BRITISH JOURNAL OF BIOMEDICAL SCIENCE
2020, VOL. 77, NO. 4, 168–184
https://doi.org/10.1080/09674845.2020.1826136

REVIEW

Understanding the dynamics of COVID-19; implications for therapeutic intervention, vaccine development and movement control

S Salvamani[a], HZ Tan[a], WJ Thang[a], HC Ter[a], MS Wan[a], B Gunasekaran[b] and A Rhodes[a,c]

[a]Division of Applied Biomedical Sciences and Biotechnology, School of Health Sciences, International Medical University, Kuala Lumpur, Malaysia; [b]Dept of Biotechnology, Faculty of Applied Sciences, UCSI University, Kuala Lumpur, Malaysia; [c]Dept of Pathology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

ABSTRACT

The COVID-19 disease is caused by the SARS-CoV-2 virus, which is highly infective within the human population. The virus is widely disseminated to almost every continent with over twenty-seven million infections and over ninety-thousand reported deaths attributed to COVID-19 disease. SARS-CoV-2 is a single stranded RNA virus, comprising three main viral proteins; membrane, spike and envelope. The clinical features of COVID-19 disease can be classified according to different degrees of severity, with some patients progressing to acute respiratory distress syndrome, which can be fatal. In addition, many infections are asymptomatic or only cause mild symptoms. As there is no specific treatment for COVID-19 there is considerable endeavour to raise a vaccine against SARS-CoV-2, in addition to engineering neutralizing antibody interventions. In the absence of an effective vaccine, movement controls of varying stringencies have been imposed. Whilst enforced lockdown measures have been effective, they may be less effective against the current strain of SARS-CoV-2, the G614 clade. Conversely, other mutations of the virus, such as the Δ382 variant could reduce the clinical relevance of infection. The front runners in the race to develop an effective vaccine focus on the SARS-Co-V-2 Spike protein. However, vaccines that produce a T-cell response to a wider range of SARS-Co-V-2 viral proteins, may be more effective. Population based studies that determine the level of innate immunity to SARS-CoV-2, from prior exposure to the virus or to other coronaviruses, will have important implications for government imposed movement control and the strategic delivery of vaccination programmes.

ARTICLE HISTORY
Received 15 August 2020
Accepted 16 September 2020

KEYWORDS
SARS-CoV-2; COVID-19

Introduction

The world in 2020, or to be more accurate humankind, is attempting to control the coronavirus disease 2019 (COVID-19) pandemic and to come to terms with the health consequences and economic havoc bestowed on just about every nation. In this review, the events leading from the discovery of the virus that causes this disease, to its subsequent dissemination globally are catalogued. Moreover, the scientific data on the molecular structure of the virus are examined, as are its mode of infection, the pathophysiology of COVID-19, the epidemiology of the disease and the treatments and vaccines currently in clinical trial. The purpose of the review is to compile knowledge on key aspects of the virus and COVID-19 and in so doing to ascertain the implications for therapeutic intervention, vaccine development and movement control.

Timeline of events in the spread of the SARS-CoV-2 virus

On 12 December 2019 in the Chinese city of Wuhan in Hubei Province, the first cases of an unknown acute respiratory tract infection were documented [1], with some of the patients developing progressive respiratory failure [2]. Samples from seven of the patients with severe pneumonia (six of whom were employed in the local seafood market) and who were being cared for in the intensive care unit of Wuhan Jin Yin-Tan Hospital, were sent to the Wuhan Institute of Virology for the diagnosis of the causative pathogen. As the Institute was a laboratory with an interest in investigating coronaviruses (CoV), pan-CoV PCR primer sets were first used to test the samples, as the outbreak had occurred in winter and in a market; a similar environment to that of the 2003 Severe Acute Respiratory Syndrome (SARS) outbreak. Five samples were found to be PCR-positive for CoVs. One sample (WIV04), collected from bronchoalveolar lavage fluid, was analysed further by metagenomics and next-generation sequencing technology to identify potential aetiological agents. Subsequent analyses showed the new virus, since named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), to have 96.2% overall genome sequence identity with a virus (BatVoVRaTG13) previously detected in bats (*Rhinolophus affinis*) from Yunnan province [2], suggesting that the bat CoV and human SARS-CoV-2 share the

CONTACT A Rhodes carhodes60@gmail.com Division of Applied Biomedical Sciences and Biotechnology, School of Health Sciences, International Medical University, No 126 Jalan Jalil, Perkasa 19, Bukit Jalil, 57000 Kuala Lumpur, Malaysia

same ancestor. Consequently, this phylogenetic relationship provides evidence that SARS-CoV-2 may have originated in bats, though alternative hosts such as turtles and pangolins have also been suggested [1–4].

By 10 January 2020, Wuhan had 44 cases of the disease (now known as COVID-19) caused by the SARS-CoV-2 virus and one reported death and until 23 January, 81% of the reported cases were from Hubei province. Lockdown was subsequently imposed on Wuhan. Unfortunately, this period coincided with Chinese New Year when there was mass movement of citizens to their hometowns, and by the time of the lockdown over 5 million Wuhan residents had already left the city. By 1 March 2020, 79,986 cases of COVID-19 were confirmed in China with most provinces reporting rapid increases in cases [5,6].

The first case of COVID-19 reported outside China was on 13 January in Thailand, three days after China had reported the first death from the disease, and involved a resident of Wuhan who had travelled to the country [6]. Similarly, many of the early cases reported in countries outside China during January to February 2020, to include Singapore, Malaysia, Vietnam and the Philippines, involved persons that had a history of travel to Wuhan. The subsequent significant increase in numbers with the disease frequently followed mass gatherings, such as large religious events that occurred in South Korea and Malaysia, emphasizing the person-to-person transmissibility of the disease [3].

By 11 March 2020 COVID-19 had infected more than 100 000 people in 100 countries, with Italy having the largest number of cases outside China with 12,462 cases and 827 deaths and WHO officially declared COVID-19 a pandemic [7]. The Italian region of Lombardy initially saw the first wave of infections, before spreading to the rest of Italy and the country subsequently closed its borders. By 15 March 2020 other European countries, including Spain, Germany and France, were seeing exponential increase in cases, with Italian health policy experts warning the rest of Europe, including the UK, to prepare for the predicted upsurge in cases following the initial 2–3 week lag phase seen in both Italy and in China [7,8].

In the UK the first case of COVID-19 was reported on 23 January in a visitor from Hubei province, China, with the second case being a close household contact who developed symptoms five days later, with positivity for both cases confirmed at the public health laboratories at Colindale, North London [9]. By 3 March 2020, the number of reported UK cases had risen but was still relatively low at 51. Approximately three weeks later, with just over 6000 confirmed cases, the UK Government introduced strict physical distancing measures instructing individuals to stay at home and avoid leaving their house except for essential work, daily exercise, and shopping for essential items [10,11].

The first case of COVID-19 in the United States was confirmed on 20 January 2020, arriving via an international flight from China [12]. Approximately, 1 month later on 26 February, 12 travel-related COVID-19 cases had been diagnosed in the United States, in addition to three cases in patients with no travel history and 46 cases reported among repatriated U.S. citizens [13]. A further 1 month, and over 160,000 additional cases in the US had been reported in several states, the majority of which had arisen from local transmission, indicating disseminated community spread of SARS–CoV-2 in the US [12]. As of September 2020, the COVID-19 pandemic is widely disseminated throughout the communities of most of the US states, and with the US recording over 7.5 million cases, the highest in the world [14]. The countries of Latin America are similarly hard hit, with Brazil having over 4 million cases, whilst in Asia, India has the second largest number of cases in the world, at 4.2 million. The vast majority of the countries of the world have reported cases of SARS-CoV-2 infection and at the time of writing globally there are over 27 million infections and over 90,000 reported deaths attributed to the COVID-19 disease. The nations with the largest numbers of cases from each continent are shown in Figure 1 [14,15].

The molecular structure of SARS-CoV-2 and mechanisms of infection

Coronaviruses are positive-single stranded RNA viruses and they contain a large RNA genome, approximate length of 27 to 32 kb with a 5′-capped and 3′ poly-A tail [16]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped virus that contains four major structural proteins. The three viral membrane proteins are named; membrane (M) protein, spike (S) protein and envelope (E) protein [17–19] (See Figure 2). Nucleocapsid (N) proteins, which are surrounded by the viral membrane, are important in replication and

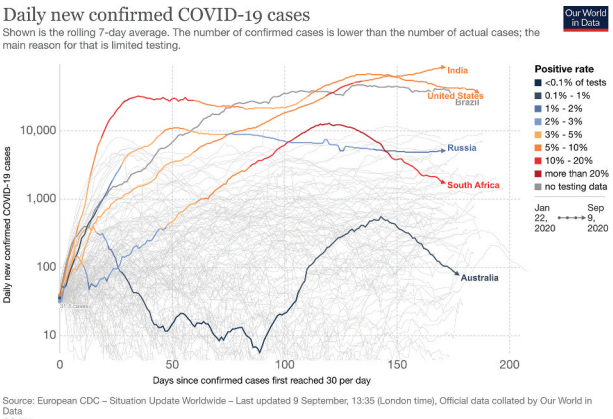

Figure 1. The number of PCR confirmed SARS-CoV-2 cases as of 9 September 2020 for nations with the highest numbers of cases from each continent. Our World in Data, Oxford University, and The European Centre for Disease Prevention & Control [14,15].

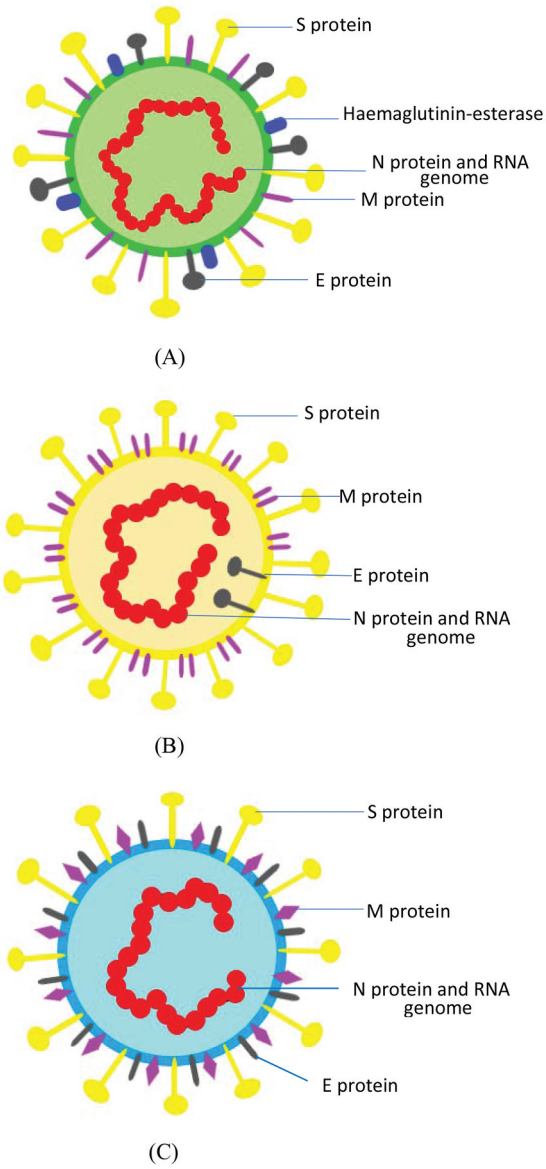

Figure 2. Structures of Coronaviruses (A) SARS-CoV-2 (B) SARS-CoV-1 (C) MERS-CoV. Diagrams adapted from Shereen et al., 2020 and Viral Zone 2020, SIB Swiss Institute of Bioinformatics) [18,19].

transcription in the nucleocapsid. The S protein is responsible for the entry and attachment of the virus to the host cells through the interaction of binding to the host receptor, causing the fusion of viral membrane and host membrane. S protein contains two subunits; S1 and S2. A receptor-binding domain (RBD) in the S1 subunit mediates the binding to the host receptor, while the S2 subunit mediates the fusion of viral membrane and host membrane [20]. The RBD recognizes the host angiotensin-converting enzyme 2 (ACE2) receptor, which is highly abundant in type II alveolar cells. This inhibits the action of ACE2 in the regulation of angiotensin II signalling [21]. After the fusion of host and viral membrane, the virus particle releases the RNA genome into the cytoplasm. Transcription regulatory sequences located between the open reading frames (ORFs) are the sites where transcription termination occurs. The production of two large polypeptides, pp1a and pp1ab, is guided by a frameshift between ORF1a and ORF1b [22]. The uncoated RNA translates the viral proteases; pp1a, pp1b and chymotrypsin-like protease (3CLpro). One or two papain-like proteases convert 16 units of non-structural protein (nsp 1 to nsp 16) to form a replication-transcription complex (RTC) in double-membrane vesicles (DMVs). Non-structural proteins are essential in the replication and transcription processes [23]. The replication of the virus can cause mild symptoms of influenza-like illness owing to the direct cytopathic effect of the virus [24]. After the replication of the RTC, sub-genomic RNAs are synthesized. N proteins, S protein and E protein are translated and inserted into the endoplasmic reticulum (ER). Then, they move into membranes that are located between the ER and Golgi apparatus [25]. Virion-containing vesicles are formed by assembling newly synthesized sub-genomic RNAs, N proteins and E protein. Once the fusion of virion-containing vesicles and plasma membrane of the cell occurs, the virus will be released by exocytosis and attached to the new cell. The cycle is repeated to further infect more cells [2].

Molecular comparison of SARS-CoV-2, SARS-CoV-1 and MERS-CoV

All the three viruses; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and Middle East respiratory syndrome coronavirus (MERS-CoV) contain the S protein, E protein, M protein and N protein. Whilst the viruses share some structural similarities, there are also some notable differences (Figure 2).

The S proteins are essential in many species of the coronaviruses since they play an important role in penetrating and infecting the host cells. However, they do display some difference between species at the molecular level. The SARS-CoV-2 and SARS-CoV-1 are very similar in that their RBD binds to the ACE2 receptor. However, SARS-CO-V2 has six mutations occurring in regions of the RBD, resulting in higher binding affinity to the ACE2 receptor compared to that of SARS-CoV-1. This may be responsible for the differences in pathogenicity seen between the two viruses [26]. A characteristic of the RBD of the MERS-CoV, compared to the other two coronaviruses, is that it has an external subdomain, which is able to bind with the cellular receptor dipeptidyl peptidase-4 (DPP4) to transfer its genomic material into the host cell [27]. The M protein structures present in SARS-CoV -2, SARS-CoV-1 and MERS-CoV, all share similar structures and functions and interacts with either N or E proteins to release viral particles. The basic role of N protein is to bind with the single positive strand of the RNA genome and is associated with the hijacking and infection of human cells. The N protein contributes to the process of budding of the virus only when it interacts with the M protein [28]. One of the main

structural differences between SARS-CoV-2, SARS-CoV -1 and MERS-CoV, is that the SARS-CoV-2 virus possesses the haemagglutinin-esterase (HE) protein, which is absent in the other two viruses. When viewed under the electron microscopy, the HE spike comprises of a crystalline structure that has a globular head and a membrane stalk [29]. Its main role in SARS-CoV-2 is to attach and destroy the sialic acid receptors that appear on the host cell The HE enzymes also help in enhancing the attachment and incorporation between the viral genome and the host's cell cytoplasm [30].

The clinical features of COVID-19

The incubation period for SARS-co-V2 falls within the range of 2 to 14 days (median 5.1) [31]. Symptoms usually develop after 11.5 days of infection [32]. The clinical features of the COVID-19 disease can be classified according to different degrees of severity as; mild, moderate, severe, and critical (Table 1). In addition, some patients are asymptomatic.

The course of the disease

Two different studies from Wuhan serve to illustrate the course of the disease and the elapsed time at critical stages [33,34] (Table 2). The duration from the onset of illness to death is largely dependent on the patient's immune status and the age of the patient. The older the patient especially those above 60 years old, the shorter the duration from the onset of illness to death compared to those below 60 years old [34].

Long-term complications following acute respiratory distress syndrome (ARDS)

Patients who develop ARDS can suffer long-term impairment of the lungs [32]. Pulmonary fibrosis or restrictive lung disease can develop in the survivors of ARDS with evidence of rapidly progressing fibrotic changes in pulmonary fibrosis seen in some lung CT scans [35]. Progressive pulmonary fibrosis can be due to unchecked cellular proliferation, accumulation of fibroblasts and myofibroblasts and excessive deposition of collagen and other extracellular matrix components [36]. Consequently, the lung function declines and causes early mortality. Besides, ARDS and pulmonary fibrosis, chronic ventilation can be associated with neurological impairment such as cognitive decline. This might be due to elevation of cytokines causing systemic inflammation in these COVID-19 patients [37,38].

Table 1. Summary of the clinical features of COVID-19 based on the severity of the disease [31,32].

Severity	Clinical features
Mild	Mild fever, Dry cough, Sore throat, Runny nose, Nasal congestion, Headache, Sneezing, Fatigue, Myalgia, Muscle pain, Tiredness, Loss of smell, Malaise, Nausea, Vomiting, Diarrhoea, Abdominal pain
Moderate	Fever (persistent or >37.8°C), Dry cough, Tachypnoea, Shortness of breath
Severe	Moderate fever or absence of fever, Dyspnoea, Tachypnoea, Hypoxia, Diarrhoea, Vomiting, Nausea, Respiratory distress (respiratory rate >30/minute), Finger oxygen saturation ≤93% at resting state, $PaO_2/FiO_2 \leq 300$ mmHg, >50% lung involvement within 24 to 48 hours
Critical	Chest pain, Shortness of breath, Movement impairments, Loss of speech, Septic shock/sepsis, Multiple organ dysfunction

Table 2. Summary of the time course of COVID-19 illness in two different studies from Wuhan, China [33,34].

Huang et al. (2020)	Median time (Interquartile Range)
From onset of symptoms to;	
First hospital admission	7 days (4–8)
Dyspnoea	8 days (5–13)
Acute respiratory distress syndrome (ARDS)	9 days (8–14)
Mechanical ventilation	10 days (7–14)
Intensive Care Unit (ICU) admission	10.5 days (8–17)
Zhou et al. (2020) Median time	
Duration of fever	12 days (8–13)
Duration of persistent cough	19 days (12–23)
From the onset of symptoms to;	
Discharge	22 days (18–25)
Mechanical ventilation	14.5 days (12–19)
Death	18.5 days (15–22)
Complications	***Developed at;***
Septic shock	9 days (7–13)
ARDS	12 days (8–15)
Acute cardiac injury	15 days (10–17)
Acute kidney injury	15 days (13–19.5)
Secondary infection	17 days (13–19)

The cytokine storm

Some individuals with severe COVID-19 show a form of a classical cytokine release syndrome, frequently referred to as a cytokine storm [39]. Dysregulation of the immune response to SARS- CoV-2 leading to the lysis of macrophages, dendritic cells and B and T cells, may be the underlying cause of this. Once macrophages are activated by interferon gamma, they enhance large-scale release of a wide range of cytokines [40,41]. High levels of pro-inflammatory cytokines and chemokines are correlated with poor COVID-19 outcomes, similar to that reported after the 2003 SARS epidemic [42,43]. When inflammatory cytokine-producing cells are activated, a virus-induced damage involving predominantly the alveolar epithelium of the lungs occurs [44]. In particular, interferon gamma enhances the immune-mediated damage contributing to the pathogenesis of acute lung injury [45,46]. Studies carried out in patients with ARDS identified different phenotypes depending on the biomarkers found in the serum: ARDS patients with high expression of angiopoietin, plasminogen activator inhibitor 1, interferon gamma and IL-6 had a poorer outcome and a higher mortality compared to ARDS subjects without inflammatory markers [47]. IL-6 is a particularly important component of the cytokine storm as it is able to directly activate T cells [39].

The epidemiology of COVID-19, to include transmissibility and measures to control the virus

It is difficult to accurately compare statistics on the numbers of COVID-19 positive cases between nations due to the differences between countries in testing strategies to include selection criteria for testing. It is generally considered that official figures, under-represent the actual numbers of cases [14,15]. As the number of infections reported in a country will depend on the amount of testing done it is important to not only determine the number of cases but also the number of tests carried out relative to the population size. The positivity rate per test in a country will be influenced by both the scale of the epidemic and both the amount of testing. For example, New Zealand, has one of the lowest positivity rates in the World (<0.1%) and it requires hundreds or thousands of tests to discover one positive case. In contrast, the US and India positivity rates at 5–10% are over fifty-times higher, whilst in South Africa at 10–20% they are over one hundred-times higher requiring considerably fewer tests before a positive case is discovered [15] (Figure 1 and Table 3). It is considered that a country with a high positive rate is not testing widely enough to identify all cases, with the World Health Organisation (WHO) suggesting a positivity rate of 3–12% as a general indicator of adequate testing [15].

With respect to global death rates from COVID-19, as of September 2020, the US has recorded the highest cumulative number of fatalities from the disease, followed by Brazil and India and with the UK having the highest rates within Europe (Figure 3 and Table 3). However, it is important to emphasise that comparison of the death rates from COVID-19 between nations is fraught with difficulties, as there are differences in how each nation reports the deaths. For example, early in 2020, the COVID-19 deaths recorded by Public Health England included all cases in England with a positive test result, irrespective of the elapsed time interval or ultimate cause of death, with this anomaly not being identified until August 2020 [48]. Therefore, even within the countries of the UK, there has been disparity between how COVID-19 deaths are recorded. In an attempt to overcome the lack of comparability between nations, attempts have been made to look at excess mortality, by comparing the overall death rates over the period of the pandemic to that of an earlier time period. Excess mortality is defined as actual deaths from all causes, minus 'normal' deaths. This type of data is only available for several countries, again making worldwide comparisons difficult. However, within Europe, England had the highest rate of excess mortality during the COVID-19 pandemic for the age group 15–64 years. Whereas Spain had the highest rate in the over 85-year age group [15].

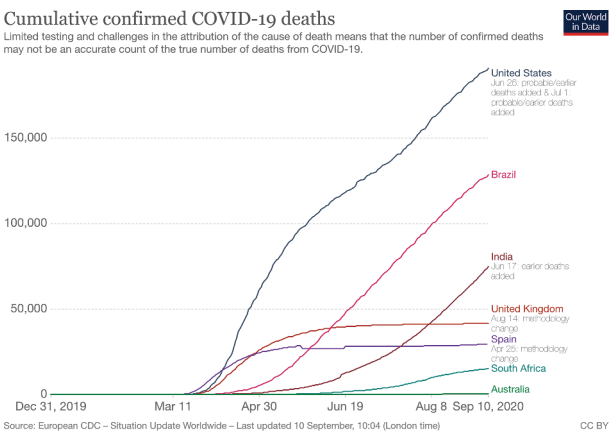

Figure 3. Nations from each continent recording the highest cumulative numbers of deaths attributable to COVID-19. Our World in Data, Oxford University [15].

Movement control and government response stringency

Evidence shows that the virus is spread by respiratory droplets, close person-to-person contact and contact with virus-contaminated surfaces (Shah et al. 2020) [3]. Consequently, in the absence of a vaccine health authorities in virtually all the nations of the world have introduced various steps to reduce spread of the disease by limiting social contact between their citizens and the citizens of other countries, including but not limited to: lockdown of affected neighbourhoods/cities/states, physical distancing, quarantining infected persons and their contacts, wearing of face masks and restricting travel. The stringency of these government enforced movement controls has been assessed by the Oxford COVI9-19 Government Response Tracker [49] which produces a score based on seven response indicators based on the severity of the restrictions introduced by a nation. For example, China and India have a higher score on this index, indicating more restrictive lockdown measures, than the UK and Sweden [49] (Table 3). Interestingly, plotting the government response tracker over time, shows very similar curves for Brazil and the US, indicating a similar level of restrictions brought in by the governments of both nations and over a similar time period (Figure 4). In contrast, New Zealand which has had relatively fewer cases and deaths from the disease, instigated very stringent measures but for a relatively short period of time (Figure 5). In comparison, the restrictions brought in by both China and India have been of both high stringency and for long periods (Figure 5); though with the stringency curve for China occurring much earlier, reflecting the earlier peak of the epidemic in China compared to the rest of the world. Italy was the first European country to record COVID-19 cases and instigated stringent lockdown in the Lombardy region [7,8]. The lockdown curves for Italy, the UK and Sweden shown in Figure 6 coincide with the time of the exponential increase in reported

Table 3. Demographic data of selected countries from each continent, including the number of reported cases of SARS-CoV-2 infection, the test positivity rate, cumulative deaths from COVID-19 and government lockdown stringency, as of 7 September 2020.

Country	Population	Median age	Positive cases*	Test positive rate*	Cumulative deaths	Stringency index#
China	1.4 billion	38.4	90,058	No data	47,30	81.02
India	1.4 billion	28.4	4.20 million	5–10%	71,642	100
US	331 million	38.3	7.52 million	5–10%	188,941	72.69
Brazil	213 million	33.5	4.14 million	No data	126,650	81.02
UK	68 million	40.5	347, 152	0.1–1%	41,551	79.63
Italy	61 million	47.3	277, 634	2–3%	35,541	96.17
Sweden	10 million	41.1	84,985	0.1–1%	5,835	46.30
New Zealand	5 million	38.0	1,425	<0.1%	24	96.30

Key: *Refers to cumulative number of PCR confirmed positive cases, and the proportion of tests carried out that are positive. Whilst there is official data on the number of positive cases from China and Brazil, data on the numbers of tests carried out is not available. # Government response stringency index, lockdown measures scaled from 0 to 100 (100 = strictest). Data source [14,15,54]

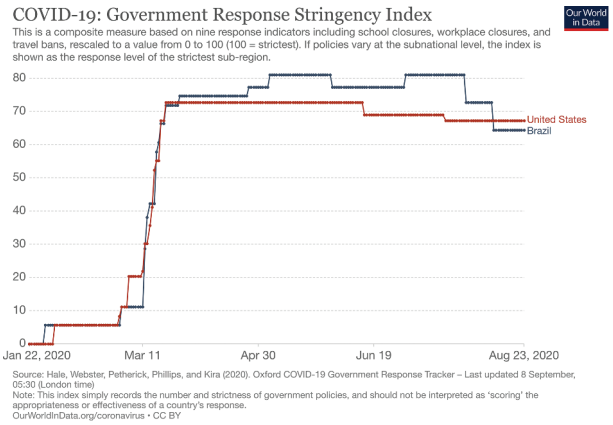

Figure 4. The government stringency indices for the United States of America and Brazil. The Oxford COVID-19 Government Response Tracker [49].

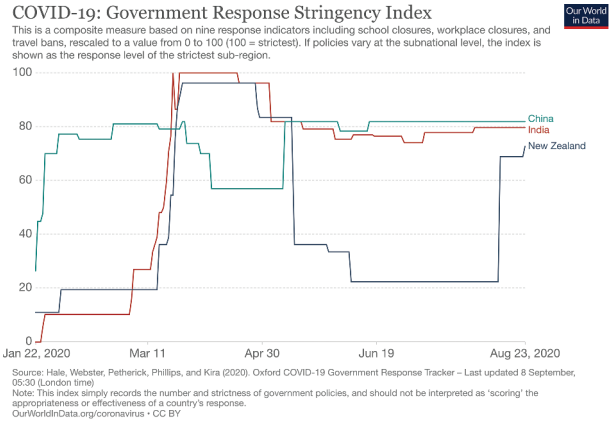

Figure 5. The government stringency indices for China, India and New Zealand. The Oxford COVID-19 Government Response Tracker [49].

infections and reflect the 2–3 week lag period between the height of the Italian epidemic and the first wave of the disease in the UK, Sweden and other European countries [7,8]. Sweden is of particular interest due to its relatively low-level stringency lockdown measures as reflected in a low score on the government response tracker compared to other countries (Figure 6).

The aims of the health authorities in the respective countries are to impose movement control measures

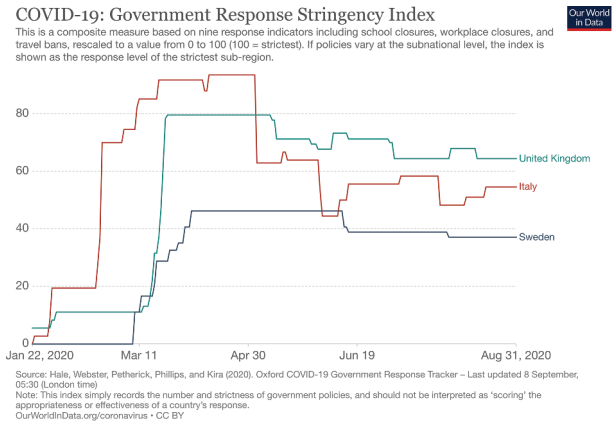

Figure 6. The government stringency indices for the UK, Italy and Sweden. The Oxford COVID-19 Government Response Tracker [49].

until the rate of transmission (R_0) is less than 1. The R_0 of SARS-CoV-2 without implementing any control or in the absence of a vaccine is determined to be in the range 2.2–3.6 [50,51,52]. This means that one infected person has the potential to infect two or more additional persons, i.e., without any control measures there would be an exponential increase in the numbers of cases. Hence, reducing R_0 halts this exponential trajectory; frequently referred to as 'flattening the curve'. Once the 'curve is flattened' most countries start to lift some of the restrictions. If these kinds of controls were not instigated prior to, or during, the exponential phase it is likely that the health services of a country would be unable to cope with the numbers of critically ill patients. Consequently, the most vulnerable of its citizens would likely succumb to the disease because of the limited number of costly mechanical respiratory support systems in any one nation [7,8].

Risk factors associated with SARS-CoV-2 infection and COVID-19

Age is one of the most important risk factors in infection from SARS-CoV-2 and in mortality from COVID-19, with those of the age of 60 years and above having a higher risk of acquiring the disease and with high

mortality rates compared to those below 60 years old [53]. In this respect, in comparing incidences of infection and death from the disease between countries, it is important to take account of differences in the population pyramid between different countries of the world. For example, the median age of the population of the developed nations of the UK and Italy are 40.5 years and 47.3 years, respectively. Whereas for the populations of the developing countries of Brazil and India they are 33.5 years and 28.4 years, respectively (Table 3) Similarly, the proportion of citizens who are of 60 years of age or older (the COVID-19 vulnerable age group) is just over 20% for the UK and 35% for Italy whilst for Brazil and India, it 14% and 10%, respectively [49]. Consequently, when it comes to the risk factor of age most of the developed countries of the world have a greater proportion of their population with potentially higher susceptibility to COVID-19 than developing nations, due to the differing population dynamics [54].

Of those that have died from COVID-19, many had diabetes, cardiovascular diseases, cancer, or were former smokers. However, the cause of death was acute respiratory distress syndrome (ARDS) pneumonia, i.e., they would not have died if they had not acquired SARS-CoV-2 infection [8]. Smoking increases gene expression of ACE2; the receptor for the virus, therefore potentially increasing the likelihood of infection in smokers compared to non-smokers [55]. A weakened immune status and chronic lung disease can also increase the severity of the disease and the mortality rate [56]. Additionally, obesity is thought to increase the severity of lower respiratory tract infection and is associated with an almost three-fold increased incidence of COVID-19, with an odds ratio of 2.91 (95% CI 1.31–6.47) [57]. Conversely, there is evidence to show that Vitamin D protects against respiratory pathogens and decreases the risk of acquiring acute respiratory tract infections. Hence, Vitamin D deficiency may have a role to play in susceptibility to infection [58].

Ethnicity and COVID-19

Studies from the US, UK and Europe have reported increased risk of mortality from COVID-19 in Black, Asian and Minority Ethnic (BAME) groups [59–63]. Pareek et al. [59] emphasize the importance of teasing out the interplay of socioeconomic, behavioural, biological (genomic) and co-morbidity factors responsible for the differences seen between ethnicities in acquiring SARS-co-V2 infection and in outcome to COVID-19. However, there is a need to guard against the assumption that there is a biological or genomic element to play in disparities of health between what are essentially socially devised categories, as eloquently pointed out by Saini [64]. For example, it is well documented that those of African-Caribbean descent living in the UK and US have a higher incidence of hypertension. However, there is no convincing evidence to show that this is due to an underlying difference in genetic susceptibility to developing hypertension, even though the ethnicity of the patient frequently influences how she/he is managed [64]. Consequently, there is no strong evidence that this risk factor (hypertension) for mortality from COVID-19 amongst the African-Caribbean community in the UK and US, has a genetic component to it [64]. More likely, socioeconomic status, deprivation, diet and stress resulting in a greater susceptibility to chronic disorders such as diabetes, obesity and hypertension. In addition, there are a disproportionally higher number of health-care workers from the BAME community working in the UK NHS, than from the Caucasian community, therefore a higher proportion of UK BAME citizen exposed to SARS-coV-2 infected patients [64]. Those members of the community living on low income or income support will also more likely to be living in accommodation that is more densely populated, than those of higher socioeconomic status; hence, increasing the likelihood of viral transmission. All these, essentially environmental or social factors, as opposed to biological variables, may well prove to be the most likely cause of greater susceptibility to COVID-19, though further studies are required to address these issues.

Treatment of COVID 19

Currently, there are no specific antiviral therapies against SARS-CoV-2 [65]. However, under investigation are a range of strategies such as virus-targeted drugs, host-targeted drugs and plasma and antibody therapies [66] (Table 4).

Virus-targeted drugs

Remdesivir

Remdesivir is a nucleoside analogue that has been shown to inhibit RNA-dependent RNA polymerase (RdRP), thus blocking early virus replication [67]. A high affinity between remdesivir and SARS-CoV-2 RNA polymerase was shown by computer modelling [68]. In addition, Gao et al. reported the binding between remdesivir and SARS-CoV-2 RdRP, showing its potential for COVID-19 treatment [67]. Remdesivir has been shown to block the replication of SARS-CoV-2 *in vitro* and in animal models, and that of SARS-CoV and MERS-CoV in animal models [69,70]. About 68% of patients with severe COVID-19 have shown oxygen improvement after being treated with remdesivir [69,71].

Table 4. Candidate drugs for COVID-19 treatment [67–70].

Candidate drugs	Potential mechanism(s) of action
Remdesivir	• Inhibits the synthesis of viral RNA [69] • Inhibits SARS-CoV-2 RNA polymerase [69] • Possesses broad-spectrum activity against coronaviruses [69]
Lopinavir/ritonavir	• Inhibits viral [69] • May cause SARS virus inhibition and ameliorate the adverse effects of infection [70]
Favipiravir + interferon alpha	• Inhibits the synthesis of viral RNA [68] • Induces innate antiviral response [70]
Favipiravir + baloxavir marboxil	• Inhibits the synthesis of viral RNA [70]
Chloroquine or hydroxychloroquine	• Disrupt viral release after entering cell [68] • Disrupts the binding of virus to receptor of cell [70] • Possesses immunomodulatory effect [70] • When compared to chloroquine, hydroxychloroquine has greater stability and is associated with lesser adverse effects [70]
Hydroxychloroquine + azithromycin	• The effect of hydroxychloroquine is listed as above • Azithromycin – potentially having antiviral activity and provide prevention to secondary bacterial infection [70]
Interferon beta-1a	• May oppose interferon beta suppression by SARS-CoV-2 [70]
Interferon alpha	• Inhibits animal and human coronavirus replication [67]
Tocilizumab	• Inhibits interleukin-6 signalling, which may counteract cytokine release syndrome in critical COVID-19 [69]
p21-activated protein kinases 1 (PAK1) inhibitors	• May inhibit viral entry into cell since coronaviruses exploit micropinocytosis for cell entry, in which this process is PAK1-dependent [69]

Lopinavir and Ritonavir combination

Lopinavir–Ritonavir is a drug approved for HIV-1 treatment. Lopinavir works as a protease inhibitor, blocking the maturation of virus particles, thus inhibiting late-stage HIV-1 replication [69,71]. Ritonavir inhibits CYP3A enzymes, lowering the breakdown rate of lopinavir in the liver, thus enhancing lopinavir activity [71]. Lopinavir has shown activity against MERS-CoV in both *in vivo* and *in vitro* studies. Case reports suggested that virologic clearance and survival were achieved when lopinavir–ritonavir is combined with interferon-α and ribavirin [71].

Favipiravir

Favipiravir is an RdRP inhibitor approved in Japan to treat influenza, and is the first approved anti-COVID-19 drug in China [66,69] Favipiravir is a guanine analogue that causes interference to viral replication by incorporating into viral RNA [65]. Favipiravir-treated patients showed better improvement rate in chest imaging and quicker viral clearance compared to lopinavir/ritonavir-treated patients in clinical trials conducted in China [72]. Nevertheless, potential drug–drug interaction should be considered as favipiravir is metabolized in the liver to form an inactive oxidative metabolite which is excreted by the kidney [71].

Host-targeted drugs

Chloroquine or hydroxychloroquine

Chloroquine and hydroxychloroquine are drugs used to treat malaria and as an anti-inflammatory agent for treating autoimmune diseases [71] Chloroquine suppresses the virus replication by increasing the endosomal pH [69,71]. Immunomodulatory effects via inhibition of cytokine production and suppression of lysosomal activity and autophagy in host cells have been reported [71]. Strong antiviral effect against SARS-CoV-2 has been shown in *in vitro* studies [73]. Hydroxychloroquine, a chloroquine analogue, possesses greater stability and anti-SARS-CoV-2 activity. Accelerated recovery and virus clearance were noted in hydroxychloroquine and azithromycin-treated COVID-19 patients [74]. However, severely ill COVID-19 patients treated with the said combinations showed disappointing results [75], suggesting the need for larger and controlled clinical studies. Since zinc has been demonstrated to block RdRP and chloroquine/hydroxychloroquine are zinc ionophores, supplementation of zinc may be essential to examine the effect of chloroquine/hydroxychloroquine on SARS-CoV-2 [76,77].

Plasma and antibody therapies

Plasmapheresis is used to modulate the immune response and eliminate cytokines through extracorporeal blood filtration [68]. Compared to vaccination, plasma therapy allows direct antibody administration into circulation instead of depending on the induction of immunity [78,79]. Convalescent sera have previously been shown to decrease the viral burden in MERS and SARS patients [80]. Clinical improvement and decrease in viral load were also shown by convalescent plasma-treated COVID-19 patients [80]. Alternatively, treatment could be done by administering purified monoclonal antibodies (mAbs) with neutralizing capacity [81]. In addition, due to the ability to control composition and dosing, mAbs therapy possesses improved efficacy compared to convalescent plasma treatment and can prevent the ADE from poorly neutralizing or non-neutralizing antibodies present in plasma [82]. The robustness of mAb treatment over convalescent plasma treatment was highlighted by studies conducted recently with Ebola patients [83,84]. Besides, the treatment using mAb against respiratory syncytial virus (RSV), rabies virus, and influenza virus has been demonstrated to be effective and safe [85–87].

The neutralizing antibodies (NAbs) against coronaviruses mainly target the S protein, which is a

homotrimeric glycoprotein. Early attempts on acquiring NAbs focused on the reassessment of SARS-CoV specific mAbs extracted from SARS-CoV outbreak that could have the potential to cross-neutralize the virus [71,88]. Nevertheless, the ability to neutralize SARS-CoV-2 virus or to bind to SARS-CoV-2 S protein was not shown by the majority of the SARS-CoV NAbs [71,88–90]. Recently, attention has focused on obtaining new SARS-CoV-2 NAbs from patients recovered from COVID-19 [91–96]. Multiple NAbs yielded from the receptor-binding domain (RBD) of S protein fragments are able to neutralize SARS-CoV-2 by targeting various RBD epitopes [91–96].

Moreover, with technology advancement, recombinant fully human antibodies can be utilized instead of convalescent plasma [97]. The idea of humanizing the mouse immune system genetically has rendered a source of naturally chosen, fully human antibodies [98]. Presently, despite being restricted to antibodies against infectious agents, independent human antibody source can be achieved by sorting individual B cells from previously infected human patients and cloning the antibody genes of these B cells [97]. With respect to COVID-19, the prospective aim of this approach is to produce a diverse and huge antibody collection to permit the selection of pairs of individual antibodies with great potency that could bind to the critical RBD of S protein, thereby providing suitable partners for the therapeutic antibody cocktail that possess the ability to reduce the probability of virus escape mutants [99].

Vaccine development

Currently, the spike glycoprotein is a main target for SARS-CoV-2 vaccine development [69,100]. Ideal future SARS-CoV-2 vaccines should produce a long-lived antibody-mediated immunity with protective neutralizing antibody titre that does not result in antibody-dependent enhancement (ADE) on re-infection [100]. In addition, an optimal SARS-CoV-2 vaccine should avoid inducing an unwanted T^H2 cell response and the generation of IL10 and IL14 cytokines [100]. Table 5 details some of the main vaccines to SARS-Co-V-2 undergoing clinical evaluation [101].

Four vaccines that are currently, in or shortly to enter phase 3 clinical trials are mRNA-1273 SARS-CoV-2 vaccine, COVID-19 RNA Vaccine (BNT162b1), the Russian vaccine (Gam-COVID-Vac) and ChAdOx1 nCoV-19 vaccine (AZD1222) (Table 4).

The mRNA-1273 SARS-CoV-2 vaccine (developed by the American biotechnology company, Moderna) is known as a nucleoside-modified messenger RNA (mRNA)-based vaccine that is encapsulated in lipid nanoparticle. It encodes a perfusion stabilized S glycoprotein of SARS-CoV-2, which mediates membrane fusion for viral entry. Phase 1 clinical trials were conducted in humans as an assessment of mRNA-

Table 5. Candidate vaccines for COVID-19 under clinical evaluation [100].

Name of Vaccine	Developer	Type of candidate vaccine	Immunogen	Country
mRNA-1273	Moderna/NIAID	Lipid nanoparticle-encapsulated mRNA	S protein	USA
BNT162-01	BioNTehc/Fosun Pharma/Pfizer	3 LNP-mRNAs	Receptor-binding domain antigen/S protein	Germany
ChAdOx1 nCoV-19	University of Oxford/AstraZeneca	ChAdOx1-S	S protein	UK
Ad5-nCoV	CanSino Biological Inc./Beijing Institute of Biotechnology	Adenovirus Type 5 Vector	S protein	China
Gam-COVID-Vac/Gam-COVID-Vac Lyo	Gamaleya Research Institute	Adenovirus-based	S protein	Russia
Inactivated SARS-CoV-2 vaccine -	Sinovac	Inactivated + alum	Whole virus	China
	Wuhan Institute of Biological Products/Sinopharm	Inactivated	Whole virus	China
Inactivated SARS-CoV-2 vaccine	Beijing Institute of Biological Products/Sinopharm	Inactivated	Whole virus	China
Inactivated SARS-CoV-2 Vaccine	Institute of Medical Biology, Chinese Academy of Medical Sciences	Inactivated	Whole virus	China
INO-4800	Inovio Pharmaceuticals	DNA plasmid vaccine with electroporation	S protein	USA
GX-19	Genexine Consortium	DNA Vaccine (GX-19)	S protein	Korea
SARS-CoV-2 rS	Novavax	Full length recombinant SARS CoV-2 glycoprotein nanoparticle vaccine adjuvant with Matrix M	S protein	Australia
SCB-2019	Clover Biopharmaceuticals Inc./GSK/Dynavax	Native like trimeric subunit spike protein vaccine	S protein	Australia
Recombinant new coronavirus vaccine (CHO cell)	Anhui Zhifei Longcom Biopharmaceutical	Adjuvant recombinant protein	Receptor-binding domain (RBD) of S protein	China

1273's safety, immunogenicity and reactogenicity. In 3 different dose concentrations (25 μg, 100 μg and 250 μg) of the first vaccine, the antibody responses increased with higher dose after vaccination. After the second vaccination, the responses of serum neutralizing activity were similar to that of convalescent serum specimens, serving as a control. For the first vaccination, over 50% of the participants experienced solicited adverse events including fatigue, headache, chills, pain at the injection site and myalgia. After the second vaccination, it was reported that systemic adverse events were more prevalent, especially with the highest dose. At least one severe adverse event was found in three participants with the highest dose (250 μg) [102]. The phase 2 trial of mRNA-1273 focused on two doses (50 μg and 100 μg) and was accessed in 600 healthy adults (age of 18 or above). While for phase 3 trial, the mRNA-1273's safety, immunogenicity, and efficacy at a dose of 100 μg compared to the placebo is being evaluated in about 30 000 participants (age of 18 or above) for up to 2 years [103].

Germany's BioNTech and United States's Pfizer co-developed BNT162b1, is an RNA vaccine that is incorporated with nucleoside modified RNA (modRNA). The RBD of the S protein of SARS-CoV-2, which is targeted by virus-neutralizing antibodies, is being encoded by BNT162b1 [104]. The RBD antigen expressed by BNT162b1 has an increased immunogenicity due to the addition of a T4 fibritin-derived 'foldon' trimerization domain. BNT162b1 is formulated in lipid nanoparticles (LNPs) to increase the delivery efficiency into cells after injection through the intramuscular route [105]. For the phase 1/2 trials of BNT162b1, the safety and immunogenicity of BNT162b (doses of 10 μg and 30 μg) was assessed in individuals between 18 and 55 years old. The systemic events and local reactions were dependent on the dose, and their severity ranged from mild to moderate. The SARS-CoV-2 neutralizing titres and the concentration of RBD-binding IgG were raised corresponding to the level of dose and after a second dose. The geometric mean concentration of RBD-binding IgG was found to be 1.8 to 2.8 times greater compared to that seen in the sera of a group of patients convalescing from COVID-19 [106]. The phase 2/3 trials involve the study of the vaccine's efficacy in participants between 18 and 85 years old [107].

The Gamaleya Research Institute (Moscow, Russia) developed Gam-COVID-Vac is an adeno-based (rAd26-S+ rAd5-S) vaccine employing a non-replicating viral vector. The vaccine delivers the gene for the SARS-CoV -2 S protein through the adenovirus vector to initiate an immune response. There are two forms of Gam-COVID-Vac; frozen [Gam-COVID-Vac] and lyophilized [Gam-COVID-Vac-Lyo]. In two-phase clinical trials of Gam-COVID-Vac, the vaccines were administered intramuscularly on 76 volunteers, in which the volunteers were separated into two batches with each batch consisting of 38 individuals. In phase 1, 18 individuals had received the vaccine with each 9 of them receiving rAd26-S and rAd5-S, respectively. In phase 2, both rAd26-S and rAd5-S vaccines were applied to a group of 20 volunteers. Both forms of the vaccine were reported to be well tolerated and safe. The most frequent occurring adverse event was the pain at the site of injection, followed by hyperthermia, headache, asthenia, and pain of joint and muscle. Nevertheless, the majority of the adverse events were not severe. Antibodies against SARS-CoV-2 glycoprotein were generated by all the participants. The heterologous rAd26-S and rAd5-S vaccines managed to induce robust cellular and humoral immune responses in participants [108]. The phase 3 trials will investigate safety, immunogenicity and efficacy of Gam-COVID-Vac against SARS-CoV-2-induced infection in adults, involving 40,000 individuals (age above 18). They will be separated randomly into two groups with 10,000 individuals receiving placebo and 30,000 individuals administered with Gam-COVID-Vac combined vector vaccine [109].

The University of Oxford, UK developed ChAdOx1 nCoV-19 (AZD1222) vaccine comprises the replication-deficient simian adenovirus vector ChAdOx1, consisting of SARS-CoV-2 S protein in full length, with a tissue plasminogen activator leader sequence. A coding sequence for the codon-optimized S protein were expressed by ChAdOx1 nCoV-19. It was reported that a single vaccination with ChAdOx1 nCoV-19 has led to an induction of cellular and humoral immune responses in rhesus macaques. It was shown to protect them from lower respiratory tract infection after they were challenged with a high dose of SARS-CoV-2 [110]. The phase 1 and 2 trials of this vaccine are a single-blind and randomized controlled trial conducted on healthy adults in the UK and was compared with a control vaccine, the licenced meningococcal group A, C, W-135, and Y conjugate vaccine (MenACWY; Nimenrix, Pfizer, UK). In the phase 1/2 trials, there were a total of 1077 participants, with 543 individuals receiving the ChAdOx1 nCoV-19 vaccine, and 534 individuals receiving the MenACWY control vaccine. It was found that both systemic and local reactions were more frequent in the ChAdOx1 nCoV-19 group. The peak of the responses of spike-specific T-cells was found on the 14^{th} day in the ChAdOx1 nCoV-19 group, and responses of anti-spike Ig G increased by 28^{th} day, and were boosted after a second dose. Moreover, when measured in a microneutralisation assay (MNA_{80}) and in 50% plaque reduction neutralization assay ($PRNT_{50}$) after a single dose, 91% (32 of 35 participants) and 100% of the participants were found to have neutralizing antibody responses against SARS-CoV-2, respectively. In addition, all the

participants were found to possess neutralizing activity after a booster dose. A strong correlation was observed between the neutralizing antibody responses and antibody levels. ChAdOx1 nCoV-19 is reported to be safe, and antibody responses were increased by homologous boosting [111]. Large assessment of this vaccine was encouraged due to these favouring results and the initiation of both cellular and humoral immune responses. For the phase 2 trial of ChAdOx1 nCoV-19, the efficacy against COVID-19 was accessed in adults (age of 18 or above), while its safety was accessed in both children and adults [112]. For the phase 3 trial, the efficacy, safety and immunogenicity of ChAdOx1 nCoV-19 are being tested on 30,000 participants, in which the participants are randomly separated in a 2:1 ratio, receiving IM doses of AZD1222 or saline placebo (control group) [113].

Prevalence, immunity, the SARS-CoV-2 G614 strain and implications for movement control and vaccine development

Understanding the dynamics and extent of immunity to SARS-CoV-2 in the community is of fundamental importance. A thorough knowledge of the prevalence of infection and an understanding of the nature and the extent of innate immunity within the population will ultimately inform policymakers on the need or not for further movement control and lockdowns. Furthermore, knowledge of the antigenic specificity eliciting an effective neutralizing immune response and the longevity of this response has important implications for vaccine design.

In the UK, the REal-time Assessment of Community Transmission (REACT) study recently reported on a national prevalence survey of SARS-CoV-2 virus swab-positivity (PCR based) in the English community [114]. In this large, nationally representative survey of SARS-CoV-2 infection, prevalence of infection was approximately 1 in 1000 and decreasing at the end of the lockdown period in May 2020. The results confirmed the efficacy of enforced measures to contain the spread of SARS-CoV-2, with an estimate of R below 0.6 by the end of the lockdown. There were regional differences, with the highest prevalence in London, a focus of transmission early in the UK epidemic. As with New York and other global cities, this may be because of its role as a major transport, business and tourism hub [115].

Whilst the UK REACT survey looked at the prevalence of the SARS-CoV-2 virus infection within the community, a recent large (61,000 participants) nationwide population study based in Spain, one of the European countries most affected by COVID-19, showed approximately only 5% seroprevalence for the Spanish population with respect to IgG and IgM antibodies to SARS-CoV-2. Based on these results, from a country hit hard by the COVID-19 pandemic, seroprevalence remained low and would be insufficient to provide herd immunity, without an excessive number of deaths in the most vulnerable. Consequently, the authors concluded that physical distancing and identification and isolation of new cases were essential to control the epidemic [116].

Other workers have investigated the dynamics of the immune response in SARS-CoV-2-infected individuals. Seow et al. [117] conducted a longitudinal evaluation of antibody response in individuals up to 94-days post-infection, using sequential serum samples to measure titres and neutralizing antibody response in individuals with differing levels of disease and differing viral loads. The magnitude of the neutralizing response was dependent on the severity of the disease, with declining neutralizing antibody titres observed during the follow up period. Interestingly, the IgM and IgA-specific responses to the viral proteins (spike, the receptor-binding domain and nucleoproteins) rapidly declined after twenty to 30 days, compared to the longer lasting IgG response: an important consideration for testing strategies and for seroprevalence studies [117]. For individuals with low infection rates, the neutralizing antibody titres were found to be at or below the level of detection after only 50 days. This obviously has implications for vaccine development if the challenge results in a relatively transient response. Antibody responses to other human coronaviruses have been found to be similarly transient, in some cases as little as 12 weeks. However, antibodies to SARS-CoV and MERS have been detected up to 12–34 months after infection [118,119].

Based on what is known from other acute viral epidemics such as SARS, a likely scenario is that individuals exposed to the SARS-CoV-2 virus will produce specific CD4+ and CD8 + T-lymphocytes and neutralizing specific antibodies which help to clear the acute infection. In addition, some of the B and T Cells are likely to be retained long term as immunological memory cells to effectively provide for protective immunity against SARS-CoV-2 [120]. Grifoni et al. [120] used peptide megapools comprising the 25 SARS-CoV-2 viral epitopes to determine the predominant targets of SARS-CoV-2 specific CD4 and CD8 cells by testing the blood from a cohort of individuals convalescing from COVID-19, in addition to an unexposed cohort (samples collected 2015–2018). Earlier studies on other coronaviruses, such as SARS-CoV-1 and the MERS virus, found that the viral spike protein (S) accounted for approximately two-thirds of CD4 T cell reactivity, with N and M proteins only accounting for limited activity or none in one study [121]. In contrast, Grifoni and colleagues [120] found the pattern quite different for SARS-CoV-2, with S, M and N proteins all co-dominant and each recognized by all the COVID-19 cases in the cohort. Significant CD4 T cell

responses were also seen to be directed against other SARS-CoV-2 proteins, i.e., nsp3, ORF3s, ORF7a, nsp12 and ORF8. The results suggest that whilst a COVID-19 vaccine consisting of only SARS-CoV-2 spike would be capable of producing a specific CD4 T cell response, inclusion of other structural antigens to include M and N viral proteins may better reflect the CD4 T cell response observed in COVID-19 disease. With respect to SARS-CoV-2 specific CD8 T cells, importantly it was found that response to the spike (S) protein was not the dominant response, with the virus generating similar reactivity to nsp6, ORF3a and N. The results indicating that vaccines produced to elicit only a CD8 response to just spike (S), will have a narrow range of reactivity. Consequently, an optimal vaccine might benefit from additional epitopes, namely those on M, nsp6, ORF3a and N. With respect to the concerns of a vaccine generating a T_H2 response [82], i.e., the 'cytokine storm', the Grifoni et al. [120] study recorded little or no T_H2 cytokines in the convalescing patient samples. Lastly, as a key to understanding whether cross-reactivity immunity exists between different coronaviruses, the study used the same antigens and series of experiments to look for CD4 and CD8 T cell cross-reactivity in the samples collected from the unexposed cohort of individuals collected prior to the emergence of COVID-19 (samples from 2015 to 2018). Importantly, CD4 T cell responses were seen in 40–60% of unexposed individuals reflecting some degree of pre-existing immunity to SARS-CoV -2, though whether this immunity is sufficient in influencing the clinical outcome is as yet unknown. However, in this respect, Kissler et al. [122] have modelled that any amount of cross-protective coronavirus immunity in the population could have a substantial impact on the course of the COVID-19 pandemic [122].

An important consideration in vaccine development for SARS-CoV-2 is the extent to which the main strain of the virus, as detected in Wuhan in January 2020, persists and the extent to which mutated versions of the virus become the predominant strain. If there is a gradual accumulation of mutations resulting in a new strain of the virus with antibody resistance, there will be a need to develop new vaccines every few years, as is seen with the influenza virus. In order to address this issue Korber et al. [123] have developed a bioinformatic system for tracking changes in the SARS-CoV-2 spike sequence. Phylogenetic analysis of the global sampling of SARS-CoV-2 is performed by the Global Initiative for Sharing All Influenza Data (GISAID) database (https://www.gisaid.org/ [124]. Korber et al.'s [123] analysis pipeline tracks SARS-CoV -2 mutations based on the regular updates in the GISAID database, which are linked to the location and date of sampling. This has subsequently allowed for regional tracking of SARS-CoV-2 mutations over time. As the overall mutational rate for the virus is very low, the authors set a low 0.3% threshold for Spike mutations to be considered of interest, that is the reported sequences need to be different by 0.3% or greater, than the original Wuhan reference sequence. In this respect, even single amino acid changes are worth monitoring, as point mutations have been shown to confer resistance to neutralizing antibodies in MERS-CoV [125] and SARS-CoV-1 [126]. Korber et al. [123] monitored the frequency of such mutations in SARS-CoV-2 over time in different geographic regions of the World. The first significant variant to stand out using this type of analysis is D614G, which is now the predominant strain of SARS-CoV-2 globally. In the D614G variant, an amino acid change in Spike is caused by an A to G nucleotide mutation at position 23,403 in the Wuhan reference strain. This is frequently accompanied by a C to T mutation in the 5′ UTR (position 241 in the Wuhan sequence), a silent C to T mutation (position 3,037) and a C to T mutation at position 14,408 resulting in an amino acid change in RNA-dependent RNA polymerase (RdRp P323L). The results of these mutations appear to make G614 more infective than the original D614 strain, in addition to producing a higher viral load [123]. The SARS-CoV-2 strain containing these four mutations is now the main haplotype globally. Before March 2020 it was only found in 10% of sequences worldwide, during March 67% of sequences, and by May 2020 it represented 78% of 12,194 global sequences. The transition from D614, the Wuhan reference strain, to G614 being the main strain of the virus occurred at different times throughout the world, starting first with Europe, then North America, Oceania, followed by Asia [123]. As the appearance of the G614 strain occurred during periods of lockdown in many countries, it is presumed that selective pressure allowed G614 to become the predominant strain at a time when infection with the D614 strain would have been inhibited. Whilst the G614 is more infective than D614, and will result in a higher viral load, evidence so far shows that it does not result in greater disease severity, in that it has shown not to be associated with hospitalization status [123].

Other mutations in SARS-CoV-2 may well impact on the clinical relevance of infection, such as deletions occurring in the open reading frame (ORF) 8, and in particular, a 382 nucleotide deletion (Δ382) which truncates open reading frame (ORF) 7b and removes the ORF8 transcription-regulatory sequence, eliminating ORF8 transcription [127]. A recent study suggests that one of the biological functions of ORF8 protein in SARS-CoV-2 is to mediate immune evasion by down-regulating MHC-1 [128]. Limited evidence to date suggests that the deletion does not affect the infective capabilities of the virus, or prevent the disease, but is associated with a less severe clinical outcome. Patients infected with the Δ382 variant had less severe infections in terms of hypoxia requiring supplemental oxygen, had a more effective immune response and had

lower concentrations of pro-inflammatory cytokines and growth factors associated with severe COVID-19 [127]. The Δ382 variant emerged in Wuhan early in the epidemic and was exported by travellers to both Singapore and Taiwan, arising as a co-infection with the wild-type virus but becoming the dominant strain in the second week of illness [127]. Interestingly, genomic data shows that the Δ382 variant is not related to the G614 clade [123] but to the original D614 Wuhan strain [129]. Additional deletions in the SARS-CoV-2 ORF8 have been reported in cases of COVID-19 from Bangladesh (345 nucleotides), Australia (138 nucleotides) and Spain (62 nucleotides), but with no accompanying clinical data [130,131].

Summary

The series of events involved in the spread of the SARS-CoV-2 virus, its molecular structure, the pathophysiology of COVID-19 and some details of therapeutic interventions and SARS-CoV-2 vaccines in clinical trials have been reviewed in addition to some of the latest epidemiological surveys on SARS-CoV-2 prevalence and seroprevalence in the community. Knowledge from surveys such as these along with a thorough understanding of the dynamics of the immunological response to the virus will be key to controlling the pandemic and its effects. The recent UK REACT study [114] shows the efficacy of enforced lockdown measure in reducing the (R_0), though such efforts of containment may not be as effective with more infective strains of SARS-CoV-2 such as the G614 clade [123]. Conversely, whilst selective pressure favours more infective strains of the virus, other mutations, such as the Δ382 variant could result in a less virulent virus [127], reducing the clinical relevance of infection, and therefore, in turn, the need for stringent movement control, particularly once vaccines become available. The Spanish population-based study emphasises the low level of seroprevalence in the Spanish population with respect to IgG and IgM antibodies to the virus [116]. However, whether this is still the case following the subsequent waves of the pandemic occurring in Europe and other continents remains to be seen. Questions also remain regarding the longevity of the immune response to the virus, as seen with the King's College London study, which showed the neutralising antibody response to be relatively transient [117]. The front runners in the race to develop an effective vaccine and currently in or progressing to phase 3 clinical trials have been reviewed, all of which focus on the SARS-Co -V-2 Spike protein [102,106,108,111] Whether more effective vaccines could be manufactured that produce a CD4 and CD8 response to a wider range of SARS-Co -V-2 viral proteins, as inferred by the work of Griffoni et al. [120], remains to be seen. In addition, the manufacture of potent genetically engineered neutralising antibodies may lead to the adoption of more effective immunisation strategies [96–98]. Lastly, population-based studies that determine the level of innate immunity to SARS-CoV-2 existing in the community, from prior exposure to the virus or indeed to other coronaviruses [120,122] will have important implications for the stringencies of government-imposed movement control and upon the strategic delivery of vaccination programmes.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

A Rhodes http://orcid.org/0000-0002-1187-0939

References

[1] Guo Y-R, Cao Q-D, Hong Z-S, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak – an update on the status. Mil Med Res. 2020;7:11.
[2] Zhou P, Yang X-L, Wang X-G, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579:270–273.
[3] Shah UM, Safri SNA, Thevadas R, et al. COVID-19 outbreak in Malaysia: actions taken be the Malaysian government. Int J Infect Dis. 2020;97. DOI:10.1016/j.ijid.2020.05.093.
[4] Zhu N, Zhang D, Wang W-L, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382:727–733.
[5] Kraemer MUG, Yang C-H, Gutierrez B, et al. The effect of human mobility and control measures on the COVID-19 epidemic in China. Science. 2020;368:493–497.
[6] Sun J, He W-T, Wang L, et al. COVID-19: epidemiology, evolution and cross-disciplinary perspectives. Trends Mol Med. 2020;26:483–495.
[7] Saglietto A, D'Ascenzo F, Zoccai GB, et al. COVID-19 in Europe: the Italian lesson. Lancet. 2020;395:1110–1111.
[8] Remuzzi A, Remuzzi G. Covid-19 and Italy: what next. Lancet. 2020;395:1225–1228.
[9] Lillie PJ, Samson LA, Li A, et al. Novel coronavirus disease (Covid-19): the first two patients in the UK with person to person transmission. J Infect. 2020;80:600–601.
[10] Jarvis CI, Van Zandvoort K, Gmma A, et al. Quantifying the impact of physical distance measures on the transmission of COVID-19 in the UK. BMC Med. 2020;18:124.
[11] Mahse E. Covid-19: UK could delay non-urgent care and call doctors back from leave and retirement. BMJ. 2020;368:m854.
[12] Moghadas S, Shoukat A, Fitzpatrick MC, et al. Projecting hospital utilization during the COVID-19 outbreaks in the United States. PNAS. 2020;117:9122–9126. www.pnas.org/cgi/doi/10.1073/pnas.2004064117
[13] Burke RM, Midgely CM, Dratch A, et al. Active monitoring of persons exposed to patients with confirmed COVID-19 – United States. MMWR Morb Mortal Wkly Rep. 2020;69:245–246.
[14] European Centre for Disease Prevention and Control. COVID-19 situation update for the EU/EEA and the UK, as of 7th September 2020; [cited 2020 Aug 9].

Available from: https://www.ecdc.europa.eu/en/cases-2019-ncov-eueea.
[15] Richie H, Oritiz-Ospina B. Our world in data 2020, Oxford University; [cited 2020 Sept 7]. Available from: https://ourworldindata.org/coronavirus..
[16] Wang C, Liu Z, Chen Z, et al. The establishment of reference sequence for SARS-CoV-2 and variation analysis. J Med Virol. 2020;92:667–674.
[17] Jin Y, Yang H, Ji W, et al. Virology, epidemiology, pathogenesis, and control of COVID-19. Viruses. 2020;12:372.
[18] Shereen MA, Khan S, Kazmi A, et al. Covid-19 infection: origin, transmission, and characteristics of human coronaviruses. J Adv Res. 2020;24:91.
[19] SIB Swiss Institute of Bioinformatics. Structural diagram of SARS-CoV and MERS. Viral zone; 2020 [cited 2020 Aug 15]. Available from: https://www.sib.swiss/.
[20] Tai W, He L, Zhang X, et al. Characterization of the receptor-binding domain (RBD) of 2019 novel coronavirus: implication for development of RBD protein as a viral attachment inhibitor and vaccine. Cell Mol Immunol. 2020;17:613–620.
[21] Wan Y, Shang J, Graham R, et al. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. J Virol. 2020;94:e00127–20.
[22] Cascella M, Rajnik M, Cuomo A, et al. Features, evaluation and treatment coronavirus (COVID-19). In: StatPearls [Internet] eds. Treasure Island (FL): StatPearls Publishing, 2020. PMID: 32150360.
[23] Tok TT, Tatar G. Structures and functions of coronavirus proteins: molecular modeling of viral nucleoprotein. Int J Virol Infect Dis. 2017;2:001–007.
[24] Sharma R, Agarwal M, Gupta M, et al. Coronavirus disease 2019 (COVID-19). In: Saxena S, editor. Medical virology: from pathogenesis to disease control. Springer: Singapore. 2020. 55–70. DOI:10.1007/978-981-15-4814-7_6
[25] Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. Methods Mol Biol. 2015;1282:1–23.
[26] Aiping W, Peng Y, Baoying H, et al. Genome composition and divergence of the novel coronavirus (Covid-19). Cell Host Microbe. 2020;27:325–328.
[27] Yan-Hua L, Gao H, Xiao Y et al. Bioinformatic analysis on potential anti viral targets against a spike protein of MERS. 2018 9th International Conference on Information Technology in Medicine and Education (ITME); 2018; Hangzhou. p. 67–71.
[28] Masters PS, Kuo L, Ye R, et al. Genetic and molecular biological analysis of protein-protein interactions in coronavirus assembly. Adv Exp Med Biol. 2006;581:163.
[29] Wang M, Ludwig K, Böttcher C. The role of stearate attachment to the hemaglutinin-esterase-fusion glycoprotein HEF of influenza C virus. Cell Microbiol. 2016;18:692–704.
[30] De Groot RJ. Structure, function and evolution of the hemaglutinin-esterase proteins of corona and toroviruses. Glycoconj J. 2006;23:59–72.
[31] Lauer SA, Grantz KH, Bi Q, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. Ann Intern Med. 2020;172:577–582.
[32] Butler MJ, Barrientos RM. The impact of nutrition on COVID-19 susceptibility and long-term consequences. Brain Behav Immun. 2020;87:53–54.
[33] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497–506.
[34] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054–1062.
[35] Spagnolo P, Balestro E, Aliberti S, et al. Pulmonary fibrosis secondary to COVID-19: a call to arms? Lancet Respir Med. 2020;8:750–752.
[36] George PM, Wells AU, Jenkins RG. Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy. Lancet Respir Med. 2020;8:807–815.
[37] Heneka MT, Golenbock D, Latz E, et al. Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. Alzheimer's Res Ther. 2020;12. DOI:10.1186/s13195-020-00640-3.
[38] Helms J, Kremer S, Merdji H, et al. Neurologic features in severe SARS-CoV-2 infection. N Engl J Med. 2020;382:2268–2270.
[39] Bindoli S, Felicetti M, Sfriso P, et al. The amount of cytokine-release defines different shades of Sars-Cov2 infection. Exp Biol Med. 2020;245:970–976.
[40] Garcia-Borrega J, Goedel P, Ruger MA, et al. In the eye of the storm: immune- mediated toxicities associated with CAR-T cell therapy. Hemisphere. 2019;3:e191.
[41] Li X, Geng M, Peng Y, et al. Molecular immune pathogenesis and diagnosis of COVID-19. J Pharm Anal. 2020;10:102–108.
[42] Reghunathan R, Jayapal M, Hsu LY, et al. Expression profile of immune response genes in patients with severe acute respiratory syndrome. BMC Immunol. 2005;6:2.
[43] Zhang Y, Li J, Zhan Y, et al. Analysis of serum cytokines in patients with severe acute respiratory syndrome. Infect Immun. 2004;72:4410–4415.
[44] Nicholls J, Dong XP, Jiang G, et al. SARS: clinical virology and pathogenesis. Respirology. 2003;8:S6–8.
[45] Mock JR, Tune MK, Dial CF, et al. Effects of IFN-c on immune cell kinetics during the resolution of acute lung injury. Physiol Rep. 2020;8:e14368.
[46] Aggarwal NR, King LS, D'Alessio F. Diverse macrophage populations mediate acute lung inflammation and resolution. Am J Physiol Lung Cell Mol Physiol. 2014;306:L709–25.
[47] Bos LD, Schouten LR, van Vught LA, et al. Identification and validation of distinct biological phenotypes in patients with acute respiratory distress syndrome by cluster analysis. Thorax. 2017;72:876–883.
[48] Loke YK, Heneghan C. Why no one can ever recover from COVID-19 in England – a statistical anomaly. July 16th 2020. The centre for evidence-based medicine. University of Oxford; [cited 2020 Aug 9]. Available from: https://www.cebm.net/covid-19/.
[49] Hale T, Webster S, Petherick A et al. Oxford COVID-19 Government Response Tracker. Blavatnik School of Government, Oxford University; [cited 2020 Aug 9]. Available from: https://www.bsg.ox.ac.uk/research/research-projects/coronavirus-government-response-tracker.
[50] Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Eng J Med. 2020;382:1199–1207. .
[51] Liu Y, Bayle AA, Wilder-Smith A, et al. The reproductive number of COVID-19 is higher compared to SARS coronavirus. J Travel Med. 2020;27:taaa021. .

[52] Linka K, Peirlinck M, Kuhl E. The reproduction number of COVID-19 and its correlation with public health interventions. medRxiv. 2020. DOI:10.1101/2020.05.01.20088047
[53] Mahase E. Covid-19: death rate is 0.66% and increases with age, study estimates. BMJ. 2020b;369:m1327.
[54] Population Pyramids of the World 1950–2100. [accessed 2020 Sep 15]. Available from: https://www.populationpyramid.net/singapore/2020/
[55] Cai G. Bulk and single-cell transcriptomics identify tobacco-use disparity in lung gene expression of ACE2, the receptor of 2019-nCov. Preprints. 2020;2020020051. DOI:10.20944/preprints202002.0051.v2
[56] Zhang J, Wang X, Jia X, et al. Risk factors for disease severity, unimprovement, and mortality in COVID-19 patients in Wuhan, China. Clin Microbiol Infect. 2020;26:767–772.
[57] Gao F, Zheng KI, Wang X-B, et al. Obesity is a risk factor for greater COVID-19 severity. Diabetes Care. 2020;43:e72–e74.
[58] Martineau AR, Jolliffe DA, Hooper RL, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. BMJ. 2017;356:i6583.
[59] Pareek M, Bangash MN, Pareek N, et al. Ethnicity and COVID-19: an urgent public health research priority. Lancet. 2020;395:1421–1422.
[60] Aldridge RW, Lewer D, Katikireddi SV, et al. Black, Asian and minority ethnic groups in England are at increased risk of death from COVID-19: indirect standardization of NHS mortality data. Wellcome Open Res. 2020;5:88.
[61] Patel P, Hiam L, Sowemimo A, et al. Ethnicity and covid-19. Public health England's review of disparities in covid-19 is a serious missed opportunity. BMJ. 2020;369:m2282.
[62] Khunti K, Singh AK, Pareek M, et al. Is ethnicity linked to incidence or outcomes of covid-19? BMJ. 2020;369:m1548.
[63] Kirby T. Evidence mounts on the disproportionate effect of COVID-19 on ethnic minorities. Lancet Respir Med. 2020;8:547–548.
[64] Saini A. Stereotype threat. Lancet. 2020;395:164–165.
[65] Khuroo MS, Khuroo M, Khuroo MS, et al. COVID-19 vaccines: a race against time in the middle of death and devastation. J Clin Exp Hepatol. 2020. DOI:10.1016/j.jceh.2020.06.003
[66] Guo G, Ye L, Pan K, et al. New insights of emerging SARS-CoV-2: epidemiology, etiology, clinical features, clinical treatment, and prevention. Front Cell Dev Biol. 2020;8. DOI:10.3389/fcell.2020.00410.
[67] Gordon CJ, Tchesnokov EP, Woolner E, et al. Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potency. J Biol Chem. 2020;19:4773–4779.
[68] Wu D, Koganti R, Lambe UP, et al. Vaccines and therapies in development for SARS-CoV-2 infections. J Clin Med. 2020;9:1885.
[69] Uddin M, Mustafa F, Rizvi TA, et al. SARS-CoV-2/COVID-19: viral genomics, epidemiology, vaccines, and therapeutic interventions. Viruses. 2020;12:526.
[70] Chaplin S. COVID-19: a brief history and treatments in development. Prescriber. 2020;31:23–28.
[71] Shih H-I, Wu C-J, Tu Y-F, et al. Fighting COVID-19: A quick review of diagnoses, therapies, and vaccines. Biomed J. 2020. DOI:10.1016/j.bj.2020.05.021.
[72] Cai Q, Yang M, Liu D, et al. Experimental treatment with Favipiravir for COVID-19: An open-label control study. Engineering. 2020. [accessed 2020 Sep 15]. DOI:10.1016/j.eng.2020.03.007
[73] Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;30:269–271.
[74] Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020;56:105949.
[75] Molina JM, Delaugerre C, Le Goff J, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. Med Mal Infect. 2020;50:384.
[76] Shittu MO. Afolami OI improving the efficacy of chloroquine and hydroxychloroquine against SARS-CoV-2 may require zinc additives—a better synergy for future COVID-19 clinical trials. Infez Med. 2020;28:192–197.
[77] Lundstrom K. Coronavirus pandemic—therapy and vaccines. Biomedicines. 2020;8:109.
[78] Zhang N, Li C, Hu Y, et al. Current development of COVID-19 diagnostics, vaccines and therapeutics. Microbes Infect. 2020;22:231–235.
[79] Casadevall A, Pirofski L-A. The convalescent sera option for containing COVID-19. J Clin Investig. 2020;130:1545–1548.
[80] Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA. 2020;323:1582.
[81] Brouwer PJM, Caniels TG, van der Straten K, et al. Potent neutralizing antibodies from COVID-19 patients define multiple targets of vulnerability. Science. 2020;369:643–650.
[82] Kulkarni R, Bramhachari PV. Dynamics of immune activation in viral diseases. Singapore: Springer; 2020. p. 9–41.
[83] Mulangu S, Dodd LE, Davey RT Jr, et al. A randomized, controlled trial of Ebola virus disease therapeutics. N Engl J Med. 2019;381:2293–2303.
[84] van Griensven J, Edwards T, de Lamballerie X, et al. Evaluation of convalescent plasma for Ebola virus disease in Guinea. N Engl J Med. 2016;374:33–42.
[85] Hershberger E, Sloan S, Narayan K, et al. Safety and efficacy of monoclonal antibody VIS410 in adults with uncomplicated influenza A infection: re sults from a randomized, double-blind, phase-2, placebo-controlled study. EBioMedicine. 2019;40:574–582.
[86] Gogtay NJ, Munshi R, Ashwath Narayana DH, et al. Comparison of a novel human rabies monoclonal antibody to human rabies immunoglobulin for post-exposure prophylaxis: a phase 2/3, randomized, single-blind, noninferiority, controlled study. Clin Infect Dis. 2018;66:387–395.
[87] Sandritter T. Palivizumab for respiratory syncytial virus prophylaxis. J Pediatr Health Care. 1999;13:191–195.
[88] Tian X, Li C, Huang A, et al. Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody. Emerg Microbes Infect. 2020;9:382–385.
[89] Wang C, Li W, Drabek D, et al. A human monoclonal antibody blocking SARS-CoV-2 infection. Nat Commun. 2020;11:2251.

[90] Wrapp D, Wang N, Corbett KS, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020;367:1260–1263.
[91] Pinto D, Park Y-J, Beltramello M, et al. Structural and functional analysis of a potent sarbecovirus neutralizing antibody. bioRxivorg. 2020. DOI:10.1101/2020.04.07.023903.
[92] Chen X, Li R, Pan Z, et al. Human monoclonal antibodies block the binding of SARS-CoV-2 spike protein to angiotensin converting enzyme 2 receptor. Cell Mol Immunol. 2020;17:647–649.
[93] Zost SJ, Gilchuk P, Case JB, et al. Potently neutralizing human antibodies that block SARS-CoV-2 receptor binding and protect animals. bioRxivorg. 2020. DOI:10.1101/2020.05.22.111005.
[94] Robbiani DF, Gaebler C, Muecksch F, et al. Convergent antibody responses to SARS-CoV-2 infection in convalescent individuals. bioRxivorg. 2020. DOI:10.1101/2020.05.13.092619.
[95] Ju B, Zhang Q, Ge J, et al. Human neutralizing antibodies elicited by SARS-CoV-2 infection. Nature. 2020;584:115–119.
[96] Rogers TF, Zhao F, Huang D, et al. Rapid isolation of potent SARS-CoV-2 neutralizing antibodies and protection in a small animal model. bioRxivorg. 2020. DOI:10.1101/2020.05.11.088674.
[97] Hansen J, Baum A, Pascal KE, et al. Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail. Science. 2020;369:1010–1014.
[98] Macdonald LE, Karow M, Stevens S, et al. Precise and in situ genetic humanization of 6 Mb of mouse immunoglobulin genes. Proc Natl Acad Sci U S A. 2014;111:5147–5152.
[99] Baum A, Fulton BO, Wloga E, et al. Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies. Science. 2020;369:1014–1018.
[100] Sharpe H, Gilbride C, Allen E, et al. The early landscape of coronavirus disease 2019 vaccine development in the UK and rest of the world. Immunology. 2020;160:223–232.
[101] World Health Organization. Laboratory testing for coronavirus disease (COVID-19) in suspected human cases: interim guidance. World Health Organization. [accessed 2020 Sep 15]. Available from: https://apps.who.int/iris/handle/10665/331501. License: CC BY-NC-SA 3.0 IGO
[102] Jackson LA, Anderson EJ, Rouphael NG, et al. An mRNA vaccine against SARS-CoV-2 - preliminary report. N Engl J Med. 2020. DOI:10.1056/NEJMoa2022483.
[103] A study to evaluate efficacy, safety, and immunogenicity of mRNA-1273 vaccine in adults aged 18 years and older to prevent COVID-19 - full text view - ClinicalTrials.Gov [Internet]. Clinicaltrials.gov. [cited 2020 Sep 12].
[104] He Y, Zhou Y, Liu S, et al. Receptor-binding domain of SARS-CoV spike protein induces highly potent neutralizing antibodies: implication for developing subunit vaccine. Biochem Biophys Res Commun. 2004;324:773–781.
[105] Pardi N, Tuyishime S, Muramatsu H, et al. Expression kinetics of nucleoside-modified mRNA delivered in lipid nanoparticles to mice by various routes. J Control Release. 2015;217:345–351.
[106] Mulligan MJ, Lyke KE, Kitchin N, et al. Phase 1/2 study to describe the safety and immunogenicity of a COVID-19 RNA vaccine candidate (BNT162b1) in adults 18 to 55 years of age: interim report. bioRxiv. 2020. DOI:10.1101/2020.06.30.20142570.
[107] Trial A. Investigating the safety and effects of one BNT162 vaccine against COVID-19 in healthy adults - full text view - ClinicalTrials.Gov [Internet]. Clinicaltrials.gov. [cited 2020 Sep 12].
[108] Logunov DY, Dolzhikova IV, Zubkova OV, et al. Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia. Lancet. 2020. DOI:10.1016/S0140-6736(20)31866-3.
[109] Clinical trial of efficacy, safety, and immunogenicity of gam-covid-vac vaccine against COVID-19 - full text view - ClinicalTrials.Gov [Internet]. Clinicaltrials.gov. [cited 2020d Sep 12].
[110] Folegatti PM, Ewer KJ, Aley PK, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. Lancet. 2020;396:467–478.
[111] van Doremalen N, Lambe T, Spencer A, et al. ChAdOx1 nCoV-19 vaccination prevents SARS-CoV-2 pneumonia in rhesus macaques. bioRxivorg. 2020. DOI:10.1101/2020.05.13.093195.
[112] Clinical Trials Register [Internet]. Clinicaltrialsregister.eu. [cited 2020 Sep 12]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001228-32/GB
[113] Phase III double-blind, placebo-controlled study of AZD1222 for the prevention of COVID-19 in adults - full text view - ClinicalTrials.Gov [Internet]. Clinicaltrials.gov. [cited 2020o Sep 12].
[114] Riley S, Ainslie KEC, Eales O, et al. Community prevalence of SARS-CoV-2 virus in England during May 2020: REACT study. medRxiv. 2020. DOI:10.1101/2020.07.10.20150524.
[115] Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics,comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA. 2020;323:2052.
[116] Pollan M, Perez-Gomez B, Pastor-Barriuso R, et al. Prevalance of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study. Lancet. 2020;396:535–544.
[117] Seow J, Graham C, Merrick B, et al. Longitudinal evaluation and decline of antibody responses in SARS-CoV-2 infection. medRxiv. 2020. DOI:10.1101/2020.07.09.20148429.
[118] Gorse GJ, Donovan MM, Patel GB. Antibodies to coronaviruses are higher in older compared with younger adults and binding antibodies are more sensitive than neutralizing antibodies in identifying coronavirus-associated illnesses. J Med Virol. 2020;92:512–517.
[119] Edridge A. Coronavirus protective immunity is short-lasting. medRxiv. 2020. DOI:10.1101/2020.05.11.20086439.
[120] Grifoni A, Weiskopf D, Ramirez SI, et al. Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals. Cell. 2020;181:1489–1501.
[121] Li CK, Wu H, Ma S, et al. T cell responses to whole SARS coronavirus in humans. J Immunol. 2008;181:5490–5500.
[122] Kissler SM, Tedijanto C, Goldstein E, et al. Projecting the transmission dynamics of SARS-CoV-2 through the post-pandemic period. Science. 2020;368:860–868.

[123] Korber B, Fischer WM, Gnanakaran S, et al.Tracking changes in SARS-CoV-2 spike: evidence that D614G Increases Infectivity of the COVID-19 virus. Cell. 2020. DOI:10.1016/j.cell.2020.06.043

[124] Elbe S, Buckland-Merrett G. Data, disease and diplomacy: GI- SAID's innovative contribution to global health. Glob Chall. 2017;1: 33–46.

[125] Tang X-C, Agnihothram SS, Jiao Y, et al. Identification of human neutralizing antibodies against MERS-CoV and their role in virus adaptive evolution. Proc Natl Acad Sci USA. 2014;111:E2018–E2026.

[126] Sui J, Aird DR, Tamin A, et al. Broadening of neutralization activity to directly block a dominant antibody-driven SARS-coronavirus evolution pathway. PLoS Pathog. 2008;4:e1000197.

[127] Young BE, Fong S-W, Chan Y-H, et al. Effects of a major deletion in the SARS-CoV-2 genome on the severity of infection and the inflammatory response: an observational cohort study. Lancet. 2020. DOI: 10.1016/S0140-6736(20)31757-8.

[128] Zhang Y, Zhang J, Chen Y, et al. The ORF8 protein of SARS-CoV-2 mediates immune evasion through potently downregulating MHC-I. bioRxiv. 2020. DOI:10.1101/2020.05.24.111823.

[129] van Dorp L, Richard D, Tan CC, et al. No evidence for increased transmissibility from recurrent mutations in SARS-CoV-2. bioRxiv. 2020. DOI:10.1101/2020.05.21.108506.

[130] Su YCF, Anderson DE, Young BE, et al. Discovery and genomic characterization of a 382-nucleotide deletion in ORF7b and ORF8 during the early evolution of SARS-CoV-2. MBio. 2020;11:e01610–20.

[131] Gong Y-N, Tsao K-C, Hsiao M-J, et al. SARS-CoV-2 genomic surveillance in Taiwan revealed novel ORF8-deletion mutant and clade possibly associated with infections in Middle East. Emerg Microbes Infect. 2020;9:1457–1466.