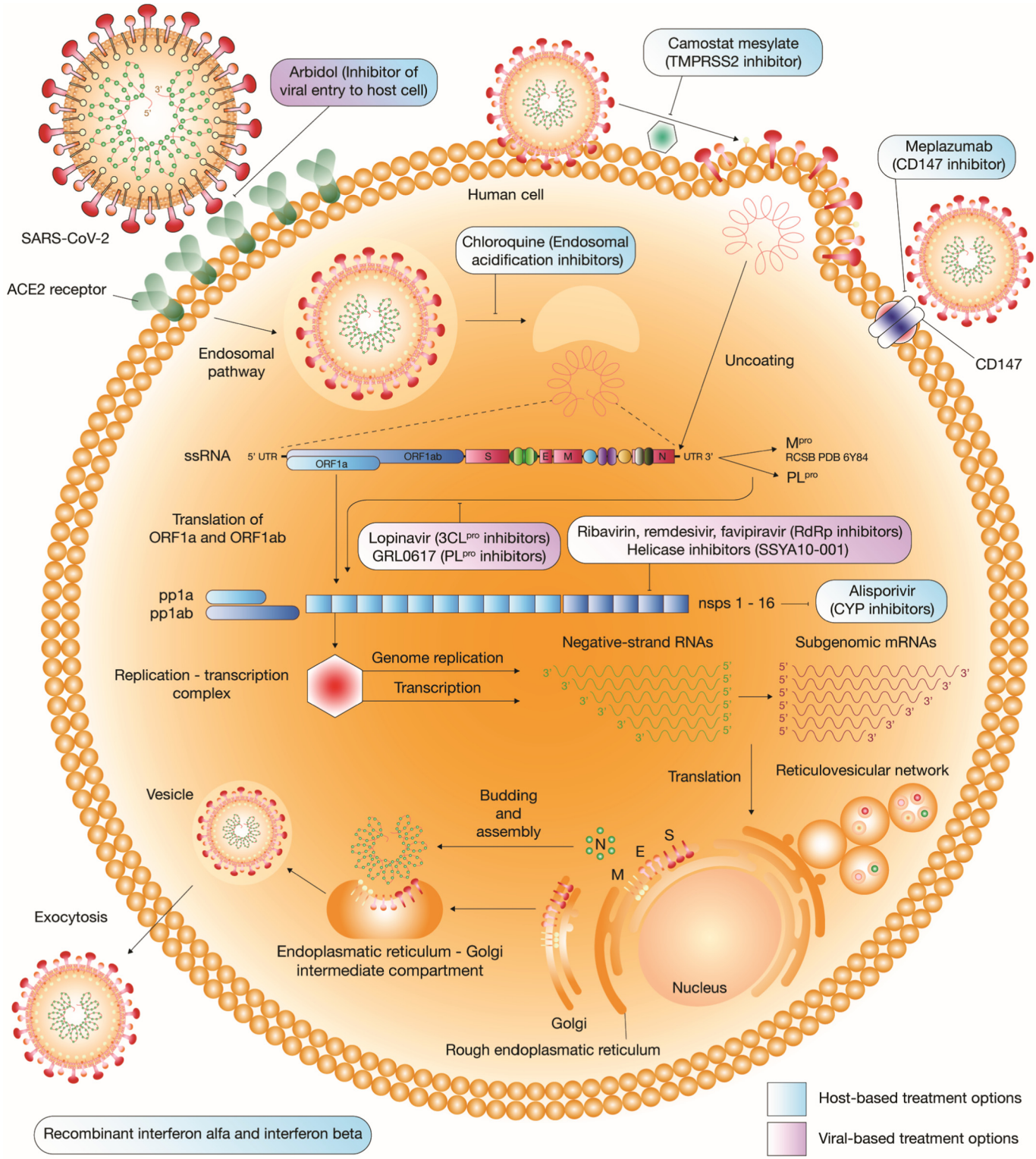

Fig. 4. . SARS-CoV-2 replication cycle and its inhibitors. SARS-CoV-2 infection begins with the attachment of the spike (S) protein with the host cell receptor. Two cellular receptors have been identified for SARS-CoV-2 so far: angiotensin-converting enzyme 2 (ACE2) and CD147. After receptor interaction, the cleavage of S protein by the cell surface-associated transmembrane protease serine 2 TMPRSS2 promotes the fusion of viral and cell membranes. Following the release of the nucleocapsid to the cytoplasm, the viral genomic RNA is translated through ribosomal frameshifting to produce polyproteins pp1a and pp1ab, which undergo cotranslational proteolytic processing into the 15 non-structural proteins (nsp1-nsp10 and nsp12-nsp16) that form the replication-transcription complex (RTC). The RTC is involved in the genomic RNA replication and in the transcription of a set of nested subgenomics mRNAs required to express the structural and accessory protein genes. New virions are assembled by budding into the intracellular membranes of the ER-Golgi intermediate compartment membranes and released through exocytosis. Additionally, there are detailed host-based treatment options in blue and viral-based treatment options in pink.

the immune response against viruses and other intracellular pathogens, specific antibody producing plasma cells, and finally the production of memory T and B cell subsets.

Immune responses following SARS-CoV-2 infection can be a double-edged sword. A rapid and robust Type I IFN orchestrated response can lead to virus clearance and – given that antiviral lymphocytes are

activated and expanded – immune memory. Conversely, a late activation of innate immunity, possibly owing to is usually associated with severe pathology that can lead to pneumonia, ARDS, septic shock, multi-organ failure and, eventually, death. In this line, a delayed Type I IFN response and inefficient SARS-CoV-2 clearance by alveolar macrophages can promote excessive viral replication that can lead to severe pathology accompanied by increased viral shedding and, thus, viral transmissibility.

Accordingly, in patients whose immune system is weakened or otherwise dysregulated, such as older men with comorbidities, severe COVID-19 is clearly more likely to occur (He et al., 2020; Yang et al., 2020a; Zhou et al., 2020b).

A recent study has demonstrated that the average duration of SARS-CoV-2 viral shedding was 20 days after COVID-19 onset, raising a debate as to the optimal time of patient isolation(Bai et al., 2020a). However, in terms of transmission viral shedding seems to be more relevant in the early phases of the infection as it can precede COVID-19 symptoms by 2–3 days whilst up to 50% of infections are associated with viral shedding by asymptomatic cases (Schoggins and Rice, 2011; Kell and Gale Jr, 2015; Tong et al., 2020) Therefore, individuals that mount efficient containment-phase immune responses accompanied by decreased inflammatory responses will not experience infection- or immune response-mediated overt manifestations, but may be important silent spreaders of SARS-CoV-2.

1.5.1. Innate immunity

Type I IFNs are mainly produced by plasmacytoid dendritic cells (pDCs) and have a plethora of antiviral effects such as blocking cell entry and trafficking of viral particles, inducing RNase and DNase expression to degrade virus genetic material, enhancing presentation of viral antigens by MHC-I, inhibiting protein synthesis, inducing apoptosis of infected cells and activating anti-viral subsets such as macrophages and cytotoxic NK cells and T lymphocytes (Yoneyama and Fujita, 2009).

Pathogen recognition receptors like cytosolic RIG-I and MDA-5 (Diebold, 2008; Ma and Suthar, 2015) or endosomal Toll-like receptors (TLRs) 7 and 8 that recognize viral RNA (Nelemans and Kikkert, 2019) are responsible for the activation of signaling cascades that activate the transcription factors NF-κB, interferon regulatory factor (IRF) 3 and IRF7 that translocate to the nucleus and induce proinflammatory cytokines and Type I interferon (IFN) production. In turn, Type I IFNs activate the downstream JAK-STAT signal pathway resulting in expression of IFN-stimulated genes (ISGs) (Dandekar and Perlman, 2005; Channappanavar and Perlman, 2017).

Our experience from SARS-CoV and MERS-CoV infection has shown that delayed type I IFN production and excessive recruitment and activation of infiltrating proinflammatory cells (neutrophils and monocytes-macrophages) are possible mediators of lung dysfunction and bad prognostic factors for the outcome of the infection. Delayed type I IFN production allows for highly efficient viral replication that, in turn, results in recruitment of hyperinflammatory neutrophils and monocytes. Therefore, the pathogen recognition receptors (PRRs) of these proinflammatory cells recognize high numbers of their ligands and subsequently secrete excessive amounts of proinflammatory cytokines that lead to septic shock, lung pathology, pneumonia or acute respiratory distress syndrome.

It has been shown that in severe cases both SARS-CoV and MERS-CoV fruitfully employ an immune evasion mechanism whereby early type I IFN responses to viral infection are dampened (Channappanavar and Perlman, 2017). This can be achieved by blocking signaling both upstream, as well as downstream of type I IFN expression. SARS-CoV can inhibit IRF3 nuclear translocation, whereas MERS-CoV can impede histone modification (Kindler et al., 2016). Additionally, both viruses can inhibit IFN signaling by decreasing STAT1 phosphorylation (de Wit et al., 2016). Due to the many sequence similarities of SARS-CoV-2 with SARS-CoV and MERS-CoV it would be enticing to speculate that similar mechanisms are also present, however further studies are needed to shed light to this hypothesis.

Hyperactivated neutrophils and monocytes-macrophages are the usual source of the cytokine storm. In this aspect, absolute neutrophil counts and neutrophil to lymphocyte ratio (NLR) were strongly associated with disease severity in a large cohort of COVID-19 patients and were proposed as markers of adverse disease prognosis (Qin et al., 2020).

Interestingly, the increased amounts of proinflammatory cytokines in serum associated with pulmonary inflammation and extensive lung damage described both in SARS (Wong et al., 2004a) and MERS diseases (Mahallawi et al., 2018) were also reported in the early study of 41 patients with COVID-19 in Wuhan (Huang et al., 2020a). Evidence shows that the leading cause of COVID-19 mortality is respiratory failure caused by acute respiratory distress syndrome (ARDS). There is an association with a cytokine storm mediated by high-levels of proinflammatory cytokines including IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A, and TNF-α. ARDS was associated with increased fatality and subsequent studies confirmed IL-6 and C-reactive protein are significantly upregulated in patients that died compared to convalescent patients (Kindler et al., 2016) Moreover, a recent study of 452 patients in Wuhan identified that severe cases showed significantly higher cytokines and chemokines such as tumor necrosis factor-α (TNF-α), IL-2, IL-6, IL-8, and IL-10 expressed (Qin et al., 2020).

In accordance with these findings, therapeutic strategies are being tested. A phase 3 randomized controlled trial of IL-1 blockade (anakinra) in sepsis has shown significant survival benefit in patients with hyperinflammation, without apparent increased adverse events (Shakoory et al., 2016). Currently, a multicenter, randomized controlled trial of tocilizumab (IL-6 receptor blockade, licensed for cytokine release syndrome), is being trialed in patients with COVID-19 pneumonia presenting with high levels of IL-6 in China (ChiCTR2000029765) (*Chinese Clinical Trial Registry*, 2020). Moreover, several clinical trials are exploring if the well-established antiviral (Savarino et al., 2003) and anti-inflammatory effects of hydroxychloroquine will be effective in treating patients with COVID-19 as has previously been suggested for SARS-CoV infection (Vincent et al., 2005). This has also been demonstrated *in vitro* for SARS-CoV-2 (Yao et al., 2020). In contrast, Janus kinase (JAK) inhibition has been proposed as a potential treatment in order to reduce both inflammation and cellular viral entry in COVID-19 (Richardson et al., 2020a). Thus, it comes as no surprise that in a recent correspondence, Lancet authors have identified the following potential therapeutic options for cytokine storm syndrome including ARDS the use of corticosteroids, selective cytokine blockade (eg, anakinra or tocilizumab) and JAK inhibition (Mehta et al., 2020).

1.5.2. Adaptive immunity

Virus presentation to the different T cell subsets stands on the crossroads between innate and adaptive immune responses. Studies on SARS-CoV and MERS-CoV (Hajeer et al., 2016) presentation have identified several susceptibility and protection conferring HLA alleles. The dearth of similar data regarding SARS-CoV-2 antigen presentation to T cells and possible virus evasion mechanisms of this process suggests it is a virgin investigation field to be explored.

Apart from the sustained inflammation and cytokine storm, lymphopenia has been implicated as a major risk factor for ARDS and mortality in the context of COVID-19 (Chan et al., 2020a). Similar findings were described for SARS-CoV infected patients who had considerable decreases of CD4+ T and CD8+ T cells (Keicho et al., 2009). However, in convalescent patients, specific T-cell memory responses to SARS-CoV were still found 6 years post infection (Tang et al., 2011). Though it is still very early to trace memory responses against SARS-CoV-2, the observations linking lymphopenia with severe pathology are similar to patients diagnosed with severe acute respiratory syndrome (SARS) during the 2003 epidemic.

In a study of 452 Chinese patients in Wuhan, severe cases tended to have lower lymphocyte counts. This dearth of lymphocytes was mainly attributed to significantly lower T cell counts in severe cases. Numbers of CD8+ T lymphocytic cells responsible for recognizing and killing

infected cells were found to be significantly lower in patients with severe manifestations of COVID-19. Additionally, severely affected patients presented with a higher naïve CD4+ to memory T cells ratio, suggesting that the adaptive immune system in the severe infection subgroup was less activated. Furthermore, these patients had less numbers of regulatory T cells (Tregs), especially induced Tregs. Tregs form the T cell subset responsible for controlling excessive inflammatory responses and their absence can lead to production of cytokine storm and enhancement of tissue pathology. Overall, this data suggest that dysregulation of T cell mediated immune responses may play a pivotal role in COVID-19 pathogenesis and severity (Qin et al., 2020).

Production of protective antiviral antibodies and long-lived memory B cells are fundamental for avoiding reinfection with the virus and form the basic principles behind vaccination. Less research has been completed relating to humoral immunity compared to than cellular against coronaviruses. However, in view of COVID-19 patient sera portraying some cross-reactivity with SARS-CoV, but not with other coronavirus, it might imply that similar mounting of humoral responses could be expected (Zhu et al., 2020). Studies conducted during the SARS epidemic have revealed that seroconversion is induced as early as day 4 after disease onset and that IgG protective antibodies lasted for as long as 2 years after infection (Liu et al., 2006) Anti-SARS-CoV IgM in turn disappeared after 12 weeks (Li et al., 2003b).

Preliminary data suggests that humoral responses are robust and follow a similar pattern. A study including 173 COVID-19 positive Chinese patients showed that 93.1% of the patients demonstrated anti-SARS-CoV-2 seroconversion. There was no late stage data available for the remainder of patients. Anti-SARS-CoV-2 antibodies were detected as early as 4 days' post disease onset, with a median time of positivity for IgM and IgG seroconversion being 11- and 14-days after disease onset, respectively. Interestingly, high antibody levels were not always found to be enough to clear the virus, as critically ill patients were found to have significantly higher virus specific antibody titers. However, the authors argue that combining viral nucleic acid and seroconversion detection significantly raised the detection sensitivity for patients (Zhao et al., 2020a). Another recent study where a new ELISA assay for anti-SARS-CoV-2 specific antibody detection was developed reported the existence of IgA specific antibody in patients' serum apart from the expected IgM and IgG isotypes. Notably, among IgG subtypes tested IgG3 exhibited the highest reactivity followed by IgG1, while IgG4 showed no reactivity with viral antigens. However, the small number of sera used ($n=4$) implies that further investigation is needed to corroborate these results (Amanat et al., 2020). Nonetheless, since we are currently in early stages of SARS-CoV-2 pandemic more studies need to be carried out to shed light on antibody persistence (both IgM and IgG) and protective effects.

Recently, macaques re-challenged with SARS-CoV-2 after a primary infection did not show signs of re-infection, suggesting that protective immunity and memory responses were fruitfully mounted. This finding can also impact vaccine production strategies (Bao et al., 2020).

Importantly, COVID-19 convalescent sera were shown to hold promise as a passive immune therapy alternative to facilitate disease containment (Casadevall and Pirofski, 2020). To the best of our knowledge, at least one pharmaceutical company, Takeda, is preparing to purify antibody preparations from COVID-19 convalescent sera against SARS-CoV-2 (Hopkins, 2020).

A recently published case report of a patient with mild-to-moderate COVID-19 revealed the presence of an increased activated CD4+ T cells and CD8+ T cells, antibody-secreting cells (ASCs), follicular helper T cells (TFH cells), and anti-SARS-CoV-2 IgM and IgG antibodies, suggesting that both cellular and humoral responses are important in containing the virus and inhibiting severe pathology (Thevarajan et al., 2020).

Antibody-dependent enhancement (ADE) is a mechanism whereby non-protective antibodies produced during an infection with an agent either mediate increased uptake of this agent into target cells or cross-recognize a different pathogen and facilitate its entrance to target cells (Sariol et al., 2018). Evidence emerging over the past 2 decades suggests that antibodies against different coronavirus can cross-react to some extent and mediate ADE (Yang et al., 2005). ADE in the context of SARS-CoV was thought to be mediated by antibodies produced against 229E-CoV (Yip et al., 2014) and was contemplated as contributing to high mortality rates in China (Ho et al., 2005). The described mechanism suggests that low affinity or low title anti-Spike protein antibodies rather than neutralizing the virus result in Fc receptor mediated infection of immune cells, further aggravating the dysregulation of anti-SARS-CoV immune responses (Jaume et al., 2011). Indeed, *in vitro* as well *as in vivo* experimental models have shown that ADE hinders the ability to manage inflammation in the lung and elsewhere. This may lead to ARDS and other hyperinflammation-induced clinical manifestations also observed in several of the documented cases of severe COVID-19 (Yoshikawa et al., 2009; Channappanavar et al., 2016). While the molecular and immunological host response to SARS-CoV-2 infection has

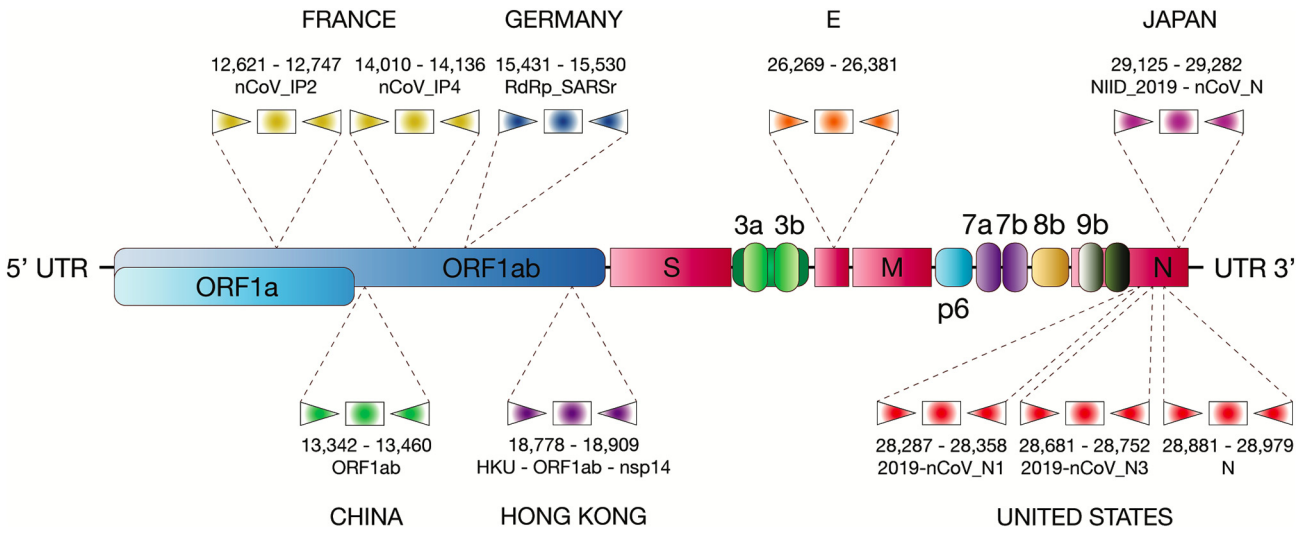

Fig. 5. qRT-PCR primer-probe set positions listed by WHO. USA CDC (2019-nCoV_N1, N2, and N3), the University of Hong Kong (HKU-N and HKU-ORF1b_nsp14), Charité universitätsmedizin Berlin establishment of virology in Germany (RdRp_SARSr and E), National Institute of Health in Thailand (WH-NIC N), National Institute of Infectious Disease in Japan (NIID_2019-nCoV_N), China CDC (N and Orf1ab), Institut Pasteur, Paris, France (nCoV_IP2, IP4 and E). E: envelope protein gene, S: spike protein gene; N: nucleocapsid protein gene. Nsp14: non-structural protein 14 gene, Orf1: open reading frame 1; RdRp: RNA-dependent RNA polymerase gene; The number below amplicons are genome positions as listed in SARS-CoV-2, GenBank MN908947.3

not yet been fully elucidated to confirm ADE is occurring, anti-SARS-CoV-2 antibodies have been shown to partially cross-react with SARS-CoV, suggesting enhancement is a possibility. With this in mind, ADE in populations previously exposed to other coronavirus can partially explain the geographic discrepancies observed in COVID-19 pathogenesis and severity. Finally, ADE can have several implications in vaccine development as low-affinity or low-titer antibody producing vaccines can increment susceptibility rather than confer protection against the pathogen as has previously been described for a Dengue vaccine (Halstead, 2016a; Halstead, 2016b; Halstead, 2016c).

1.6. Molecular diagnosis methods to detect COVID-19

1.6.1. RT-qPCR

Detection methods based on nucleic amplification are often used in the case of SARS-CoV, MERS-CoV and other viruses because of high sensitivity and specificity, particularly in the acute phase of infection (Kelly-Cirino et al., 2019). Case identification and surveillance of COVID-19 spread is mainly carried out by quantitative RT-PCR (RT-qPCR) targeting SARS-CoV-2 sequences. Recently, the WHO compiled a list including various protocols for detection of SARS-CoV-2, developed by researchers in China, Germany, Hong Kong, Japan, Thailand, France, and USA (WHO 2020). Relative positions of RT-qPCR primer-probe sets on the SARS-CoV-2 genome are shown in Fig. 5 and detailed in Table 1. (See Fig. 6.)

Although RT-qPCR assay is considered the gold-standard method to detect viruses such as SARS-CoV and MERS-CoV (Drosten et al., 2003; Corman et al., 2012), currently available RT-qPCR assays targeting SARS-CoV-2 have important considerations. Firstly, due to the genome similarity of SARS-CoV-2 to SARS-CoV (82% of nucleotide identity (Chan et al., 2020b)), some of the primer-probe sets described by different groups and listed in the WHO Coronavirus disease (COVID-19) technical guidance (WHO, 2020a), have cross-reaction with SARS-CoV and other bat-associated SARS-related viruses, therefore, it is important to run confirmatory tests.

Most of the tests enlisted in this review are currently available for use under a EUA by the FDA, a policy that aims to quicken the approval process for US labs developing tests for COVID-19. The approval is part of a concerted effort to make up for a lost time after delays and then a global shortage of the essential chemicals needed to make new tests (Table 2). Some companies have developed high-throughput equipment that automates sample RNA extraction, PCR assembly, and detection, thus avoiding some bottlenecks during the processing of samples mainly caused by the unavailability of reagents, consumables, and the lack of trained staff. For example, Xpert® Xpress SARS-CoV-2 is designed for use on Cepheid's GeneXpert® Systems that allows the addition of the patient's sample on cartridges where RNA extraction and PCR are carried out, allowing rapid diagnosis of large numbers of cases (AvellinoCoV2 Test, n.d.).

Table 2 Summarizes Commercially Available COVID-19 Diagnostic Tests with EUA status updated to March 26th, 2020. For the list of tests approved after this date see Supplementary Table 1.

1.7. Reverse transcription loop-mediated isothermal amplification (RT-LAMP)

Loop-mediated isothermal amplification (LAMP) is a one-step isothermal amplification reaction that couples amplification of a target sequence with 4 to 6 primers, to ensure high sensitivity and specificity, under isothermal conditions (63-65°C), using a polymerase with high

Table 1
Information of primers and probes recommended by WHO.

Target	Country	Institute	Name	Position	Reference
RdRp/Orf 1	China	China CDC	ORF1ab – F	13342–13362	(China, 2020)
			ORF1ab – R	13442–13460	
			ORF1ab – P	13377–13404	
	Germany	Charité	RdRp_SARSr - F	15431–15452	(Corman et al., 2020a)
			RdRp_SARSr – R	15505–15530	
			RdRp_SARSr – P2	15470–15494	
	Hong Kong	HKU	HKU – ORF1b – nsp14F	18778–18797	(Hong Kong University, 2020)
			HKU – ORF1b – nsp14R	18889–18909	
			HKU – ORF1b – nsp14P	18849–18872	
	France	Institut Pasteur, Paris	nCoV_IP2-12669F	12621–12641	(Institut Pasteur, Paris, 2020)
			nCoV_IP2-12759R	12727–12747	
			nCoV_IP2-12696bP	12696–12716	
			nCoV_IP4-14059F	14010–14030	
			nCoV_IP4-14146R	14116–14136	
			nCoV_IP4-14084P	14084–14104	
N	Japan	National Institute of Infectious Diseases	NIID_2019 – nCOV_N_F2	29125–29144	(WHO, 2020a)
			NIID_2019 – nCOV_N_R2	29263–29282	
			NIID_2019 – nCOV_N_P2	29222–29241	
	Thailand	National Institute of Health	WH – NIC N – F	28320–28339	(Department of Medical Sciences, Ministry of Public Health, Thailand, 2020)
			WH – NIC N – R	28358–28376	
			WH – NIC N – P	28341–28356	
	USA	CDC	2019 – nCoV_N1 – F	28287–28306	(Centers for Disease Control and Prevention, 2020)
			2019 – nCoV_N1 – R	28335–28358	
			2019 – nCoV_N1 – P	28309–28332	
			2019 – nCoV_N2 – F	29164–29183	
			2019 – nCoV_N2 – R	29213–29230	
			2019 – nCoV_N2 – P	29188–29210	
			2019 – nCoV_N3 – F	28681–28702	
			2019 – nCoV_N3 – R	28732–28752	
			2019 – nCoV_N3 – P	28704–28727	

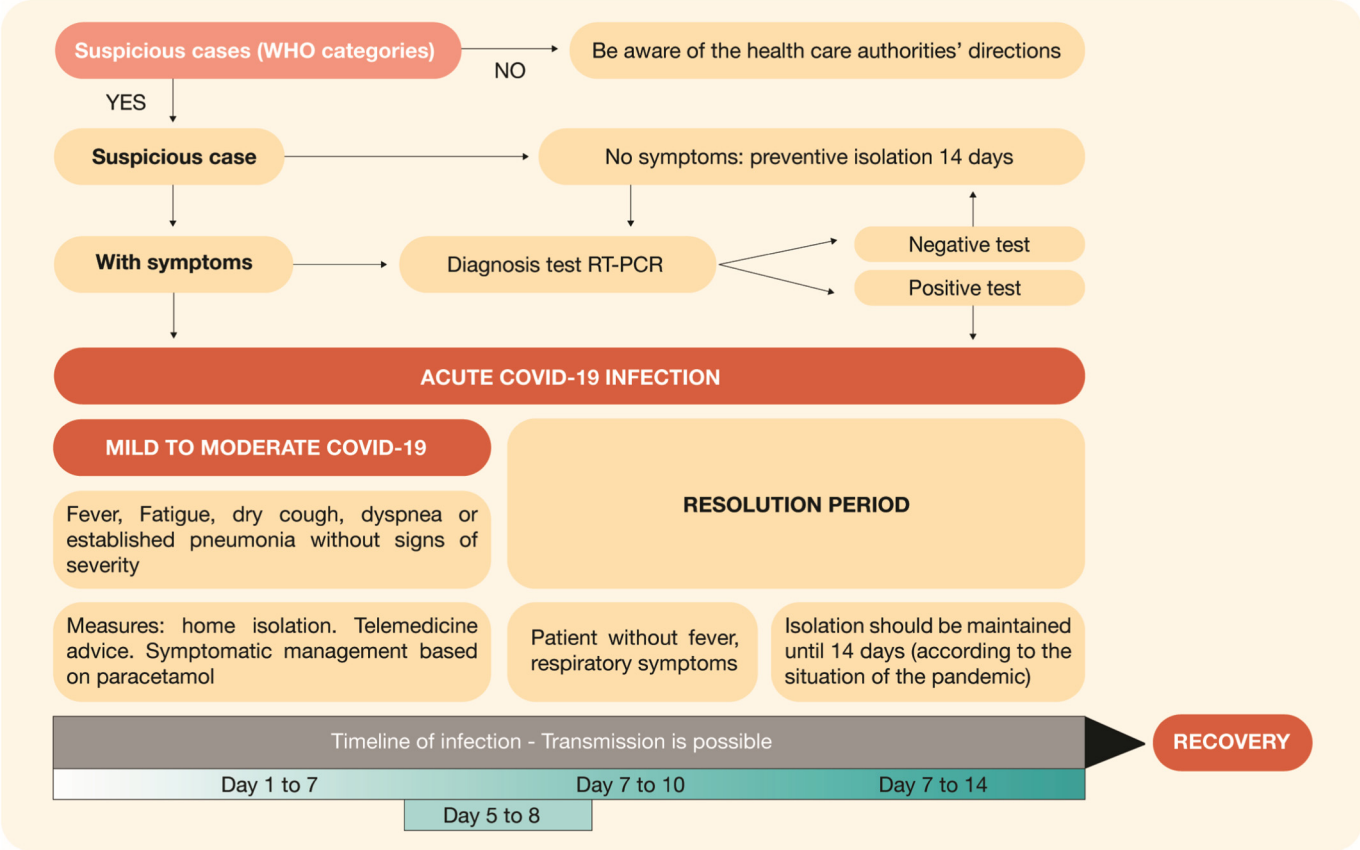

Fig. 6. Clinical features of patients with COVID-19.

strand displacement activity (Notomi et al., 2000). In the case of an RNA sample, LAMP, is preceded by the reverse transcription of the sample RNA. RT-LAMP has been used before for the detection of various pathogens (Perera et al., 2017). including SARS-CoV-2 and other respiratory viruses (Park et al., 2020; Shen et al., 2020a). Recently, it received emergency use authorization (EUA) from the US Food and Drug Administration (FDA) for a point-of-care test for the detection of Novel Coronavirus (COVID-19), delivering positive results in as little as 5 minutes and negative results in 13 minutes (Abbott, 2020).

1.7.1. Serological tests

Serological tests also, called immunoassays, are rapid and simple alternatives for screening of individuals that have been exposed to SARS-CoV-2 based on the qualitative or quantitative detection of SARS-CoV-2 antigens and/or anti-SARS-CoV-2 antibodies. There are several types of serological tests available, including ELISA (enzyme-linked immunosorbent assay), IIFT (indirect immunofluorescence test), lateral flow immunoassays and neutralization tests. Immunoassays assays are very useful because they allow to study the immune response(s) to SARS-CoV-2 in a qualitative and quantitative manner. In addition, help to determine the precise rate of the infection (Amanat et al., 2020; Pang et al., 2020), and to determine more precisely the fatality rate of the infection (Amanat et al., 2020). Several SARS-CoV-2 targeted serological tests are commercially available or in development (FIND, n.d.). A recently developed kit, reported a sensitivity of 88.66% and specificity of 90.63% (Li et al., 2020) using SARS-CoV-2 IgG-IgM combined antibody rapid (within 15 minutes) test (Li et al., 2020). Despite their simple and fast readout and their potential for being used outside laboratory environments (bedside, small clinics, airports, train stations, etc.), serological tests have a critical disadvantage; given the fact that antibodies specifically targeting the virus would normally appear after 6 days or longer (Cohen, 2020) after the illness onset (Al Johani and Hajeer, 2016), tests based on this principle have a lag period of approximately 4 to 7 days post-infection. During this lag period, infected and non-infected individuals will both result in a negative output. In addition, it is important to highlight that because serological tests depend on the ability to produce antibodies, intrinsic immunological differences and/or responses between individuals, can significantly affect the outcome of these tests. Recently, some commercially available immunoassays received CE Mark for professional use (Shenzhen Bioeasy Biotechnology, n.d.; Diagnostics, 2020), and therefore are registered as in vitro diagnostic devices.

Currently, there are a plethora of antibody tests for COVID-19 with variable performance (sensitivity varying from 45 to 100%, specificity from 96 to 100%, reviewed in (Foundation for Innovative New Diagnostics) (FIND, n.d.). Different manufacturers of serological assays declare that their assays have no cross reactivity to other human coronaviruses and other respiratory viruses. However, despite the data provided by manufacturers, recent studies highlighted that several of the commercially available tests have sensitivity and/or specificity issues that should be considered for using and analyzing results of many of these tests (Adams et al., 2020; Gonzalez et al., 2020; Kontou et al., 2020; Lassaunière et al., 2020; Whitman et al., 2020).

As mentioned before, immunoassays -particularly tests detecting anti-SARS-CoV-2 IgM and/or IgG- indicate that the person has been exposed to the virus. In the case of other viral infections, having antibodies targeting a pathogen has often been considered an indication of having immunity against that pathogen (Rouse and Sehrawat, 2010). Based on this idea, some governments have suggested using serological tests, to determine who has developed immunity against SARS-CoV-2 and provide positive individuals a "risk-free certificate" or "immunity passports", which would enable them to travel or to return to work, assuming that they are protected against re-infection (https://www.who.int/news-room/commentaries/detail/immunity-passports-in-the-context-of-covid-19, n.d.). However, based on the limited knowledge of

Table 2
Commercially available COVID-19 diagnostic tests with EUA status.

Company/ Organization	Test Name	Instrument	Test type	Time	Ref.
Carbon Health	COVID-19 Home Test Kits	NA	PCR	3 hours	(Coronavirus in California, 2020)
IDbyDNA	Explify Platform for respiratory diseases	NA	NGS	24 hours	(IDbyDNA, 2020)
Cepheid	Xpert® SARS-CoV-2	GeneXpert® System	PCR	45 minutes	(https://www.cepheid.com/, 2020)
Roche	cobas SARS-CoV-2 Test	cobas 6800 and 8800	PCR	4 hours	(Roche. cobas® SARS-CoV-2 Test, 2020)
Abbott	Abbott RealTime SARS-CoV-2 EUA test	m2000 RealTime system	PCR	1200 in 24 hours	(Abbott, 2020)
CDC USA	CDC 2019-Novel Coronavirus (2019-nCoV) Real-Time RT-PCR Diagnostic Panel (CDC)	NA	PCR	4 hours	(CDC, 2020)
DiaSorin Molecular	Simplexa COVID-19 Direct	LIAISON® MDX	PCR	6 hours	(COVID-19 Test DiaSorin Molecular, 2020)
Thermo Fisher	TaqPath COVID-19 Combo Kit	Applied Biosystems 7500	PCR	3.5 hours	(Thermo Fisher Scientific, 2020)
Hologic	Panther Fusion® SARS-CoV-2 test,	Panther Fusion ® System,	PCR	1150 in 24 hours	(Coronavirus Update, 2020)
Quidel	Lyra SARS-CoV-2	Applied Biosystems 7500 Fast DX	PCR	75 minutes	(Quidel, 2020)
GenMark Diagnostics.	ePlex SARS-CoV-2 Test	ePlex system	PCR	2 hours	(GenMark Receives, n.d.)
Integrated DNA Technologies	IDT 2019-Novel Coronavirus kit	NA	PCR	5 hours	(IDT, 2020)
LGC, Biosearch Technologies	2019-nCoV CDC-qualified Probe and Primer Kits for SARS-CoV-2	NA	PCR	-	(https://www.biosearchtech.com/products/pcr-kits-and-reagents/pathogen-detection/2019-ncov-cdc-probe-and-primer-kit-for-sars-cov-2, n.d.)
Wadsworth Center	New York SARS-CoV-2 Real-time RT-PCR Diagnostic Panel	NA	PCR	-	(Wadsworth Center, 2020)
Quest Diagnostics	Coronavirus Disease 2019 (COVID-19) Test	NA	PCR	4 days	(IDT, 2020)
BioMérieux/BioFire Defense	BioFire COVID-19 test	Filmarray® 2.0 and Torch	PCR	45min	(IDT, 2020)
Laboratory Corporation of America	LabCorp 2019 Novel Coronavirus test	NA	PCR	4 hours	(https://www.labcorp.com/coronavirus-disease-covid-19, n.d.)
Novacyt/Primerdesign	COVID-19 Genesig Real-Time PCR assay	NA	PCR	-	(https://www.genesig.com/products/10039-coronavirus-covid-19-ce-ivd, n.d.)
PerkinElmer	PerkinElmer New Coronavirus Nucleic Acid Detection Kit	NA	PCR	-	(https://perkinelmer-appliedgenomics.com/home/products/new-coronavirus-2019-ncov-nucleic-acid-detection-kit/, n.d.)
Abbot	ID NOW™ COVID-19 test	ID NOW platform	Isothermal amplification	5 min.	(Abbott, 2020)
BGI	Real-Time Fluorescent RT-PCR kit for detecting SARS-2019-nCoV	NA	PCR	3 hours	(https://www.genesig.com/products/10039-coronavirus-covid-19-ce-ivd, n.d.)
Cellex	qSARS-CoV-2 IgG/IgM Rapid Test	NA	Serological	10 min.	(https://medcitynews.com/2020/04/fda-oks-cellexs-antibody-based-test-for-covid-19/, n.d.)
Ipsum Diagnostics	COV-19 IDx assay	NA	PCR	4 hours	(https://www.genomeweb.com/molecular-diagnostics/ipsum-diagnostics-coronavirus-test-gets-fda-emergency-use-authorization, n.d.-a)
Luminex Molecular Diagnostics	NxTAGCoV Extended Panel Assa	ARIES® M1 Systems	PCR	4 hours	(Corporation, n.d.)
Mesa Biotech	Accula SARS-CoV-2 test	Accula System	PCR	30 min.	(https://www.genomeweb.com/regulatory-news-fda-approvals/mesa-biotech-covid-19-test-receives-fda-emergency-use-authorization, n.d.-b)
NeuMoDx Molecular	NeuMoDx SARS-CoV-2 Assay	NeuMoDx™ Molecular Systems	PCR	80 min.	(NeuMoDx Secures, 2020)
Qiagen	QiaStat-Dx Respiratory SARS-CoV-2 Panel	QIAstat-Dx Analyzer,	PCR	1 hour	(https://corporate.qiagen.com/newsroom/press-releases/2020/20200318_qiastat_covid19_ce-ivd, n.d.)

how immunity to this virus works (Tay et al., 2020), there is not enough evidence to declare a person immune, or to confirm that people who have anti-SARS-CoV-2 antibodies are protected from a re-infection.

1.7.2. Alternative methods

Even though COVID-19 can be diagnosed using qPCR as the gold standard, inadequate access to reagents and equipment has slowed disease detection even in developed countries such as the US. Several low cost and rapid tests using different approaches have been described.

The CRISPR-based SHERLOCK (Specific High Sensitivity Enzymatic Reporter UnLOCKing) technique for the detection of COVID-19 and the DETECTR (developed by Mammoth Biosciences) prototype rapid detection diagnosis kit using CRISPR to detect the SARS-COV-2 in human samples have been described (Broughton et al., 2020).

The use of RNA aptamers, have recently emerged as a powerful background-free technology for live-cell RNA imaging due to their fluorogenic properties upon ligand binding, a technology that could be of use to diagnose SARS-CoV-2 infection (Cawte et al., 2020).

Finally the use of next generation sequence (Explify®) might be used to detect and identify bacterial, viral, fungal, and parasitic pathogens by their unique genome sequences (IDbyDNA, 2020).

1.8. Clinical features of COVID-19

In COVID-19 symptomatic infection, the clinical presentation can range from mild to critical scenarios. The symptoms of a lower respiratory infection, pneumonia, is the most serious manifestation of COVID-19 infection.

Studies derived from the Wuhan population have established the most common clinical characteristics at the beginning of the disease: fever, fatigue and cough (Wang et al., 2020a). Other descriptive studies of Wuhan patients with confirmed COVID-19 have reported a similar range of clinical findings. In cohorts of patients outside of Wuhan, this clinical behavior is similar. At Zhejian province cohort of 62 people, only 1 case required mechanical ventilation assistance (Xu et al., 2020b).

1.9. Evolution of the disease: spectrum of clinical manifestations

The spectrum of symptoms of COVID19 infection are characteristic of a mild disease in most of the cases, however, it is important to point that the progression could lead to a severe respiratory distress.

1.9.1. Asymptomatic infection

Asymptomatic infection (while incubation occurs) was described both in the first cases in Wuhan and in other cohorts. A group of isolated patients were screened for SARS-CoV-2, where 17% (629 cases) were positive for the test, and half of these cases had no symptoms. On the other hand, there are reports of cases without overt symptoms in which there were ground glass images in the chest tomography in up to 50% of patients (Shen et al., 2015).

Of the asymptomatic cases studied in Wuhan city, the 2.5% of people exposed developed specific symptoms in 2.2 days, and the remaining 97.5% were symptomatic in the following 11.5 days (CI, 8.2–15.6 days). The median estimated incubation period was 5.1 days (95% CI, 4.5 to 5.8 days) (Lauer et al., 2019).

1.9.2. Acute infection: mild and moderate

Some patients with initially mild symptoms had symptom progression over the course of one week (Chen et al., 2020b). The descriptive studies available so far have concluded that the majority of cases are mild infections (more than 80% of cases); with up to 15% of patients being sever in most cohorts, and less than 5% have been considered as critical cases with high vital risk (Medical Association A., 2019).

In a study describing 138 patients with COVID-19 pneumonia in Wuhan, the most common clinical characteristics at the onset of the disease were described. This is consistent with other international cohorts (Table 3) (Wang et al., 2020a).

It is important to note that fever is not always present and up to 20% of patients could had a low grade temperature between 37.5 to 38 degrees Celsius or normal temperature (Huang et al., 2020b). If these patients required hospitalization, 89% developed a fever during the course of the illness. Rarer accompanying symptoms included headache without warning signs, odynophagia and rhinorrhea. Gastrointestinal symptoms such as nausea and watery diarrhea were relatively rare (Xu et al., 2020b).

Dyspnea develops after a median of 5 to 8 days from the onset of symptoms. It is important to notice that, if dyspnea is an important clinical finding, not all the patients with this symptom will develop severe respiratory distress or require oxygen supplementation (Wang et al., 2020a).

According to World Health Organization (WHO) guidelines, COVID-19 infection can present as pneumonia without signs of severity, and could be managed in the outpatient setting. This is applicable to those patients who do not need supplemental oxygen (Who, 2020).

Table 3
Clinical Manifestations of COVID 19 infection.

Clinical manifestations	Presentation n=138 n (%)	ICU* n=36 n (%)	Non-ICU n=102 n (%)
Fever	136 (98.6)	36 (100)	100 (98)
Fatigue	96 (70)	29 (80.6)	67 (65.7)
Dry Cough	82 (59.4)	21 (58.3)	61 (59.8)
Anorexia	55 (40)	24 (66.7)	31 (30.4)
Myalgia	48 (34.8)	12 (35.3)	36 (35.3)
Dyspnea	43 (31.2)	23 (63.9)	20 (19.6)
Sputum production	37 (27)	8 (22.2)	29 (28.4)
Pharyngalgia	24 (17.4)	12 (33.3)	12 (11.8)
Diarrhea	14 (10.1)	6 (16.7)	8 (7.8)
Nausea	14 (10.1)	4 (11.1)	10 (9.8)
Dizziness	13 (9.4)	8 (22.2)	5 (4.9)
Headache	9 (6.5)	3 (8.3)	6 (5.9)
Abdominal pain	5 (3.6)	3 (8.3)	0 (0)
Vomiting	5 (3.6)	3 (8.3)	2 (2.0)

* ICU: intensive care unit, Source: Wang D et al., 2020 (Wang et al., 2020a).

Table 4
Severe COVID-19 disease definitions in adults.

Clinical scenario	Criteria	
Adolescent or adult: fever or suspected respiratory infection, plus one of:	Respiratory rate >30 breaths/min Severe respiratory distress; or SpO2 ≤93% on room air.	
Acute respiratory distress syndrome (ARDS): Onset: within 1 week of a known clinical insult or new or worsening respiratory symptoms.	Chest imaging (radiograph, CT scan, or lung ultrasound): bilateral opacities, not fully explained by volume overload, lobar or lung collapse, or nodules. Origin of pulmonary infiltrates: respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic cause of infiltrates/edema if no risk factor is present.	
	Oxygenation impairment in adults	Mild ARDS: 200 mmHg < $PaO2/Fio_2$ a ≤ 300 mmHg (with PEEP or CPAP ≥ 5 cmH_2O, or non-ventilated) Moderate ARDS: 100 mmHg < $PaO2/Fio_2$ ≤ 200 mmHg (with PEEP ≥ 5 cmH_2O, or non-ventilated) Severe ARDS: $PaO2/Fio_2$ ≤ 100 mmHg (with PEEP ≥ 5 cmH_2O, or non-ventilated). When PaO2 is not available, $SpO2/Fio_2$ ≤ 315 suggests ARDS (including in non-ventilated patients).

1.9.3. Severe infection and critical state

As previously mentioned, the most serious manifestation of COVID 19 infection is pneumonia, characterized by cough, dyspnea, and infiltrates on chest images; the latter is indistinguishable from other viral lung infections.

Acute respiratory distress syndrome (ARDS) is a major complication of COVID pneumonia in patients with severe disease. This develops in 20% after a median of 8 days. Mechanical ventilation is implemented in 12.3% of cases (Guan et al., 2020a).

In different case reports, the need for supplemental oxygen via the nasal cannula was required in approximately 50% of hospitalized patients. 30% required non-invasive mechanical ventilation, and less than 3% required invasive mechanical ventilation with or without Extracorporeal Membrane Oxygenation (ECMO) (Wu et al., 2020d).

It is important to mention that the proportion of severe cases is highly dependent on the study population and may be related to the epidemiological behavior of the infection in each country. Additionally, the number of people tested will influence the denominator. In Italy, the average age of people infected with COVID-19 is between 60 and 65 years, and 16% of those hospitalized require admission to the intensive care unit (ICU) (Remuzzi and Remuzzi, 2020).

The WHO recommendations had established that severe COVID-19 disease could be defined by the following parameters in Table 4 (Who, 2020).

Adapted from: WHO, 2020. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected (WHO, 2020c).

The Surviving Sepsis Campaign (SSC) has directed some recommendations to the population with COVID 19. This guideline focuses on the critical management of severe cases and makes recommendations through an exhaustive review of the literature. For more details, the clinical algorithm includes those recommendations in the critical scenario (Poston et al., 2020).

1.9.4. Risk factors for severe disease

Among the established risk factors for the development of ARDS is age greater than 65 years, diabetes mellitus and hypertension, in at least 40% of patients (Xu et al., 2020b).

It should be clarified that, although advanced age is identified as a risk factor for a severe infection, those of any age may suffer from severe illness from COVID-19. The descriptions made so far of the patients from China have determined that almost 90% of the patients were between the ages of 30 and 79 years (cohort of 44,500 cases) (Medical Association A., 2019).

In other population settings, such as in the United States, more than 60% of confirmed patients were older than 45 years. (CDC, et al. 2020) In most of the described cohorts, mortality was associated with age, with 80% of the deceased in China being over 65 years old, and in the USA the case fatality rate was up to 15% in adults over 70 years.

The Massachusetts General Hospital has suggested additional factors that can be considered risk for severe COVID 19 infection, detailed in Table 5 (Ginsberg, 2010).

The document was developed by the Infectious Diseases Division in conjunction with the front-line support departments. Their recommendations are continually updated as more data comes out.

1.9.5. Clinical diagnosis and screening

The clinical characteristics of symptomatic cases and their severity has been described. In addition to the symptoms reported by the patients, the findings on physical examination may be absent during mild COIVD-19 infection. Those with moderate to severe COVID-19 infection have various signs during pulmonary auscultation, however the most common findings include: wet rales; global decrease in respiratory sounds and increased thrill (Jin et al., 2020).

Early recognition is essential to classify cases as potential cases and initiate one of the most important measures to contain the pandemic, isolation.

The Center of Disease Control (CDC) and the WHO have established clinical scenarios that should be considered as a high suspicion of COVID 19 infection:

1. Close contact with a confirmed or suspected COVID-19 case, including through work in healthcare settings. Close contact includes being within approximately 2 meters of a patient for an extended period of time without wearing personal protective equipment or having direct contact with infectious secretions without wearing personal protective equipment.
2. Anyone who has resided or been traveling in areas where widespread community transmission has been reported.
3. Any patient who has had potential exposure through attending events or has spent time in specific settings where cases of COVID-19 have been reported.

The scenarios described respond to the context of a high suspicion of COVID-19 infection. The world health authorities (CDC, WHO) continually update these contexts. There have been multiple case definitions and clarifications regarding when to perform a COVID-19 test:

- They have pointed out the importance of fever, cough and dyspnea as sentinel symptoms, since these should form part of the clinical judgment that guides doctors. This allows to expand the group of suspicious patients.
- In cases of severe respiratory distress of undetermined etiology and that do not meet the previously indicated criteria, a screening for COVID-19 would be indicated.
- In areas of limited resources, the suggestion is to prioritize cases that require hospital care, and in this way guide the epidemiological fence to order isolation and protect the most vulnerable people (chronically ill and over 65 years of age), as well as test those with the greatest possibility of exposure (travelers and health personnel).

1.9.6. Laboratory findings

Currently, there is no laboratory data profile that is framed in COVID 19 infection. From a cohort of 43 patients confirmed with COVID 19, these findings were classified as mild, moderate and severe disease (Gao et al., 2020).

IL-6, D-Dimer, glucose, TTP, fibrinogen and PCR values were associated with the greatest difference in the deviation of their values. Thus, the optimal threshold and area under the ROC curve for IL-6 were 24.3 pg/mL and 0.795 respectively, while for D-Dimer they were 0.28 μg/L and 0.750, respectively. The area under the ROC IL-6 curve (AUC) combined with D-Dimer was 0.840. The specificity of IL-6 and D-Dimer was up to 93.3%, while the sensitivity of IL-6 and D-Dimer in severe COVID was 96.4%, especially in early stages of severe infection.

High levels of D-dimer and more severe lymphopenia have been associated with mortality due to a prothrombotic state that determines multi-organ failure.

Table 5
Risk factors for severe COVID-19 infection Adapted from: Ginsberg, L. E. (2010). "If clinically indicated:" Is it? Radiology, 254(2), 324–325. https://doi.org/10.1148/radiol.09091736

Epidemiological – Category 1	Vital signs – Category 2	Laboratory – Category 3
Age >55 years	Respiratory rate >24 breaths/min	D-Dimer >1000 ng/mL
Diabetes mellitus	Heart rate >125 beats/min	CPK >2 folds over upper limit
Hypertension and high cardiovascular risk	Spo_2 <90% at room air	LDH >245 U/L
Immunosuppression and use of biological drugs		Elevated troponin
HIV patients regardless CD4 count		High troponin
		Lymphocyte count <0.8
		Ferritin >300 μg/L

In general, leukopenia and/or leukocytosis can be found in the interpretation of blood biometry; however, the most widely described finding is lymphopenia (Gorbalenya, 2020). It should be considered that in the context of viral pneumonia biomarkers such as Procalcitonin and PCR are not useful, as often these biomarkers are in the normal range for patients with COVID-19.

Among other findings, descriptive studies have reported considerable elevations of lactate dehydrogenase and ferritin as well as alteration in aminotransferases; although elevation ranges for these parameters have not been established (Guan et al., 2020b).

1.9.7. Imaging findings

About the imaging findings, COVID 19 viral pneumonia has similar features on imaging to other viral infections.

Although computed tomography (CT) is the test of choice, it is not useful for a definitive diagnosis due to the wide variety of images that can be found in patients with COVID 19 infection. This statement is derived from a large cohort of more than 1000 Wuhan patients, where RT-PCR confirmation of COVID 19 and chest CT images of these patients were correspondingly analyzed. CT images were determined to have a sensitivity of 98%; however, the specificity was only 25% (Ai et al., 2019).

In general, the majority of descriptive studies concur that the finding of ground glass opacifications is most common. It is typically basal and bilateral, and rarely associated with underlying consolidation. A multicenter Chinese study that retrospectively reviewed the CT scans of 101 patients found that 87% had typical ground-glass images and up to 53% had this finding along with consolidations. These findings were more frequent in the most severe and older age groups of patients (Zhao et al., 2020b).

Comparisons of image findings were made between 205 viral pneumonia patients with a respiratory panel positive for other viruses versus 219 SARS-CoV-2 positive patients. The most uncommon findings on CT images of patients with COVID 19 were: central distribution of opacifications (14%), air bronchogram (14 %), pleural thickening (15%), pleural effusion (4%), and lymphadenopathy (2.7%) (Bai et al., 2020b).

1.10. Diagnosis methods to detect COVID-19

The emergence and outbreak of SARS-CoV-2, the causative agent of COVID-19, has rapidly become a global concern that highlights the need for fast, sensitive, and specific tools to monitor the spread of this infectious agent.

Diagnostic protocols to detect SARS-CoV-2 using real-time quantitative polymerase chain reaction (RT-qPCR) were listed on the World Health Organization (WHO) website as guidance, however, various institutions and governments have chosen to establish their own protocols that might not be publicly available or listed by WHO.

There are important challenges associated with close surveillance of the current SARS-CoV-2 outbreak. Firstly, the rapid increase of cases has overwhelmed diagnostic testing capacity in many countries, highlighting the need for a high-throughput, scalable pipelines for sample processing (Myhrvold et al., 2018; Wee, 2020). Secondly, given that SARS-CoV-2 is closely related to other coronaviruses (Chan et al., 2020b), some of the currently available nucleic acid detection assays can result in false positives (Wang et al., 2020b). Thirdly, critical concern for molecular detection is the low sensitivity reported for RT-qPCR assays (Ai et al., 2019) and serological tests (Li et al., 2020), particularly in the early stages of infection. Additionally, most of the available RT-qPCR assays require sample processing and equipment only available in diagnostic and/or research laboratories.

The most common tests for COVID-19 involve taking a swab from a patient's nose and throat and checking these swabs for the genetic footprint of the virus. They are called “PCR tests”. The first PCR test for COVID-19 was developed within 2 weeks of the disease being identified (Li et al., 2020).

Even though most of the available diagnostics have focused on RT-PCR, additional methods include using microarray or microfluidic technologies, CRISPR to isolate gene segments for diagnostics, serological and full genetic sequencing are available. It is important to note that the FDA has so far granted Emergency Use Authorization (EUA) status only to some PCR-based tests.

1.11. Differential diagnosis

COVID-19 pneumonia presents as a clinical picture that, as previously stated, may be indistinguishable from other viral pneumonias. Any viruses that causes pneumonia must be included in the differential diagnosis of COVID-19. This includes influenza, parainfluenza, adenovirus, respiratory syncytial virus, rhinovirus, human metapneumovirus, SARS-CoV, etc.

It is important to mention that coinfection is a possibility, as some reports from Italy and China had described. The most common pathogens in coinfection were Influenza virus (H1N1, H3N2), Rhinovirus and Respiratory syncytial virus (A/B). In contrast, bacterial coinfection was infrequent (Bordi et al., 2020; Corman et al., 2020b).

The bacterial infective etiology with clinical and radiographic similarities to COVID-19 are mycoplasma and chlamydia. Etiology causing non-infectious lung lesions with similar features are those autoimmune diseases with lung involvement such as vasculitis, dermatomyositis and other pneumonitis.

1.12. HIV and COVID-19 risk

It is interesting to know if there is an increased risk of acquiring a SARS-CoV-2 infection as a person living with HIV (PLWH). So far, despite the avalanche of information, there are isolated descriptions of cases of PLWH and COVID-19.

Viral pathogenesis of SARS-CoV-2 versus HIV

In SARS-CoV-2 infection, the binding to cells is mainly done by ACE2 receptors to glycoprotein S (structural spike); this is a primary determinant in viral pathogenesis and immune response, being a process independent of the CD4 receptor, and therefore different from HIV. The virion assembly is different between these 2 viruses, being that SARS-CoV-2 does it in the endoplasmic reticulum and HIV does it by budding (Xiao et al., 2020).

The viral pathophysiological process in COVID-19 results in a storm of cytokines and alterations that lead to a worse prognosis such as lymphopenia, associated with the risk of ARDS and death. Therefore, it can be affirmed that given the different infection mechanisms, there would be no synergy between both viruses, so that COVID-19 should not have a worse clinical expression in PLWH.

Clinical features of COVID-19 and HIV infection

To understand the vulnerability of an infection in PLWH, the clinical scenarios of these patients must be established. Thus, we can say that a PLWH can present itself as: 1) Patient with suppressed viral load, 2) Patient with suppressed viral load and immune discordance (CD4 + cell count <350 cells / mm3 despite suppressed HIV-1 RNA), and finally 3) Undetectable patient with a CD4 + count in considerable recovery (CD4 + cell count >350 cells/mm^3).

Taking into account that, at the moment the SARS-CoV-2 pandemic exceeds 3 million people, case reports of an HIV and COVID-19 coinfection have not shown any evidence that PLWH are at increased risk of acquiring said infection or suffering serious complications. Based on the clinical scenarios described, there has also been no impact of viral load or CD4 + cell count on the risk of contracting COVID-19 and/or developing serious complications.

On the other hand, controlled PLWHs by having a longer life expectancy may have more comorbidities, which have been related to a higher risk of having COVID-19 (diabetes, hypertension, etc.) without this being directly related to HIV and some kind of synergy with the SARS-CoV-2. Recently, researchers from Spain and the United States

(USA) have published several reports detailing the characteristics of patients with confirmed COVID-19 and suffering from HIV. Of these reports, none of them shows evidence of a worse prognosis for PLWH, and they are still the minority of cases.

In Spain, less than 1% of cases in a cohort correspond to PLWH, which have had a satisfactory evolution and less than half required an intensive care unit (Blanco et al., 2020). In the US, of the 5,700 hospitalized patients in the New York area, only 47 patients had HIV, while in San Francisco, data was published on 1233 people who had diagnosed with SARS-CoV-2 infection, of which less than 3% had HIV and none of them developed severe COVID-19 (Richardson et al., 2020b).

1.13. Antiretroviral therapy and protection/action against SARS-CoV-2

Despite the existence of in vitro studies on the efficacy of the use of lopinavir/ritonavir, it is currently known that its effect in cases of moderate and severe COVID-19 is null, and therefore at the moment no recommendation can be given nor how treatment, much less as prophylaxis (Cao et al., 2020a).

This clarification is important given that there is a belief that PLWHs could be protected if they take antiretroviral therapy. Therefore, current recommendations for PLWHs are to maintain antiretroviral therapy with the goal of controlling HIV as well as following the same standards of care as the general population to avoid acquiring a SARS-CoV-2 infection (Organización Panamericana de la Salud, 2020).

1.14. COVID-19 in pregnant women

Regarding SARS-nCoV infection in pregnant women, there is currently limited evidence about the effect of the virus on the mother or fetus. However, due to the physiological changes typical of pregnancy, especially on the immune system (immunosuppression) and the cardiopulmonary system, pregnant women are thought to be more susceptible to developing severe symptoms when they acquire the viral respiratory disease. In 2009, when Influenza A H1N1 infection occurred, only 1% of the infected population were pregnant, yet they accounted for 5% of infection-related deaths (Yang and Wang, 2020).

Some of the guidance related to the effects of the coronavirus in pregnant women and the fetus is due to previous studies of various viruses. During the SARS-CoV pandemic in 2002 and 2003, in a very small study of 12 patients, women infected during their first trimester had high a miscarriage rate (57%). During their second and third trimesters they developed intrauterine growth restriction (40%), and preterm delivery (80% [one spontaneous and 3 induced by maternal condition]), and 3 women died during pregnancy (25%) (Wong et al., 2004b). In another study of 11 pregnant patients infected with MERS-CoV, 9 presented adverse results (91%), 6 neonates were admitted to the neonatal intensive care unit (55%) and 3 of them died (27%) (Alfaraj et al., 2019). However, it is important to note the small sample size which could increase the risk of bias and low power of the study.

With information obtained so far from the Wuhan SARS-CoV-2 outbreak, the infection appears to be less severe for pregnant women, compared to previous SARS-CoV and MERS-CoV outbreaks (Yang and Wang, 2020). However, it is important to take into account that the data obtained are from reviews consist of a small number of patients. Additionally, the majority of pregnancies with confirmed SARS-Cov-2 pneumonia were in the third trimester and there were very few within the first and second trimesters. Therefore, more information should be collected with larger numbers of pregnant women with the infection. Follow-up of positively diagnosed pregnant women during in the first and second trimesters should be encouraged, to understand the impact of the new coronavirus infection on the pregnant mother, the fetus and the course of pregnancy (Chen et al., 2020c).

Mullins et al. carried out a bibliographic review of all the evidence collected until March 10, 2020, relating to any pregnant women with coronavirus diagnosed during her pregnancy or puerperium. Twenty-three studies were included but there is a high probability that reported cases overlap. In total, they found 32 women affected by COVID-19, including one with a twin pregnancy. Delivery of 30 newborns was reported, 27 by Caesarean section 3 by vaginal delivery (Mullins et al., n.d.).

The management of pregnant patients with COVID-19, in general, follows the same principles as for the wider population. It is vital to consider that the mother, fetus and, subsequently, the newborn are always considered a high-risk population. Management should include early isolation, oxygen therapy if necessary, avoid fluid overload, empirical antibiotic therapy (due to the risk of bacterial infection), maternal fetal monitoring, Doppler ultrasound is recommended within obstetric surveillance. In patients who are asymptomatic, home management is acceptable on the proviso they should seek further medical advice if their symptoms develop into more severe disease. All mothers recovering from COVID-19 infection should be monitored with a Doppler ultrasound every 2 weeks, due to the risk of developing intrauterine growth restriction (Favre et al., 2020; Rasmussen et al., 2020).

The time of termination of the pregnancy, as well as the method, also depend on several factors, including gestational age, maternal condition in relation to SARS-CoV-2 infection, presence of maternal comorbidities, and fetal condition. Decisions must be made collaboratively during multidisciplinary team discussions, with individualized management plans established for each patient (Zhang et al., 2020b).

A diagnosis of COVID-19 alone is not an indication for the termination of pregnancy, rather it should be made in combination with consideration of morbidity and mortality of both the fetus and mother. After delivery, the use of corticosteroids is recommended for antenatal fetal lung maturation, with betamethasone or dexamethasone (Liang and Acharya, 2020); taking special care in critically nursing patients, as this may worsen their condition, and may delay delivery, which is necessary for the management of these patients (Poon et al., 2020; Rasmussen et al., 2020).

1.15. COVID-19 in children

The symptoms children present with are similar to adults, as is the incubation period ranging from 1 to 14 days (mean of 5.2). A cough is the most frequent presenting symptom (65%) followed by fever (60%). There is a higher occurrence of gastrointestinal symptoms including diarrhea (15%), nausea, vomiting (10 %) and abdominal pain. These gastrointestinal symptoms are usually more variable in children than adults and are sometimes the only clinical manifestation in associations with fevers. (Dong et al., 2020b; Xu et al., 2020c).

The clinical progression and disease severity in pediatric patients is markedly different from that of adults. Over 90% of affected children are asymptomatic or have mild to moderate disease (Dong et al., 2020b). The majority of serious cases in children are related to those with significant comorbidities such as heart disease, immunosuppression, etc. To date of this review, only a few cases of children without underlying comorbidities have died as a result of COVID 19 have been reported. This difference of severity of illness between adults and children has not been clarified, however, several theories have been postulated. These include that children express more ACE2 receptors in their lungs which confer some protection to severe injuries such as those caused by RSV and which would decrease dramatically with age (Gu et al., 2016; Xia et al., 2020).

Immunological factors may also influence outcomes, as in childhood we are most exposed to frequent challenges including recent seasonal viruses such as RSV in the winter months. Most likely, it is multifactorial and depends on factors from both the host and the virus itself (Xia et al., 2020).

Abnormal radiological (CT) findings are found in asymptomatic children and consist of bilateral lung lesions (50%). Elevated CRP (C – reactive protein), Procalcitonin PCT (80%), and liver enzymes are present in

most affected children, unlike adults in whom PCT is not a reliable marker.

Virus elimination via the stool even after the negativity in the nasopharyngeal mucosa and the disappearance of symptoms makes them a potential source of contagion through the fecal-oral route (Lee et al., 2020).

1.16. SARS-COV-2 infection and cancer

Patients with cancer are generally more susceptible to infections than healthy people, because they have a state of systemic immunosuppression that is exacerbated during chemotherapy or radiotherapy (Liang et al., 2020).

In China, according to national surveillance data, coronavirus infection occurs in 1.3% of patients with malignant tumors. This is a much higher proportion than the general incidence of 0.3% (Fuhai et al., 2020). When comparing non-malignant tumors patients with malignant tumors patients have a higher risk of developing a more serious infection (OR 5.34; 95% CI: 1.80–16.18; $P = 0.0026$) and health deterioration is accelerated (HR 3.56; 95% CI: 1.65–7.69; $P < 0.0001$) even after adjusting for age (Liang et al., 2020). Further research, completed in a tertiary hospital in Wuhan, China, similarly found that 25% of patients with cancer and SARS-COV-2 infection died, most of them over 60 years of age (Yu et al., 2020).

Due to these findings, it has been proposed by many international entities that during the pandemic, for prevention, an individualized plan based on the patient's specific conditions is required, with the aim to minimize the number of visits to health institutions.

- For early-stage patients with need of post-surgical adjuvant chemotherapy, especially those whose clinical, pathologic, and molecular biologic staging suggest a better prognosis, the start time of adjuvant chemotherapy may be delayed up to 90 days after surgery without affecting the overall effect of treatment (Chavez-MacGregor et al., 2016).
- For patients with advanced cancer, the main approach should be to minimize hospitalization in COVID-19 positive installations. Replacing the existing intravenous treatment regimen with oral chemotherapy during this special period may be considered, to ensure that treatment is not interrupted for a long time during the pandemic (Binliang et al., 2020).

However, if there is a suspicion of COVID-19 infection in this population group, the same updated diagnostic guidelines and the corresponding management should be followed depending on their severity of illness. Moreover, an individualized follow-up plan should be outlined due to higher likelihood of complications in this group of population (Jazieh et al., 2020).

It should be noted that patients attending out-patient appointments for cancer have higher levels of anxiety, depression and other mental health problems than the general population. Studies have shown that approximately 50% of malignant tumor survivors have a moderate to severe fear of tumor recurrence (Reiche et al., 2004). For this reason, psychologist surveillance of out-patients in quarantine or during hospitalization should be considered.

1.17. Complications SARS-CoV-2 infection

Reported complications derived from COVID-19 describe a severe disease that requires management in an intensive care unit (ICU) in approximately 5% of proven infections. Common complications include: respiratory failure; cardiovascular dysfunction; cardiomyopathy and acute kidney injury. The average duration between symptom onset and dyspnea and ICU admission has been estimated as 7 and 10 days, respectively. This suggests there is a gradual deterioration in most cases. Older patients (mean >60 years) appear to be most susceptible to the life-threatening complications. The risk of patient-to-patient transmission in the ICU is currently unknown, therefore adherence to infection control precautions is paramount (Murthy et al., 2020; Yang et al., 2020b).

Progressive deterioration of respiratory function is undoubtedly the most common and life-threatening complication of the infection. The prevalence of hypoxic respiratory failure in COVID-19 patients is 19%, and it can progress to acute respiratory distress syndrome (ARDS), with the need of mechanical ventilation support at 10.5 days on average. One study found that between 10 and 32% of hospitalized patients require admission to the ICU due to respiratory deterioration (Murthy et al., 2020). As respiratory complications are the most common cause of severe deterioration, early identification of them will undoubtedly help in timely support. Support provided should be adapted to take into account risk factors such as advanced age, neutrophilia and organic dysfunction for the development of ARDS. The diagnostic support of pulmonary tomography is undoubtedly a valid tool; images in patients with different clinical types of COVID-19 have characteristic manifestations, but it can become an operational problem due to the difficulty in performing imaging on critically ill patients. On the contrary, lung ultrasound at the bed-side could provide an alternative to radiographs and tomography during the diagnosis of COVID-19 (Soldati et al., 2019; Soldati et al., 2020).

Since more than 70% of hospitalized patients will require supplemental oxygen, it is recommended that oxygen should be started when pulse oximetry values fall below 90%. An upper-limit of 96% saturation should be established, since higher values have been shown to be harmful (Chu et al., 2018; van den Boom et al., 2020). Regarding the use of high-flow nasal cannula (HFNC) oxygen therapy, great variability of results was recorded. This was in part because it was not possible to determine if results were dependent on the progression to orointubation, mortality, or the risk of contamination to health personnel. HFNO is still recommended for use as opposed to non-invasive mechanical ventilation wherever clinically possible (NIMV). HFNC use should be closely monitored and patients cared for in an environment where intubation can be facilitated in case of decompensating. This is due to the failure rate and need for emergency intubation. If this were undertaken in an uncontrolled environment it increase the risk of nosocomial infection of health providers (Hui et al., 2019; Loh et al., 2020; Wax and Christian, 2020).

The recommendation for starting with NIMV is of very low quality, and it is of high risk for both patients and health personnel. In adults with COVID-19 hypoxic respiratory failure, there is no direct evidence to support the use of NIMV; Furthermore, some previous studies suggested that it may be associated with an increased risk of transmission of infections to healthcare workers and may worsen severe forms of lung injury as a result of harmful transpulmonary pressures and large tidal volumes (TV). It may also delay initiation of invasive mechanical ventilation, leading to emerging intubations which could increase the risk of transmission to the healthcare team and there is increased risk to the patient (Brochard et al., 2014; Alraddadi et al., 2019; Cheung et al., 2020).

For the initiation of invasive mechanical ventilation, the recommendation for highly protective ventilation is maintained, with the use of low TV (6 ml/kg of ideal weight), plateau pressure less than 30 cm H2O, conduction pressure between 13–15 cmH_2O, respiratory rate can be carried up to 35 per minute, as needed. If hypoxemia progresses to values less than 100–150 mmHg of $PaFio_2$, there are several therapeutic options, initially increasing positive expiratory pressure (PEEP) by 2–3 cmH_2O every 15 to 30 minutes to improve oxygen saturation to 88–90%, maintaining a plateau of less than 30 cm H2O. Recruitment maneuvers are probably of little value but could be used in selected cases in the presence of a physician to control hemodynamics. If there is considerable asynchrony with positive pressure ventilation, accompanied by an increase in plateau pressure and refractory hypoxemia, deep sedation should be used followed by prompt institution of neuromuscular block. If hypoxemia has been reached refractory to the aforementioned measures, it is recommended to move quickly to ventilation in the prone position and as a final measure venous to venous ECMO (VV) should be considered if available or to refer the patient to an ECMO center (Petrucci and Iacovelli, 2004; Munshi et al., 2017; Yasuda et al., 2017; Fielding-Singh et al., 2018; Papazian et al., 2019; Matthay et al., 2020).

Routine use of corticosteroids has been discouraged, and restricting it exceptionally for patients who develop ARDS, although without reports of improvement in survival, with discrepancy in results of shorter mechanical ventilation time and ICU stay (Wang et al., 2020c).

Hemodynamic deterioration has a variability of presentation, this depends on the study population and the definition (Wu and McGoogan, 2020) – the presence of shock in the intensive care unit may be present between 25% and 35% (Wang et al., 2019; Yang et al., 2020b). Cardiomyopathy related to viral infection is one of the main causes of hemodynamic detriment, occurring in up to 23% of patients with COVID-19 (Zhou et al., 2020b). Hemodynamic failure is one of the main causes of death in these patients, with percentages of up to 40%, inconclusive risk factors are associated to date such as diabetes, hypertension, lymphopenia, and elevation of D-dimer (Ruan et al., 2020). Acute kidney injury (AKI) is present in up to 12% of critically ill patients, podocytes and proximal tubule cells are potential host cells for SARS-CoV-2, caused by the virus induced cytopathic effect. The diagnosis is based on markers of early kidney injury and urinary output (Wax and Christian, 2020).

Initial management of shock is based on fluid resuscitation, based on the application of dynamic parameters to predict response to fluids, such as variation in stroke volume (SVV), variation in pulse pressure volume (PPV) and change in stroke volume with passive leg elevation or fluid challenge above static parameters (Ruan et al., 2020). Variables such as skin temperature, capillary refill time and/or serum lactate measurement are currently valid tools to assess shock. The volume of liquids used in resuscitation should be restricted and administered in relation to dynamic assessment. A liberal water resuscitation strategy is not recommended, rather a balance of crystalloids over colloids as resuscitation liquids should be encouraged and avoiding the use of hydroxyethyl starches, albumin, dextrans or gelatins (Silversides et al., 2017; Lewis et al., 2018). Indirect evidence suggests that the target mean arterial pressure (TAM) for patients with septic shock is 65 mmHg using vasoactive support (Lamontagne et al., 2020). The recommendation of norepinephrine use as the first agent is maintained. If norepinephrine is unavailable, vasopressin or epinephrine could be used, avoiding the use of dopamine as the initial vasopressor due to the potential development of arrhythmias (Gamper et al., 2016; Møller et al., 2018). In patients with COVID-19 and shock with evidence of cardiac dysfunction and persistent hypoperfusion despite fluid resuscitation and norepinephrine use, dobutamine as inotropic is recommended. Given the development of refractory septic shock, the suggestion of the use of hydrocortisone in continuous infusion is maintained, as indirect evidence, this in favor of reducing the length of stay in the ICU and the resolution time of the shock (Møller et al., 2018).

1.18. Clinical prognosis

According to the investigative mission of the WHO in China, the case-fatality rate ranged from 5.8% in Wuhan to 0.7 % in the rest of China. Of these cases, the deaths were mostly in patients with chronic diseases (cardiovascular disease, diabetes mellitus, chronic lung disease, hypertension and cancer) and the elderly. (WHO, et al. 2020).

Other reports from China have coincided with this clinical risk profile, for example, a study that included 41 confirmed cases, 12 patients who had ARDS had as main underlying diseases: diabetes and high blood pressure. Of these cases, 6 patients died (Huang et al., 2020b).

1.19. Recovery from COVID-19 infection

According to WHO, the recovery time is estimated to be 2 weeks for patients with mild infections and 3 to 6 weeks for those with serious illnesses. On the other hand, CDC established that people who had symptoms in the mild to moderate spectrum and maintained home isolation have a resolution of 3 days after the fever decrease, and there was a substantial improvement in respiratory symptoms, even without use of medications.

Isolation may be limited to 7 days from resolution of symptoms, however, it must be adapted to the population circumstances of the epidemic (Guan et al., 2020a).

1.20. Current treatment strategies

1.20.1. Non-pharmacological measures

The evolution of the epidemiological curve in COVID-19 outbreak makes consider containment strategies in China primarily, and other countries based on non-pharmaceutical interventions (NPIs). According to the WHO, the most effective measure is hands washing (WHO, 2020d).

Five different non-pharmaceutical interventions (NPI) implemented individually and in combination as public health measures reduced contact rates in the population and therefore reduce virus transmission (Table 6) (Ferguson et al., 2020).

Increasing the level of hand cleanliness to 60% in places with a high concentration of people, like all airports in the world would have a reduction of 69% in the impact of a potential disease spreading (Nicolaides et al., 2019).

The epidemiological evolution of the COVID-19 pandemic through phases has required the application of specific measures according to the time or phase in which the virus is found in each country. The evolution in the non-pharmacological measures has been as variable as the pharmacological ones, in such a way, since January to March, it was ensured that the use of face masks was limited only to people who had contact with epidemiological foci, not to healthy people (Feng et al., 2020a). This concept was also reinforced by CDC, in order to optimize the use of masks for health workforce. Definitely the course of the pandemic was changing rapidly, which also demanded the change from containment measures to mitigation. The recommendations in the current context remain regarding the use of a facial mask in the community, but its optimization is important for health professionals. The use of the mask is not a substitute for handwashing and social distancing measures, as these ones together allow avoiding viral particles in aerosols or drops, as a low cost and accessible measure for general population (Cheng et al., 2020; WHO, 2020e). There is still non-specific information for the recommendation of masks, in general, having in several studies claims that surgical or cotton cloth masks do not prevent the spread of the SARS-CoV-2 virus (Bae et al., 2020). The evidence about the transmission of the virus in the asymptomatic period also changed the containment measures, suggesting the community use of masks. It is from this that the recommendations for the rational use of masks arise since in some countries the massive use of N95 masks was reported, masks indicated for the use of medical personnel (Feng et al., 2020b). Regarding to this non pharmaceutical recommendations, the studies suggest to priories the resources on vulnerable population, in endemic areas, older people, adult with comorbidities and health workforce. Studies are still needed on the duration of the protective effect of the masks and above all the possibility of their reuse for resource optimization. Meanwhile the most important recommendation continues to be its use in addition to hand hygiene and social distancing (Feng et al., 2020b).

1.20.2. Pharmacological treatment

Therapeutic strategies are urgently needed to be applied in the context of COVID-19, as a pandemic. In terms of this public health urgency is important to consider 2 important definitions: Drug repurposing and compassionate use of drugs. The first one, drug repurposing is a crisis arrangement in which medicines having already been proved safe in humans, in similar virus or targets in the infection process, are redirected against unique objective: SARS-CoV 2 (viral structure, infection process). The second one, compassionate use of drugs is the use of a new unofficial, not yet proven drug to treat a severe sick patient in the absence of other available treatments. These concepts have been applied with COVID-19 treatment.

Identifying targets for pharmacological use has been important to develop therapeutically drugs with roles in virus structure and

Table 6
Non-pharmacological measures.

Measure	Description
Home isolation	Stay at home is the indication for people with symptoms for 7 days. This measure allows the reduction of external contacts by 75%.
Voluntary home quarantine	If it is identified any contact with symptoms at home, the quarantine has to be kept for all members during 14 days. This measure allows the reduction of external contacts by 75%.
Social distancing of elderly people	Decreasing external contacts by 75%.
Massive measure: Social distancing	Avoid and diminish contacts from outside (schools, jobs) by 75%.
Ending activities on education centers	Closure of all schools, 25% of universities remain open. Household contact rates for student families increase by 50% during closure. Contacts in the community increase by 25% during closure.

infection process (Fig. 4). Some representative existing drugs act on targets in similar RNA viruses like Ebola, hepatitis C, influenza, and others as MERS and SARS viruses. The most important studied targets are the 2 viral proteases involved in cleavage viral peptides for replication of the virus, 3CLpro and PLpro. Thus as drug repurposing appears Lopinavir and Ritonavir (Liu et al., 2020). RdRp is other important target as the polymerase in charge of viral RNA synthesis, RNA polymerase, sttopped by Remdesivir and Favipiravir. About endocytosis process into host cells, viral spike protein and its interaction with ACE2 receptor constitute other important target blocked by arbidol, used also in Influenza. ACE2 is a negative regulator, receptor of renin-angiotensin system, involved in pressure control and inflammatory lung disease. By the knowledge of physiopathology of COVID-19 infection, we know that activities of ACE2 receptors are altered, thus some drugs are being studied around these targets, but also in vitro and experimental way. Some homologue target-drug models have been proposed between SARS-CoV and SARS-CoV-2 because of some viral similarities as the receptor RBD in S protein with 76% of sequence similarity. In the same way with PLpro sequences with 83% similar active sites (Liu et al., 2020).

Other drugs like Chloroquine and analogues (Hydroxicloroquine) acts directly on pH and blocks the ACE2 glycosylation process. In general, the most studied pharmaceutical interventions found for COVID-19 treatment include remdesivir, hydroxychloroquine, chloroquine, azytromicin, ritonavir, darunavir, lopinavir, favipiravir, interferons, convalescent plasma, biological therapy, human immunoglobulin, oseltamivir, tocilizumab and methylprednisolone. Drugs listed with their mechanisms of action on COVID 19, and adverse effects can be found on Table 7.

Actually, there is a great effort to build strong evidence. There 1,053 clinical trials in progress. Some antiviral, antimalarial and antibiotic drugs have also been shown to have in vitro activity against SARS CoV 2, but it does not guarantee clinical efficacy. For these there are several completed and in progress clinical studies. Some of them like Darunavir are in phase II, Remdesivir, cloroquine and hydroxycloroquine are in phase III of clinical trials, Lopinavir and Ritonavir (Kaletra) and Umifenovir or Arbidol in phase IV. In order to collect data quickly and get information from many countries on March 20, 2020, the WHO announced a large global trial, called SOLIDARITY. The treatments included in this big trial are: remdesivir, chloroquine and hydroxychloroquine, ritonavir / lopinavir-ritonavir / lopinavir and interferon beta. The completed and clinical trials with evidence that favors them are listed in (Supplementary Table 3) (WHO, 2020c).

The principal and secondary outcomes evaluated in clinical trials in COVID-19 are diverse from time to clinical recovery TTCR, mortality reduction, to changes from baseline in some organ function blood markers, among the most important. We can present a brief assessment of each drug considered in COVID-19 treatment.

1.20.2.1. Remdesivir. Currently, Remdesivir has been ranked as first potential drug in treatment for COVID-19, by the last publications. Remdesivir is a nucleotide analog, antiviral drug developed by Gilead Sciences. There are limited data in terms of drug-drug interactions, its use is intravenous only and its administration cannot be continued if creatinine clearance falls below 30 mL/min or ALT goes above 5× the upper limit of normal. There are 21 trials studying this molecule, 12 in recruitment, 1 finished, 1 suspended and the others in enrolling or other status. The results of the unique completed study of Remdesivir was published on April 29th (Wang et al., 2020d), without statistically significant results regarding the difference in time to clinical improvement, with a risk ratio of 1.23. The same day, it was announced by the US National Institute of Allergy and Infectious Diseases (NIAID) the good preliminary outcomes of Remdesivir based on 2 ongoing clinical trials (NCT04280705, NCT04292899), with a 31% faster time to recovery than those who received placebo ($P < 0.001$), minor time of recovery 11 days' vs 15 with placebo and possible survival benefit; after which FDA approved the emergency use of remdesivir in patients with severe COVID-19.

1.20.2.2. Lopinavir/Ritonavir. Lopinavir and Ritonavir (LPV/r) are protease inhibitors, specifically in the action of 3CL protease of SARS COV-2, used in HIV treatment. They are included in re-purposing drugs for use in COVID-19 patients and also, they had antiviral activity in last SARS-CoV and MERS-CoV pandemics. Lopinavir has shown in vitro activity for SARS COV- 2. Ritonavir increases the half-life of lopinavir (Ford et al., 2020). Both drugs have some interactions with other drugs, also they share an adverse event with others in prolonging the QT interval.

There are 53 studies registered in Clinical trials of LPV/RV, alone or combined with other drugs, 31 in recruitment, 2 randomized trials (LOTUS (Cao et al., 2020b) and ELACOI (Yueping, 2020)), 6 observational studies and cases reports.

The conclusions in the 2 reported randomized trials are similar in terms of their principal outcomes. LOTUS trial included hospitalized adult patients, positive for SARS-COV-2, in which, patients receive either Lopinavir/Ritonavir (400/100) twice a day for 14 days, plus standard care (99 patients), or just standard care (100 patients). Regarding to the significant difference in time to clinical improvement, as the principal outcome in this study, no differences were identified, either in other variables like mortality, hospitalization stay, oxygen supplementation and viral load. Lopinavir/Ritonavir has not demonstrated a benefit vs. standard care. ELACOI trial included hospitalized patients with mild/moderate COVID-19. One group received LPV/r (200 mg/50 mg twice a day), another group received ardibol and the last one received no antiviral therapy. In terms of time to viral clearance (PCR negativity) or progression to severe disease, LPV/r did not demonstrate any benefit. In general, the evidence for using LPV/r is low, considering some critical points: designs, risk of bias in sample size and certainty of evidence.

1.20.2.3. Hydroxychlororquine. Hydroxychlororquine (HCQ) initially considered an antimalarial drug, which, due to its antiviral properties against HIV by means of 2 pathways, inhibiting the entry of the virus into host cells and altering the synthesis of viral proteins, via glycosylation, was studied in vitro as a possible action against the new human coronavirus.

In vitro efficacy of HCQ (hydroxychloroquine) has been studied since the beginning of the pandemic with initially encouraging results. The points to evaluate are: Clinical improvement; viral load reduction, in days after the start of HCQ therapy; mortality and safety, tolerance and undesirable effects of HCQ treatment.

Related to clinical improvement, as study conducted in 25 New York metropolitan hospitals in which the relationship between HCQ and clinical improvement was studied. No significant differences were found in the use of HCQ in relation to increased or decreased risk of death associated with COVID-19. A single study shows the number of days of cough

Table 7
Drugs and targets in SARS-CoV-2.*

Type of drug	Target	Other diseases indication	Mechanism of action in COVID 19 (Drugs Repurposing)	Activity against SARS-CoV-2	Side effects
Antiviral drugs					
Favipiravir	RdRp, RNA dependent RNA polymerase	Influenza. Ebola, yellow fever, chikungunya, norovirus.	Inhibitor of viral RNA-dependent RNA polymerase. Pyrazinecarboxamide derivative viral RNA polymerase inhibitor.	*In vitro*	ND
Arbidol	S protein, ACE2	Influenza	Entrance. S protein- AC2 receptor	*In vitro*	Gastrointestinal effects
Antiretroviral drugs					
Lopinavir + Ritonavir	Viral proteases: 3CLpro or PLpro	Combination for HIV infection	HIV reverse transcriptase inhibitors. Rito enhance the action of other drugs by inhibition of CYP3A4 May inhibit the viral proteases: 3CLpro or PLpro	*In vitro. In vivo*	Rash, GI upset, abnormal liver tests
Remdesivir	RdRp, RNA dependent RNA polymerase	Ebola and Marburg viruses, SARS-CoV-1 and MERS	Inhibit viral replication	*In vitro, in vivo*	Abnormal liver tests, GI
Darunavir	Protease inhibitor	HIV protease inhibitor	In combination with cobicistat, a CYP3A inhibitor,	ND	Rash, GI upset, abnormal liver tests
Antimalarial drugs					
Chloroquine	endosome/ ACE2	Antimalarial actions, chloroquine has some efficacy in HIV-AIDS	Glycosylation Inhibition and elevate endosomal pH and interfere with ACE2 glycosylation	*In vitro*	Retinopathy, QT prolongation,
Hidroxichloroquine	endosome/ ACE2	Antimalarial actions, chloroquine has some efficacy in HIV-AIDS	Inhibiting virus entry into host cells	*In vitro*	QT prolongation
ANTIBIOTICS					
Azitromicin	Bacterial protein synthesis, blocking 50S ribosomal	Bacterial infections	For suspected bacterial superinfection	ND	GI effects
ANTIVIRAL DRUGS. NON-SPECIFIC					
Interferon	PKR, Mx protein	Hepatitis B virus and HCV	Inhibit viral replication by inhibition of PKR	ND	Depression, injection site reaction, flu like syndrome
NEUROAMINIDASA INHIBITOR					
Oseltamivir	Neuroaminidasa inhibitor	Influenza	Not well studied	*In vitro*	
Type of drug	**Target**	**Other diseases indication**	**Mechanism of action in COVID 19 (drugs repurposing)**	**Activity**	**Side effects**
Monoclonal antibody					
Tocilizumab	IL-6 receptors (soluble and membrane-bound)	rheumatoid arthritis, systemic juvenile idiopathic arthritis, juvenile idiopathic polyarthritis, giant -cell arteritis	Inhibit IL-6. Taper immune system in critical patients	ND	Abnormal liver tests, GI perforation
ANTIINFLAMATORY DRUGS					
Corticosteroids	Inflammation cascade	Inflammatory responses	For patients with refractory shock or acute respiratory distress syndrome	ND	Cushing Sd., diabetes, weight gain.
OTHERS					
Acetylcysteine	Mucolytic	Symptomatic relief;	Symptomatic relief	ND	Nausea, fever, vomiting,
Angiotensin receptor blockers	ACE2 Receptors			ND	Dizziness, nausea, diarrhea, headache
Thalidomide	Immunosuppressant	Myeloma	Inhibit production of TNF-α, antiangiogenic activity.	ND	Fever, low cell counts, anxiety, weight gain or loss
Pirfenidone		Idiopathic pulmonary fibrosis	Reduces fibroblast proliferation, production of fibrosis-associated proteins and cytokines	ND	
Vitamin C	Antioxidant	Sepsis, chronic process,	Module redox signaling	ND	

* There are several drugs in study to be considering in treatment for COVID-19. This table summarizes the most important in terms of principal outcomes in clinical trials or activity in vitro. ND = Non Data.

was lower in patients taking HCQ (2.0 x 0.2 days) compared to the control group (3.1 x 1.5 days) (Chen et al., 2020d). About the reduction of the viral load, controlled clinical studies was carried out in 30 adult patients with positivity for COVID-19 in Shanghai – China, in samples of pharyngeal secretion samples in which PCR was performed. The result of the study was inconclusive with 13 patients out of 15 treated with HCQ had negative PCR vs 14 of 15 patients in the control group treated without HCQ (LD and LD, 2020). An important French study was one of the most controversial because as from this study, the massive use of hydroxychloroquine began. This no randomized, open label study included mild or asymptomatic patients, of which 20 patients received HCQ and 16 patients were in the control group. PCR nasopharyngeal carriage clearance was found in 70% of the group that receiving HCQ vs 12.5% in the control group until the 6th day of the start of treatment. This effect is reinforced by Azithromycin. There were the best results in terms of viral load reduction, even though is mentioned some limitations in the study like small sample size, a short long-term outcome follow-up, and dropout of 6 patients from the study (Gautret et al., 2020). Concerning to mortality rates, a study was conducted in New York with 1376 patients hospitalized and in need of oxygen at rest and the association between the use of HCQ

and respiratory deterioration and/or death was observed in patients with positive PCR testing for COVID-19, in which, 811 patients (59%) HCQ for an average of 5 days, 565 (41%) were not treated with HCQ. The risk of ECG abnormalities (including QT prolongation or arrhythmia) among patients receiving HCQ versus those who not received was 1.50 (0.88-2.58), for cardiac arrest of 1.91 (0.96-3.81) and for hospital death was 1.08 (0.63-1.85). Thus, it concludes that the use of HCQ is not associated with either a decreased or increased clinical impairment, intubation or death (Geleris et al., 2020) Results reinforced by other study in 1438 hospitalized patients with COVID-19 diagnosis in New York city, whom received treatment with hydroxychloroquine, azithromycin, or both drugs was not associated with significantly reduction in mortality (Rosenberg et al., 2020).

Relating to safety of this drug, in a study carried out in 200 patients in which the theoretical complications of the use of HCQ and its combination with macrolides (azithromycin) were assessed by serial electrocardiograms, the following results were obtained. In 5% of patients (10) received chloroquine, 95% (191) received HCQ, and 59% (119) received combination therapy with azithromycin. No case of Torsade de Pointes was observed, nor significant differences in the corrected QT interval before the start between the 3 groups of patients. The corrected QT interval was significantly longer in the combination therapy group. 3.5% (7) of patients had to stop treatment due to abnormal lengthening of the corrected QT interval. No deaths from arrhythmias were reported (Moussa et al., 2020). In a New York study, it is reported 15.5% of patients in treatment with hydroxychloroquine + azithromycin developed cardiac arrest, abnormal ECG findings in 27.1%; similar way in group of hydroxychloroquine alone with 13.7% and 27.3, respectively, vs. azithromycin alone (6.2% and 16.1%, respectively) and neither drug (6.8% and 14.0%, respectively) (Rosenberg et al., 2020).

Although all the described limitations found in studies, FDA decides to approve the emergency use for patients affected by COVID-19 on February 27, 2020. Currently, all the bias was taken in count, so most recent studies, which have a greater number of patients, take HCQ as a drug with little evidence for the benefit of patients with COVID-19.

1.20.2.4. Interferon. Interferon (INF) is a biological antineoplastic drug, used to treat multiple hematologic malignancies and skin diseases. There are several types of INF. The alpha / beta IFNs are classified as type I, II and III IFNs. INF I and II promote the antiviral cytokine system. The expression of genes induced by INF that stimulate the cellular antiviral state together with the recruitment of specific immune cells, are the basis for clinical trials in MERS-CoV and SARS-CoV viruses, the last being the most similar to SARS- CoV-2. Thus, PAHO has proposed INF as a probably effective treatment for patients with new infection (Rosa and Santos, 2020).

Regarding to the discovered imbalance in the expression of INF-1 of the virus-host interaction, INF acts like a protector, if is applied early in SARS infection (Spiegel et al., 2004). As previously noted, for COVID-19 infection, human controlled clinical trials are ongoing. Currently, 3 clinical trials underway have been reported. The investigations propose combinations of pharmacological interventions of Interferon alone (1 study) and in combination with lopinavir / ritonavir (2 trials). In general, there is no clinical evidence in humans on the action of INF in SARS and MERS Coronavirus infections. NIH guidelines not recommends its use (NIH, 2020). Supportive therapies in immune regulation, together with the use of antivirals, are important to take into account, especially in those patients in a serious and critical state, in which they could improve the clinical response and perhaps avoid residual lung injuries.

1.20.2.5. Convalescent plasma. The convalescent plasma is extracted from recovered individuals from an infection, being an antibody transfer medium to provide passive immunity (neutralizing antibodies and globulin). The goal is to provide a rapid immune response until the patient can develop their own active immune response in the hope that there will be clinical improvement (Duan et al., 2020a). The proposal for the use of convalescent plasma in COVID-19 carries over from the apparent success in other infections such as MERS, SARS and Influenza. When analyzed by meta-analysis (cases, observational studies and gray literature) there was a lower risk of mortality in the group treated with convalescent plasma (pooled OR, 0.25; 95% CI, .14 to .45; $P < 0.001$; I2 = 0%) (Mair-Jenkins et al., 2015). However, the lack of adequately designed studies and reporting bias favoring the intervention, limits the analysis and would be considered poor quality evidence.

Currently, the available evidence of the use of convalescent plasma in COVID-19 is based on reports of confirmed critically ill patients. Thus, we can mention the first pilot study carried out from January to February in China with patients from different centers (10 cases) who were administered hyperimmune plasma (titers greater than 1:640) plus antivirals and conventional support. This study demonstrated moderate clinical improvement in most individuals, as well as viral suppression 7 days after treatment (Duan et al., 2020b). In the same country, at the Shenzhen Hospital, 5 cases of patients with severe COVID-19 were reported who met criteria for acute respiratory distress syndrome (ARDS), who were administered convalescent plasma (titration greater than 1: 1000 and neutralizing antibodies greater than 40). It was found that clinical recovery occurred approximately 12 days after the transfusion (4 patients) and 3 of the 5 patients were discharged 55 days after admission. It is important to mention that this group of patients also received antivirals, methylprednisolone and all the necessary support measures in intensive care (Shen et al., 2020b).

Following this study, a retrospective observational investigation carried out in Zhenghou University Hospital, China analyzed 6 patients with confirmed severe COVID-19, who were administered convalescent plasma (antibody titration not described) compared with a control group. Mortality in the treatment group was 5/6 patients and in the control group it was 14/15 ($P = 0.184$). Each group had one recovered patient, respectively. The 5 patients who died (100% of deaths) in the treatment group had negative viremia after plasma transfusion, compared to 21.4% (3/14) of the control ($P = 0.005$). The survival period of the treatment group was longer than the control group ($P = 0.029$) (Zeng et al., 2020).

With the limited evidence available so far, it should be pointed out that despite the fact that some studies have a control group, the others do not, and, in addition, in all case descriptions, patients received antiviral and anti-inflammatory therapies in conjunction with multiple strategies of mechanical ventilation support; therefore, multivariate analysis is essential before attributing clinical improvement to convalescent plasma in the few successful cases. Therefore, these findings do not establish a causal effect, and the efficacy of convalescent plasma remains unknown.

In the United States, the FDA has accepted investigation of convalescent plasma in patients with severe or life-threatening COVID-19 through clinical trials and in emergencies. The difficulty in conducting these clinical trials lies in finding appropriate donors and establishing tests to confirm plasma neutralizing activity. Currently, more than 50 controlled clinical trials have been registered at www.clinicaltrials.gov, and none have reported preliminary results. Of the ongoing trials, 14 studies have large samples and high quality designs (more than 1000 patients, randomized and double-blind), and seek the primary outcome of impact on mortality and evident clinical improvement (Supplementary Table 2).

1.20.2.6. Other. Oseltamivir inhibits the viral neuraminidase, used in influenza A and B therapeutics. It has no effective outcomes in COVID-19 patients. Tocilizumab, an inhibitor of IL-6 is considered in a group of critical patients, in which 75% cursed with improved respiratory function after treatment. On April 27th was reported preliminary results of an important study: CORIMUNO-TOCI (NCT04331808), a randomized, open label trial of patients who stay at hospital with COVID-19 receiving tocilizumab vs. standard of care alone; and the preliminary results reports that the participants who died or need ventilation was lower in the

group who receive Tocilizumab. There is no enough evidence to recommend or reject it (NIH, 2020). Sarilumab is a repurposing, recombinant anti-interleukin-6 receptor antibody. Also, the preliminary results reported on April 27th, announced the trial (NCT04315298) is randomized and it is in phase 2 with sarilumab 400 mg or placebo. The announce was Sarilumab reduced CRP, which 79% of reduction in the sarilumab 400 mg, 77% in the 200 group, and 21% in placebo group. 28% of patients in the sarilumab 400 mg group had died or were on a ventilator, vs. 46% in the sarilumab 200 mg group and 55% in the placebo group. The most elevated mortality rate occurs with 23% of those in the sarilumab 400 mg group died compared with 27% in the placebo group. These are catalogued as negative outcomes in severe patients.

Regarding corticosteroids; they were associated with retard virus clearance in previous MERS and SARS pandemics (NIH, 2020). Based on knowledge of the inflammatory storm that causes lung injuries, corticosteroids appear as the perfect drug due to its anti-inflammatory properties. The use of corticoids depends on the stage of the COVID-19 disease: it is not recommended on severe patients, with no acute distress respiratory syndrome, neither on patients with mechanical ventilation. It is recommended for patients with COVID-19 and refractory shock, and just ICU patients. The Chinese studies suggests a short course of corticosteroids in patients with desaturation of oxygen. If patient has a chronic condition using corticoids as treatment, it should not be suspended (NIH, 2020).

Other drugs like ivermectin, nitazoxanide, and others have been studied in the context of COVID-19 treatment, but the results are inconsistent. All of the clinical trials evidence, supporting or against the use of mentioned drugs are detailed in (Supplementary Table 2).

This review summarized some drug repurposing agents previously known to has efficacy against other virus like SARS-CoV, MERS-CoV, influenza. Actually, exist some new drugs with high potential action on targets for COVID-19 therapeutics. It is important to notice that there is no specific treatment for the coronavirus approach. In context of the scientific evidence exposed and the particular clinical features of each patient, the reader will be able to make the best clinical and therapeutic decisions.

1.21. Vaccines development

When it comes to vaccine design and manufacturing, the main objectives are to ensure its safety, its efficacy in activating specific adaptive immune responses and the production of -ideally- long term memory. Thus, eliciting protective immune responses including neutralization antibodies and/or CTL generation is of paramount importance.

Huge challenges need to be tackled in order to minimize the long and cumbersome process of vaccine generation. Among them, candidate antigen targets need to be identified, immunization routes and delivery systems investigated, animal models set, adjuvants optimized, scalability and production facility considered, target population selected, and vaccine safety and long-term efficiency evaluated.

Currently there are no approved vaccines against any human coronavirus, suggesting that their generation is quite novel. Several candidate vaccines against SARS-CoV had shown promise reaching Phase I or Phase II clinical trials (Song et al., 2019; Yong et al., 2019), but the rapid containment of SARS-CoV expansion rendered them redundant, did not allow for a test population for Phase III trials and, therefore, put their further assessment to a halt.

However, the accumulated experience from previous coronavirus vaccine designs and the sequence and structural similarity of SARS-CoV and SARS-CoV-2 are significant advantages in the current endeavor. Thorough studies conducted in SARS-CoV-specific T cells of SARS convalescent patients have shown that all memory T cell responses are directed at SARS-CoV structural proteins. T cell epitope mapping showed that CD8+ responses were targeting SARS-CoV membrane (M) and Nucleocapsid (N) proteins and CTL memory could last up to 11 years after infection (Ng et al., 2016). These data suggest that vaccine strategies employing viral structural proteins that can elicit effective, long-term memory T cell responses could yield fruitful results.

On the other hand, the S1 spike protein region containing the ACE receptor binding domain (RDB) is the obvious option when neutralizing antibody responses are considered (Du et al., 2007; Du et al., 2009; Al-amri et al., 2017). Indeed, a candidate SARS vaccine antigen consisting of the RBD of SARS-CoV Spike protein was created and found it could elicit robust neutralizing antibody responses and long-term protection in vaccinated animals (Chen et al., 2014).

The fact that COVID-19 convalescent sera shows potential as a therapeutic approach (Casadevall and Pirofski, 2020) aligns with the theory that efficient B cell responses are mounted and lead to production of protective antibodies. Two different groups, using an immunoinformatic approach mapped several CTL and B cell epitopes on different proteins of the virus (Baruah and Bose, 2020; Grifoni et al., 2020). Moreover, various CTL epitopes were found to be binding MHC class I peptide-binding grooves via multiple contacts, illustrating their probable capacity to elicit immune responses (Baruah and Bose, 2020; Grifoni et al., 2020). Consequently, these identified B and T cell epitopes could be potential targets for therapeutic vaccines.

However, important safety considerations should be taken into account before releasing a new vaccine in the market. Previous studies on macaque models have shown that a vaccine-induced anti-Spike protein antibody at the acute stage of SARS-CoV infection can provoke severe acute lung injury (Liu et al., n.d.). Similar observations of SARS-CoV vaccine-induced pulmonary injury have also been described in multiple several murine and monkey animal models (M et al., 2011). An additional factor that needs to be checked in phase II and III trials is that the vaccine does not cause ADE of the pathogen, as has previously been described. Such concerns have risen in the context of a Dengue vaccine (Martínez-Vega et al., 2017).

Classic vaccine strategies like use of attenuated virus or recombinant protein subunit administration begin to lose support in the scientific community. COVID-19 mainly affects older patients with underlying pathologies that debilitate their immune system. Use of attenuated virus vaccines is contraindicated in these populations as weakened immune systems can permit the reversion of the attenuated pathogen to its wild type state, therefore causing the pathology it was designed to prevent. On the other hand, subunit vaccine design can be challenging when the protein used contains extended glycosylation. Interestingly, nucleic acid-based vaccines showed great promise in response to emerging pathogens like the DNA vaccine designed for Zika virus, entering in Phase I clinical trials (Tebas et al., 2017). Another nucleic acid-based platform for vaccine development, mRNA vaccines, seems a revolutionary strategy. Being designed to possess improved stability and protein translation efficiency these vaccine platforms can act both as adjuvants and antigen sources alike, inducing potent immune responses (Pardi et al., 2018; Maruggi et al., 2019). The optimization of the delivery system, such as lipid nanoparticles makes them excellent design candidates (Reichmuth et al., 2016). Finally, delivery systems such as recombinant vesicular stomatitis virus particles or the administration of mRNA molecules that codify for virus-like particles have been proven extremely efficient as testified by the recent FDA approved vaccine against Ebola (Commissioner O of the, 2020).

In an unprecedentedly swift response to develop and manufacture an anti-SARS-CoV-2 vaccine, more than 40 companies and academic institutions are exploring the aforementioned strategies. An example illustrating the rapid reaction of the scientific community to the SARS-CoV-2 outbreak is that of the biopharmaceutical company Moderna, the first vaccine manufacturer that entered in Phase I clinical trials for one candidate vaccine for COVID-19. On the night of Saturday, January 11, 2020, in the headquarters of the National Institute of Allergies and Infectious Diseases (NIAID) of USA Barney Graham, Deputy Director of the Vaccine Research Center, received the SARS-CoV-2 sequence. During the weekend his group analyzed the data and on Monday, 13 of January he discussed his observations with a group of investigators of the

Table 8
COVID-19 vaccine development update by manufacturer. Vaccination strategies employed, delivery platforms used, and current development status are presented if official data are provided.

Manufacturer	Vaccine candidate	Vaccination Strategy	Delivery Platform	Current stage of development/Trial Phase ¥	Status ¥	Viruses targeted by candidate vaccines using same strategy
CanSino Biological Inc./ Beijing Institute of Biotechnology	Ad5-nCoV	Recombinant virus/Non-replicating	Adenovirus Type 5 Vector	Phase 1 ChiCTR2000030906§ Phase 2 ChiCTR2000031781§	March 17, 2020: Beginning of Phase 1 clinical trials	Ebola, MERS-CoV
Moderna/ NIAID	mRNA-1273	mRNA codifying for full-length S protein	LNP* encapsulated mRNA	Phase 1 NCT04283461§ Phase 2 (IND accepted)	March 16, 2020: Vaccine administered to first volunteer Phase 2 studies planned for July	SARS-CoV, MERS-CoV
Wuhan Institute of Biological Products/Sinopharm	Not announced	Inactivated vaccine	-	Phase 1/2 ChiCTR2000031809§	Entering Phase 2 Studies	-
Beijing Institute of Biological Products/Sinopharm	Not announced	Inactivated vaccine	-	Phase 1/2 ChiCTR2000032459§	Entering Phase 2 Studies	-
Sinovac	PiCoVacc	Formalin inactivated & alum adjuvant	Inactivated virus	Phase 1/2 NCT04352608§	Not announced	SARS-CoV
University of Oxford	ChAdOx1	Recombinant viral vector/Non-replicating	Chimpanzee adenovirus vaccine vector	Phase 1/2 NCT04324606§	April 23, 2020: Vaccine administered to first volunteer	Influenza strains, Mycobacterium tuberculosis, Chikungunya, Zika, MenB, plague
BioNTech/Fosun Pharma/Pfizer	BNT162	mRNA vaccine/ 3 LNP	Not announced	Phase 1/2 2020-001038-36 NCT04368728§	Entering Phase 2 Studies	Influenza strains
Inovio Pharmaceuticals	INO-4800	DNA vaccine	Plasmid-Electroporation facilitated entry	Phase 1 NCT04336410§	April 6, 2020: Vaccine administered to first volunteer	Lassa, Nipah, HIV, Filovirus, HPV, Zika, Hepatitis B
Takis Biotech & Applied DNA Sciences/ Evvivax	Not announced/4 candidates for COVID-19	DNA vaccine	DNA	Pre-clinical development	Phase 1 clinical trials are expected to begin in fall 2020	Lassa, Nipah, HIV, Filovirus, HPV, Zika, Hepatitis B
Zydus Cadila	Not announced/2 strategies employed	1. DNA vaccine 2. Live attenuated recombinant vaccine	1. Plasmid 2. Recombinant replicating measles virus	Pre-clinical development	Not announced	Lassa, Nipah, HIV, Filovirus, HPV, Zika, Hepatitis B
Serum Institute of India & Codagenix	Not announced	Live Attenuated Virus	Live Attenuated Virus	Pre-clinical development	*In vivo* testing pending	HAV, InfA, ZIKV, FMD, SIV, RSV, DENV
Geovax/ BravoVax	Not announced	Recombinant viral vector/Non-replicating	Modified vaccinia ankara virus like particles encoded (MVA-CLP)	Pre-clinical development	Narrowing the vaccine candidates down from 3 to 1	LASV, EBOV, MARV, HIV
Janssen Pharmaceutical Companies of Johnson & Johnson/Barda	Not announced	Recombinant viral vector/Non-replicating	Ad26 (alone or with MVA boost) – AdVac and PER.C6 systems	Pre-clinical development	Phase 1 Clinical testing starting by September 2020	Ebola, HIV, RSV
Altimmune	Intranasal COVID-19 vaccine	Recombinant viral vector/Non-replicating	Adenovirus -based NasoVAX expressing SARS2-CoV S protein	Pre-clinical development	Animal testing imminent /Clinical testing is initially scheduled for August 2020	Influenza strains (NasoVAX vaccine)
Greffex	Adenovirus-based vector vaccine for COVID-19	Recombinant viral vector/Non-replicating	Adenovirus-based vector vaccine	Pre-clinical development	Animal testing has begun	MERS-CoV
Vaxart	Not announced	Recombinant viral vector/Non-replicating	Oral Vaccine platform	Pre-clinical development	Not announced	InfA, CHIKV, LASV, NORV; EBOV, RVF, HBV, VEE
ExpreS^{2}ion	Not announced	Protein Subunit	Drosophila Schneider 2 insect cell expression system VLPs#	Pre-clinical development	Phase 1/2a clinical testing to begin within 12 months	-
Walter Reed Army Institute of Research/United States Army Medical Research Institute of Infectious Diseases	Not announced	Protein Subunit/S protein	Antigen + adjuvant	Pre-clinical development	Several vaccine candidates developed/ Animal testing has begun	MERS-CoV
Clover Biopharmaceuticals Inc./GlaxoSmithKline	COVID-19 S-Trimer	Protein Subunits/S-Trimer	Antigen + adjuvant	Pre-clinical development	February, 2020: Vaccine candidate and adjuvant identified Clinical trials pending	HIV, REV Influenza
Vaxil Bio	Protein subunit COVID-19 vaccine	Protein Subunit/ signal peptide technology	Antigen + adjuvant	Pre-clinical development	Candidate identified/Beginning	

(continued on next page)

Table 8 *(continued)*

Manufacturer	Vaccine candidate	Vaccination Strategy	Delivery Platform	Current stage of development/Trial Phase ¥	Status ¥	Viruses targeted by candidate vaccines using same strategy
	candidate	(Patented)			of trials not announced	
AJ Vaccines	Not announced	Protein Subunit	Antigen + adjuvant	Pre-clinical development	Not announced	
Generex Biotechnology/EpiVax	Ii-Key peptide COVID-19 vaccine	Protein Subunit	li-key/antigenic epitope hybrid peptide vaccine	Pre-clinical development	Intention is to begin human testing within 3 months	Influenza strains, HIV, SARSCoV
EpiVax/University of Georgia	Ii-Key peptide COVID-19 vaccine	Protein Subunit/S protein	li-key/antigenic epitope hybrid peptide vaccine	Pre-clinical development	Not announced	H7N9
Sanofi Pasteur/BARDA GlaxoSmithKline	Not announced	Protein Subunit/S protein produced in baculovirus	Antigen + adjuvant	Pre-clinical development	Human clinical trials expected to begin after June 2020	Influenza strains, SARS-CoV
Novavax	Not announced	S Protein Subunit exposed on helminthic surface	Recombinant nanoparticles	Pre-clinical development	Vaccine candidate identified/Phase 1 clinical testing to begin in May 2020	RSV; CCHF, HPV, VZV, EBOV
Heat Biologics/University of Miami	gp96-based vaccine	Protein Subunit/gp-96 heat-shock protein backbone	Antigen + adjuvant	Pre-clinical development	Not announced	NSCLC, HIV, malaria, Zika
University of						

Queensland/GlaxoSmithKlineMolecular clamp vaccine for COVID-19Protein Subunit/ Molecular clamp stabilized Spike proteinAntigen + adjuvantPre-clinical developmentFurther development prior to pre-clinical testing requiredNipah, influenza, Ebola, LassaBaylor College of MedicineRe-purposed SARS vaccine for COVID-19Protein Subunit/S1 or RBD proteinAntigen + adjuvantPre-clinical developmentNot announcedSARS-CoViBio/CC-PharmingPlant-based COVID-19 vaccineSubunit protein/Plant producedAntigen + adjuvantPre-clinical developmentNot announcedVIDO-InterVac/ University of SaskatchewanNot announcedProtein SubunitAdjuvanted microsphere peptidePre-clinical developmentNot announcedInstitute Pasteur/Themis/Univ. of Pittsburg Center for Vaccine ResearchNot announcedRecombinant replicating Viral VectorMeasles VectorPre-clinical developmentNot announcedWest Nile, Ebola, Lassa, ZikaTonix Pharma/Southern ResearchHorsepox vaccine with percutaneous administrationRecombinant replicating Viral Vector
(used also in TNX-1800 vaccine)Horsepox vector expressing S- proteinPre-clinical developmentNot announcedSmallpox, monkeypoxFudan University/ Shanghai Jiao Tong University/RNACure BiopharmamRNA vaccine candidate for COVID-19mRNA vaccine/2 candidates1. LNP* encapsulated mRNA cocktail encoding SARS-CoV-2 VLP#

2. LNP* encapsulated mRNA encoding RBD of S-proteinPre-clinical developmentNot announcedChina CDC/Tongji University/SterminaNot announcedmRNA vaccineNot announcedPre-clinical developmentNot announcedArcturus Therapeutics/Duke-NUS Medical SchoolNot announcedmRNA vaccineSelf-replicating RNA and nanoparticle non--viral delivery systemPre-clinical developmentPhase 1 clinical trials to begin in summer 2020Various candidatesBioNTech/Fosun Pharma/PfizerBNT162mRNA vaccineNot announcedPre-clinical developmentPhase 1 clinical trials expected to begin in April 2020Influenza strainsCurevacNot announcedmRNA vaccineNot announcedPre-clinical developmentCandidate expected by end of April 2020

Human clinical trials expected to begin in summer 2020RABV, LASV, YFV; MERS, InfA, ZIKV, DengV, NIPVImperial College LondonSelf-amplifying (sa) RNA vaccinesaRNA vaccineNot announcedPre-clinical developmentAnimal testing is underway/ Clinical trials expected to begin in June 2020EBOV; LASV, MARV, Inf (H7N9), RABVMedicago Inc. Plant-based COVID-19 vaccinePlant-derived VLP#VLP#Pre-clinical developmentHuman testing expected to begin in July or August 2020Influenza, Rotavirus, Norovirus, West Nile virus, Cancer * LNP = lipid nanoparticle system, § Clinical Trial Registry Identifier, ¥ According to manufacturer, # VLP = Virus like particle. Table updated until 21/05/2020; several more companies have announced their intention to manufacture COVID-19 vaccines without disclosing further information.

biopharmaceutical company Moderna. On the same day Moderna's infectious disease research team finalized the sequence for mRNA-1273, the company's first vaccine candidate against SARS-CoV-2. On February 7, 2020, the first clinical batch of Moderna was completed. On February 24, 2020, the clinical batch was shipped from Moderna to the NIH to be used in their own Phase I clinical study. On March 4, 2020, the U.S. FDA gave the green light for mRNA-1273 to begin clinical trials. Twelve days later, on March 16, 2020, the NIH announced that the first participant in its Phase I clinical study received the first dose of mRNA-1273. The time between virus sequencing to beginning of Phase I trials was a record total of 63 days.

The pharmaceutical companies that are currently on a race to produce a vaccine for COVID-19 along with the vaccine developing strategies they are using are summarized in Table 8 and Fig. 7.

As can be easily deduced from Table 8, optimistic predictions dictate that a vaccine for COVID-19 will not be ready in the next 12-18 months. An indirect course of action that could help to mitigate the impact of COVID-19 pandemic would be a plan of vaccination against influenza strains and *Strepococcus pneumoniae*. Influenza is a major universal health problem accounting for 3 to 5 million cases of severe illness and about 350 000 to 650 000 respiratory deaths yearly. For the time period from 17 February 2020 to 01 March 2020 alone the WHO laboratories tested positive for influenza viruses 62423 samples (WHO, n.d.). On the other hand, *Streptococcus pneumoniae* is the most common cause of community acquired pneumonia. In the present context of COVID-19 global outbreak vaccination against the most prevalent strains of influenza and *Streptococcus pneumoniae* would have a multifaceted effect. Firstly, it would lower the risk of severe disease, reduce hospitalization and admission to already heavily charged ICUs due to these pathologies that could prove critical for weaker health systems that would struggle to carry the burden of combined outbreaks. Moreover, vaccinating health care workers is crucial for reducing the risk of absence due to disease, thereby strengthening the healthcare workforce and minimizing the risk to infect COVID-19 hospitalized patients with additional pneumonia-causing pathogens. Lastly, COVID-19 patients vaccinated for influenza and *Streptococcus pneumoniae* allow their immune system to focus on one pathogen and, therefore, give it a better fighting chance against SARS-CoV-2 infection (Mendelson, 2020). High risk groups prioritized for vaccination for these 2 pathogens include pregnant women, persons with immunocompromised immune systems (either due to congenital or acquired immunodeficiencies), children, adults ≥ 65 years and health care professionals.

1.22. Climate and SARS-CoV-2

Numerous studies confirm that climate has an impact on virus (i.e., influenza, coronavirus, etc.) spread through manipulating the conditions of i) its diffusion, ii) the virus survival outside the host, and iii) the immunity of host population (Tamerius et al., 2011). Meteorological conditions, such as temperature, humidity, wind speed and direction, atmospheric pressure, solar radiation (including ultraviolet (UV) spectrum) and precipitation amount and intensity depend on the latitude

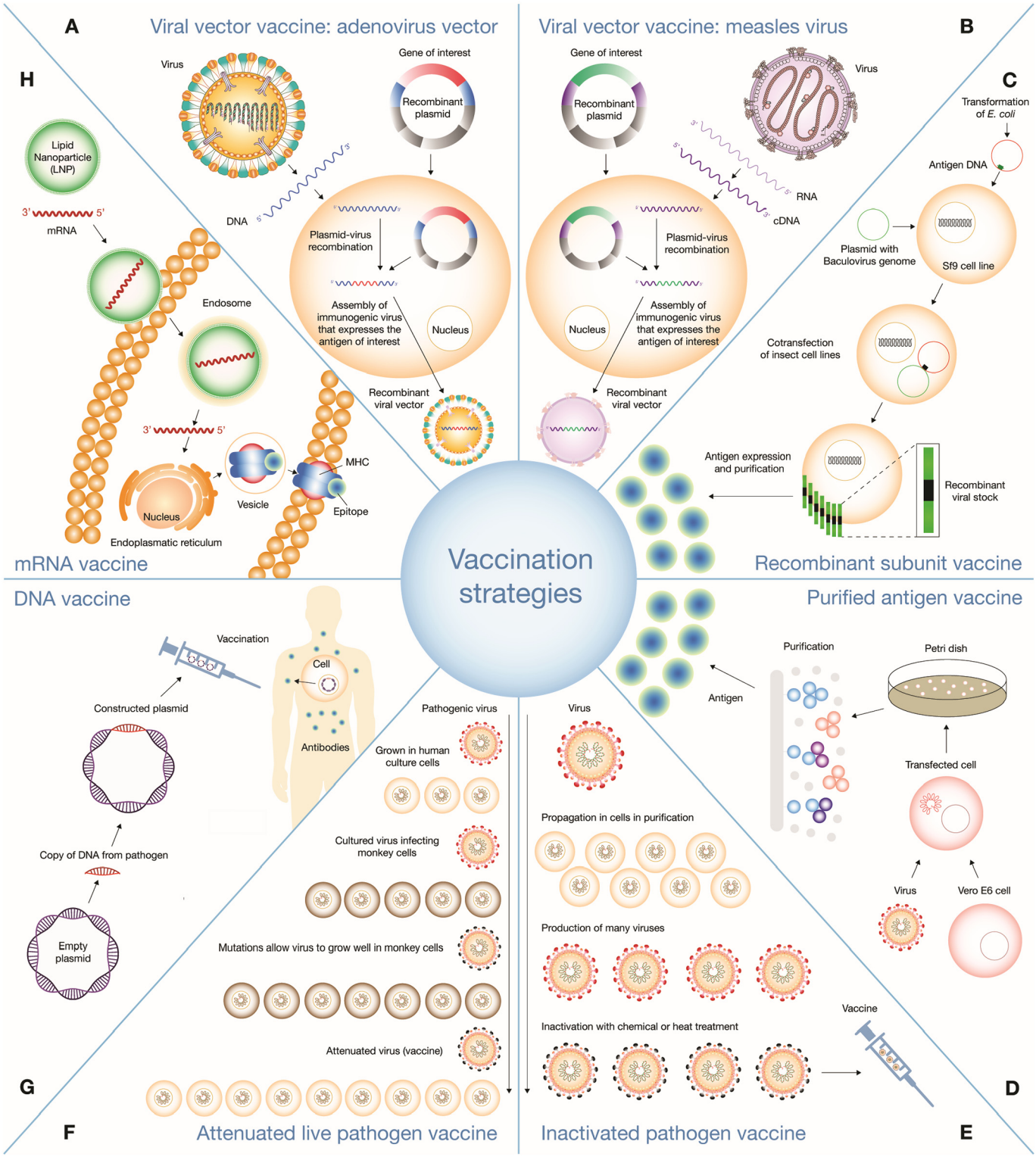

Fig. 7. Strategies used or proposed for COVID-19 vaccine development and delivery. A) and B) Adenoviral and measles recombinant viral vectors can be manipulated to express and therefore elicit robust immune responses against the Spike (S) protein of SARS-CoV-2. Recombinant subunit vaccine strategies use the Sf9-baculovirus insect cell expression system resulting in the production of high-quality antigen that can be used to elicit immune responses. D) Purified antigen vaccine strategies implicate the replication of large numbers of virus in cell cultures and the subsequent purification of viral antigens to be used for vaccination. E) Attenuated vaccines contain whole pathogen that has been submitted to heat or chemical treatment inactivation. F) Attenuated live pathogen vaccine strategies consist in administering a live pathogen that due to cell culture passaging has lost its virulence. They usually elicit robust and long-term memory immune responses without the need to administer an adjuvant. G) In DNA vaccines the DNA codifying a highly immunogenic antigen is administered and captured by professional antigen presenting cells (APCs) leading to antigen production and presentation by these cells. H) Moderna's vaccine candidate already in Phase I clinical trials uses an mRNA vaccine approach whereby the genetic information codifying for the S protein of SARS-CoV-2 is delivered in LNPs to enhance absorption by APCs. Once uptaken by APCs the mRNA induces the expression of S antigen that is subsequently mounted on and presented by MHC molecules to elicit adaptive immune response.

and the elevation of the location, thus creating distinct climatic zones in the planet. While in some regions, such as temperate climate zones, human influenza peaks have clear seasonal cycles, in others it is not as predictable (Tamerius et al., 2011; Cox, 2014; Lowen and Steel, 2014; Caini et al., 2018; Mendelson, 2020).

An array of studies, investigating the relationship between climatic factors and the activity of influenza all over the world, concluded that at the high latitudes of the world the peaks of influenza correlate with cold and dry weather conditions (i.e., winter season), while around the equatorial zone, it is more common during the months of high humidity and precipitation (Rao and Banerjee, 1993; Dosseh et al., 2000; Viboud et al., 2004; Finkelman et al., 2007; Moura et al., 2009; Tamerius et al., 2013; Roussel et al., 2016). Essentially, it depends on explicit threshold conditions based on monthly averages of specific humidity and temperature. When specific humidity drops below 11–12 g/kg and temperature drops below 18–21°C, the peak of influenza is stimulated during the cold-dry season, however, for tropical and subtropical (always humid and warm) regions, it is likely to prevail during the high precipitation (≥150 mm) months (Tamerius et al., 2013). The "cold-dry" set of climatic conditions endorses a greater survival of the virus outside human body, and, thus, results in better transmission (Lofgren et al., 2007; Lowen and Steel, 2014). Similar temperature dependency was concluded for SARS (strain CoV-P9) Coronavirus. Laboratory experiments testing virus stability, demonstrated a decreasing infectivity with increasing ambient temperatures, where at 4°C, 56°C and 75°C the survival rates outside host decreased from at least 96 to 1.5 and to 0.5 hours, respectively (Duan et al., 2003). In addition, cold air cools nasal epithelium which, in turn, decreases mechanical defenses of the respiratory and immune systems (Eccles, 2002).

Duan et. al., (2003) concluded that, even a relatively short exposure (1 hour) to UV radiation destroys viral infectivity of SARS (strain CoV-P9) Coronavirus. Other studies also correlate vitamin D secretion and influenza immunity, due to the UV role in vitamin D production (Helming et al., 2005; Cannell et al., 2006). The latter, and the reduced immune system due to melatonin oscillations during the dark (lack of sunlight hours) winter seasons could further explain winter outbreaks of influenza at high latitude regions (Dowell, 2001).

Finally, wind speed may contribute to the spread of influenza nanoparticles. While low winds might improve its transmission from one host to another, strong winds contribute to its dispersion and ventilation (Xiao et al., 2013), which could be a positive effect depending on wind direction.

2. Conclusions

The authors of this study examined the most important literature available in terms of the genetic, virology, clinical and therapeutic evidence on the SARS-CoV-2 virus and the novel Coronavirus diseases 2019 (COVID-19).

This extensive and comprehensive literature review tries to offer a good insight of the most recent information available. This review was designed to offer a good insight of the virus and the diseases to the entire medical community. This document although summarized, tries to bring well-supported information on this new disease. A disease that has been keeping us on a partial or total lockdown all over the planet.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diagmicrobio.2020.115094.

Declarations

Ethics approval and consent to participate

According to the local and international regulation, this project did no required ethical approval.

Consent to publish

Not Applicable.

Availability of data and materials

All the information used for this analysis can be found

Competing interests

The authors declare that they have no competing interests.

Funding

This work did not receive financial support of any kind.

Authors' contributions

EOP was responsible for the full conceptualization and he was in charge of drafting the document in all of the stages. KSR and LGB contributed with the Cancer and COVID-19 section and review all the manuscript. MRN completed the section about COVID-19 in children. LG and CBO completed the diagnosis section of the review. NK completed the immunological response to SARS CoV2. CM completed the virologic aspects of the manuscript. AMG, DC, HSS and LU completed the clinical section of the manuscript, the therapeutic strategies and the gynecological and complication section of the manuscript. RZ completed the environmental effects and COVID-19. NG critically review the manuscript and ALC was partially responsible for the conceptualization of the study, the genetic aspects of the virus and he completed all the figures for this work.

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