THERAPEUTIC ADVANCES in
Drug Safety

Review

Safety surveillance and challenges in accelerated COVID-19 vaccine development

Ther Adv Drug Saf

2022, Vol. 13: 1–19

DOI: 10.1177/20420986221116452

Abimbola Cole, Peggy Webster, Denny Van Liew, Maribel Salas, Omar Aimer and Marina A. Malikova

***Abstract*:** The COVID-19 pandemic, caused by a novel type of coronavirus, continues to infect people, increasing morbidity and mortality across the globe. Measures to slow the transmission of the virus have had limited impact, and people, businesses, and economies have suffered. The disease has disproportionally impacted elderly and individuals with certain pre-existing conditions and has highlighted health and social inequities in some racial and ethnic minority groups. The majority of those who contract the disease recover completely, but some experience long-lasting complications. Vaccines have the potential to end the pandemic, and through the intense collaboration of scientists in government and private sectors, more than 200 COVID-19 candidate vaccines have been or are being developed, using known platforms and previous experiences with severe acute respiratory syndrome (SARS), at unprecedented speed. The expectations for vaccine safety and quality in the setting of accelerated development are the same as during non-emergency times; however, challenges inherent with the circumstances of the pandemic situation provide opportunities to improve clinical trial conduct and strengthen pharmacovigilance systems. We have reviewed and analyzed existing PV guidelines and recommendations throughout the lifecycle of vaccine development with a focus on developing a global/worldwide effort for post-marketing vaccine safety surveillance.

Plain Language Summary

The Important Role of Pharmacovigilance in Accelerated COVID-19 Vaccine Development

This is an extensive review that intends to address important aspects of COVID-19 vaccines' accelerated development and safety surveillance. It is focused on regulatory requirements for long-term safety monitoring, practical applications, and current global efforts in developing robust pharmacovigilance systems for post-authorization surveillance.
Notably, different perspectives of authors from industry, academic institutions, and contract research organizations involved in drug safety were incorporated to reflect on various regulatory requirements and new developments in vaccine safety. All co-authors are current members of International Society of Pharmacovigilance (ISoP).

Keywords: COVID-19, equity, pharmacovigilance, safety, vaccine development

Received: 24 June 2021; revised manuscript accepted: 9 July 2022.

Correspondence to:
Abimbola Cole
GSK plc, Brentford UK.
MCPHS University, Boston, MA, USA.
Abimbola.s.cole@gsk.com
Twitter: @abimbolacola

Peggy Webster
GSK plc, Brentford, UK

Denny Van Liew
Red Nucleus, Yardley, PA, USA

Maribel Salas
Daiichi Sankyo, Inc., Basking Ridge, New Jersey USA; CCEB/CPeRT, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Omar Aimer
InnoVigilance, Laval, QC, Canada

Marina A. Malikova
Surgical Translational Research: Operations and Compliance, Department of Surgery, Boston University School of Medicine and Boston Medical Center, Boston, MA, USA

Introduction

Characterization of COVID-19 disease: presentation and epidemiology

In 2019, the coronavirus disease (COVID-19) emerged as an infectious disease, which was determined to be due to the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1–5] First cases were patients diagnosed with pneumonia developed outside of the hospital setting and linked to a cluster of acute respiratory illnesses that occurred in December 2019 in

Wuhan, China, subsequently resulting in the current pandemic. Globally, in March 2021, more than 114 million confirmed cases of COVID-19 were reported to the World Health Organization (WHO), with more than 2.5 million deaths.[1] It was determined that the SARS-CoV-2 virus spreads via small airborne droplets when sick individuals talk, cough, or sneeze in close proximity.[2–5] Since very limited information on COV-2 was available at the beginning of the pandemic, the knowledge has evolved and continue evolving over time. As reported by the US Centers for Disease Control and Prevention (CDC), most individuals who contract the virus get mild to moderate symptoms, while others suffer from a much more severe course of the disease complicated by acute respiratory distress syndrome possibly attributed to the cytokine storm. Other severe complications of COVID-19 disease include multiorgan failure, septic shock, and blood clots. Comorbidities that can worsen the disease severity include pre-existing conditions such as diabetes mellitus, cardiovascular disease, and hypertension. According to the CDC, the most critical respiratory comorbidities are pulmonary and cystic fibrosis, asthma, and pre-existing chronic obstructive pulmonary disease (COPD).[2] One of the complexities of COVID-19 is how it presents in subpopulations. Children, for example, contribute a small proportion of reported cases (1% of cases reported in children less than 10 years of age and 4% in adolescents ranging from 10–19 years old).[6–8] It was noted that children are likely to have less severe symptoms and fewer complications compared with adults, (i.e. children rarely experienced multisystem inflammatory syndrome). According to the CDC, individuals below 50 years have the risk of death less than 0.5 per 100 (or 5 in 1000), while in people older than 70 years, this risk is more than 8 per 100.[9] Based on the data obtained previously for other respiratory viruses, pregnant women may have higher risk of severe COVID-19.[10] Also, people who smoke have a higher chance of needing intensive care or dying of COVID-19-related complications *versus* non-smokers.[11] Prior research has reported gender differences in illnesses caused by viruses such as HIV, Ebola, influenza, and severe acute respiratory syndrome (SARS).[12] Early released epidemiologic data on reviews of COVID-19 statistics exhibited increased impact of the COVID-19 pandemic and higher mortality rate in Chinese and Italian men.[5,13] According to the Chinese Centers for Disease Control and Prevention, the men's death rate was 2.8% compared with the women's death rate at 1.7%.[14] This difference cannot be explained by genetic susceptibility and outcomes between genders, but rather to lifestyle factors such as smoking and consuming alcohol.[15,16] It was reported that higher prevalence of smoking in men compared with women as well as higher frequency of comorbidities (e.g. hypertension at a younger age) in men might contribute to the higher mortality in men from COVID-19 disease.[13,14] Notably in Europe, approximately 57% of the infected people were men, and 72% of those who died of COVID-19 were men.[13,17]The US government is not tracking gender-related data of COVID-19 infections as of April 2020.[13]

In terms of ethnic and racial differences in populations examined in the United States, a greater percentage of COVID-19 deaths were reported in African Americans.[18] Reasons for this include sociocultural factors such as living in smaller spaces which may make social distancing harder. In addition, African Americans often hold jobs as essential personnel (i.e. in public transit and healthcare), and thus have a greater probability of exposure to individuals with COVID-19. Compounding these risk factors is the increased prevalence of comorbidities such as diabetes, hypertension, and heart disease in the African American community. Inequities in the healthcare system also put this community at higher risk of poor outcomes. The same trends were noticed and could potentially affect Native American and Latino communities, and therefore, these communities are also at higher risk of COVID-19 infection and worse outcomes.[19,20] Moreover, a greater percentage of COVID-19 deaths have been reported in Black, Asian, or other ethnic minority communities in the United Kingdom, where poor nutrition, low socioeconomic status, and living in overcrowded properties are among some contributing factors.[21]

Long-term effects of COVID-19

A significant percentage of people recover completely from less severe cases of COVID-19 within 2–6 weeks of infection.[22] However, some may have lingering or recurring symptoms for weeks to months following their initial recovery. There are also individuals who develop long-term health complications and are unable to regain their previous health. Such disease courses have also been observed in younger healthy individuals.

Although COVID-19 often manifests in the lungs, other organs can also be affected. According to the CDC, imaging tests performed on individuals who recovered from the disease, including mild cases, displayed persistent injury to the muscles of the heart even several weeks after recovery. A potential consequence of the damage is a heightened risk of cardiac diseases such as heart failure, myocarditis, and pericarditis. Also, pneumonia caused by COVID-19 may lead to permanent damage to structures of the lungs such as the alveoli, which can lead to scarring and breathing difficulties. Younger individuals might even experience cognitive impairment, seizures, and Guillain–Barré syndrome, a rare ailment leading to short-term paralysis.[23] In addition, COVID-19 has been noted to increase the tendency of blood cells to clot. Although heart attacks and strokes generally are the result of large clots, COVID-19-related heart injury is suspected to be a result of blood clot blockage in the small heart vessels. These blood clots can also contribute to prolonged complications in the liver and kidneys. Since it is hard to determine the long-term consequences of COVID-19, experts have been studying the outcomes of similar SARS viruses. One observation has been that chronic fatigue syndrome, a complicated illness characterized by intense fatigue that gets worse with physical and mental tasks but does not ameliorate with rest, seems to develop in a number of SARS-recovered people.[24] Therefore, this syndrome could potentially also affect COVID-19-recovered people. There is yet much not understood regarding the prolonged consequences of COVID-19 on an individual's health. Doctors are recommended to carefully keep track of recovered patients to observe how their organs operate after recovery.[25]

SARS-CoV-2 and pharmacologic targets

The virus responsible for COVID-19 illness, SARS-CoV-2, is a positive-sense single-stranded RNA (Baltimore class IV) virus and is easily spread among humans.[26,27] Scientific evidence suggests it has zoonotic origins because genetically it is very similar to bat coronaviruses (96% identity on a whole genome level), supporting the hypothesis that it might have arisen from a bat virus.[28–30] Because the SARS-CoV-2 virus displays minimal genomic diversity, its introduction to humans likely occurred in late 2019.[31] Each virus particle is between 50 and 200 nm in diameter.[32] As with other coronaviruses, SARS-CoV-2 has four proteins that make up its structure: spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins. The S, E, and M proteins form the virus' envelope, while the N protein holds the RNA genome. The S glycoprotein forms peplomers (spikes) which project from the surface of the virus, giving it the 'corona' (crown-like) morphology, which can be observed via electron microscopy. The viral spikes mediate attachment to, and fusing with, the membrane of a host cell. Specifically, the outer S1 receptor-binding subunit catalyzes attachment and the S2 membrane-fusion subunit fuses the host and viral membranes.[32,33] It was shown that SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2) receptor on human cells to enter the cell.[34] S protein priming by a cell surface protein known as transmembrane protease serine 2 (TMPRSS2) is required for cellular entry.[35] Following attachment of SARS-CoV-2 to a target cell, TMPRSS2 cleaves the virus' S protein and exposes a fusion peptide within the S2 subunit.[32,33] After the viral and cell membranes fuse, the virion is enclosed within an endosome and therefore partitioned from the other components of the host cell. The virion is released from its endosome when the pH falls or when a host cysteine protease, cathepsin, opens it.[33] The virion's RNA is then released into the interior of the cell and compels the cell to begin production and dissemination of copies, which then set off to infect additional cells.[36] The SARS-CoV-2 virus generates multiple virulence factors that facilitate dissemination of new virions from the host cell and also inhibit host immune responses.[32]

Vaccine development and safety

The development of vaccines is guided by regulatory requirements for biological products and follows similar pathway as for drugs.[37,38] The development of vaccines includes Pre-Marketing (pre-licensure) and Post-Marketing phases. The Pre-Marketing Phase encompasses the Preclinical [pre–Investigational New Drug (IND)] and Clinical phases. Manufacturing companies are responsible for conducting preclinical laboratory studies in compliance with the up-to-date regulations (Good Laboratory Practice for Nonclinical Laboratory Studies) and that clinical trials are carried out following Good Clinical Practice (GCP) Guidelines. Regulatory agencies are responsible for ensuring the manufacturers' adherence to those guidance documents. During

the clinical phase, clinical investigators and manufacturers or Marketing Authorization Holders (MAH) are responsible of demonstrating the efficacy and safety of their vaccines, and regulatory agencies are also responsible for ensuring the manufacturers' adherence to guidance documents. The average vaccine development time is between 10 and 15 years.[39]

Phases of vaccine development

The preclinical phase includes the development of the manufacturing process, the identification of the immunogen, and the preclinical testing (in cells/tissues and animal models) of candidate vaccines.[40] From a safety perspective, the preclinical toxicity data will contribute to identify and characterize the potential toxic effects of vaccines. Once the risk–benefit profile of a new vaccine is established in preclinical models, the manufacturer is required by regulations to submit an IND application to regulatory authorities. Under the IND designation, the vaccine; its manufacturing process; the tests performed to control its quality, safety, and immunogenicity in animals; and the proposed clinical protocols for human studies are described. Clinical trials in humans cannot begin until regulatory authorities approve the IND application. Furthermore, the design of clinical trials must ensure that regulatory approval is issued only for effective vaccines. To help determine vaccine efficacy (VE), a comparison is made in the proportionate reduction in disease attack rate (AR) between those unvaccinated (ARU) and vaccinated (ARV).[41,42] The basic formula for this is: $VE = (ARU - ARV)/(ARU) \times 100\%$, where ARU is the attack rate of unvaccinated people and ARV is the attack rate of vaccinated people. In addition, VE can be calculated from the relative risk (RR) of disease among the vaccinated group. The equation for this calculation would be $VE = (1 - RR) \times 100\%$, where RR is the relative risk of developing the disease for vaccinated people compared with unvaccinated people.

The clinical phase is typically carried out in three distinct phases (Figure 1).[43,44] Phase I is the first phase in human testing where safety, pharmacokinetics, and immunogenicity studies are performed. If the vaccine is intended for use in children, the vaccine should be tested in decreasing order of age from the oldest to the first year of life. Phase II clinical trials are larger in sample size than phase I studies, and they are randomized and controlled to assess the immunogenicity and vaccines' safety. Phase III studies are large-scale trials designed to demonstrate benefits/efficacy and provide more detailed safety data required for vaccine approval. During this phase, the vaccine is typically used with the dose and dosing schedule that are planned for when it is marketed. In addition, the study population more closely resembles the targeted post-licensure population. The vaccine-related adverse events (AEs) associated with the intended use are estimated. In phase III, a benefit/risk assessment is carried out comparing the benefits associated with the prevention of the disease or reduction in severity of disease with the risks of experience of adverse drug reactions associated with the vaccine. The COVID-19 vaccines went through expedited regulatory review process to get an emergency use authorization (EUA) in public health crisis. According to the US Food and Drug Administration (FDA) guidance for industry entitled 'Development and Licensure of Vaccines to Prevent COVID-19', the pre-licensure safety database for preventive vaccines for infectious diseases must consist of at least 3000 study participants vaccinated with the dosing regimen intended for licensure.[45] In addition, FDA anticipates that adequately powered efficacy trials for COVID-19 vaccines will be of sufficient size to provide an acceptable safety database for each of younger adult and elderly populations, as well as no significant safety concerns arise during clinical development that would warrant further pre-licensure evaluation by regulatory authorities. If a vaccine is intended to be used in special populations such as children, pregnant women, and people with senescent or weakened immune systems, additional studies must be conducted after the vaccine has been shown to be safe, immunogenic, and efficacious in phase III studies in adult populations.

At any phase of clinical or nonclinical studies, if the results show significant concerns about safety or efficacy, the regulatory agency can request further information, additional investigations, or interrupt any ongoing clinical trial.[44]

If vaccine clinical trials confirm safety and efficacy, a Biologics License Application (BLA) is submitted for review by regulatory authorities.[46] If approved, the manufacturing process begins. In post-approval, product monitoring (strength, safety, and purity of each batch of vaccine),

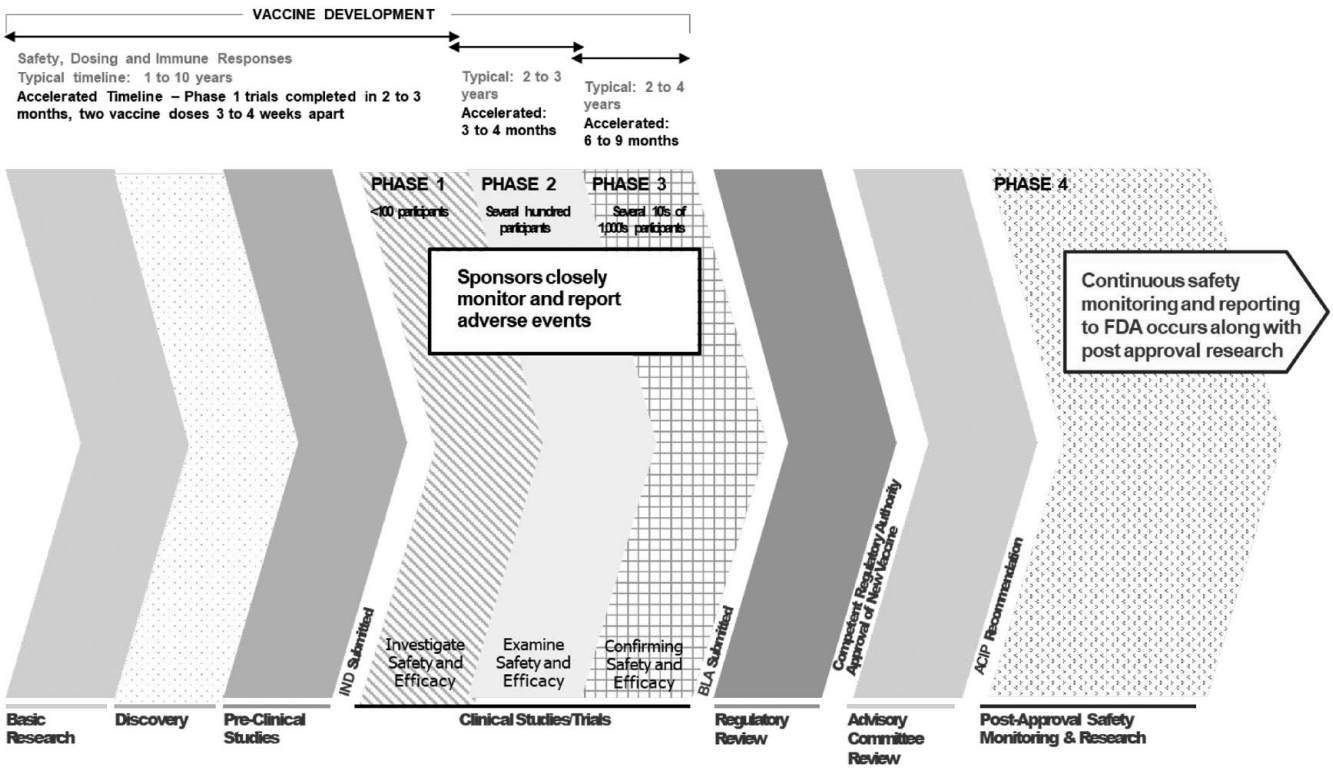

Figure 1. COVID-19 vaccine development. The typical timeline of vaccine development is at least 5 years, while the accelerating development can take 1–2 years, but irrespective of the development time spent, the vaccine must be safe at every phase while efficacy data are collected and evaluated. During *phase I*, the safe dosage range of the vaccine is estimated in a small number of healthy volunteers between 20 and 80 subjects who are closely monitored. *Phase II* is performed on a larger number (~100–300) of closely monitored patients to determine the dosage range. *Phase III* includes pivotal or registrational trials, and expanded safety studies. During phase III clinical trials, the efficacy needs to be demonstrated in randomized, double-blinded, controlled clinical trials. Endpoints might include endpoints related to clinical disease or immune response after demonstration of efficacy on clinical disease endpoints, and these are immune-correlated or surrogates of that protection. After completion of clinical phases, the *BLA submission* is performed to the regulatory authority, which will assess the efficacy and safety data to determine the risk/benefit ratio and recommend or reject the approval of a vaccine. The pre-approval inspection of the manufacturer's facilities where the vaccine will be produced is required before the final regulatory decision. The approval process of a vaccine also includes the approval of the vaccine labeling, which is directed to healthcare prescribers to understand the indication of the vaccine, the dosage and route of administration, warnings and precautions, adverse events, and other vaccines' characteristics for its proper use. Furthermore, clinical trial data are also used to support recommendations for the inclusion or not of a vaccine into national immunization program. The regulatory authorities might request *post-marketing phase IV* studies to continue the characterization of the safety profile and particularly the long-term safety and efficacy of the vaccine.
ACIP, Advisory Committee on Immunization Practices, part of the CDC, which reviews to inform recommendations for vaccine use in the United States; BLA, Biologics License Application; CDC, The US Centers for Disease Control and Prevention, which supports medical use and access recommendations and a communication network for vaccine information; FDA, US Food and Drug Administration, which reviews to inform recommendations for vaccine use in the United States; IND, Investigational New Drug Application.
https://www.cdc.gov/vaccinesafety/ensuringsafety/history/index.html

periodic inspections of facilities, and production activities will continue for the duration of the manufacturer's vaccine license.[44,46] In addition, after approval, the post-marketing safety monitoring continues, and spontaneously reported AEs are submitted to the regulatory agencies. In the United States, AEs are monitored by regulatory bodies, public health agencies, and manufacturers after being entered into the Vaccine Adverse Event Reporting System (VAERS).[47]

Accelerated COVID-19 vaccine development

The accelerated elaboration of vaccines that have been proven effective and safe is crucial in the context of a global pandemic, not only to control

the spread of illness but also to avoid unintended consequences and their impact which may outlast the pandemic itself, in exposed populations. Both the US and EU regulatory systems have dedicated significant resources to supporting the rapid development and authorization of COVID-19 vaccines.

To speed up COVID-19 vaccine development, steps that would normally have proceeded sequentially were aligned to take place simultaneously (Figure 1).[43] COVID-19 vaccines' clinical studies were carried out faster than usual, without compromising the quality of the trials, and because the pandemic provided large numbers of trial participants who could be recruited quickly.[48] Furthermore, previous experience and scientific knowledge gained while developing treatment for SARS helped in the discovery and development of COVID-19 vaccines. All the steps of the traditional vaccine development process were fulfilled, and all standards for safety and efficacy were maintained.

Guidance issued for vaccine manufacturers by the FDA explains that regulatory obligations for vaccine development and licensing, including quality, development, manufacturing and control of COVID-19 vaccines, must be met.[49] For the FDA to determine a favorable benefit–risk balance, results of at least one well-designed phase III study must clearly and convincingly demonstrate vaccine's safety and efficacy. Furthermore, in any continuous studies and for as long as feasible, manufacturers are required to collect placebo-controlled data continuously to work toward submission of a BLA and to collect safety information including the potential for vaccine-associated enhanced respiratory disease (VAERD).

Europe has followed a similar approach to speed development and authorization of COVID-19 vaccines.[50] The EU Vaccines Strategy allows for variations to usual development plans in the emergency context to reduce timelines, for example, by conducting some studies in parallel and by using a variety of trial designs and endpoints to determine efficacy. Within the European Medicines Agency (EMA), the Committee for Medicinal Products for Human Use (CHMP) and the Pandemic Task Force are working closely to coordinate activities related to the authorization and surveillance of COVID-19 vaccines. To ensure that high standards of vaccine quality, safety, and efficacy are met, regulatory processes have remained as rigorous as ever.

In September 2020, a group of vaccine manufacturers (AstraZeneca, BioNTech, GlaxoSmithKline, Johnson & Johnson, Merck, Moderna, Novavax, Pfizer, and Sanofi) pledged their commitment to conduct clinical studies and manufacturing process while adhering to high scientific and ethical standards as they worked toward potential regulatory submissions and approval applications of the first set of COVID-19 vaccines.[51]

Finally, in addition to accelerated development, there is also a pathway in the United States that allows accelerated use of a vaccine in the event of an emergency public health crisis. This pathway is called EUA.[52,53] Under section 564 of the Federal Food, Drug, and Cosmetic Act, EUA provides the FDA with the power to authorize the use of unapproved medications/vaccines to be used in emergency settings to diagnose, treat, or prevent serious or life-threatening disease. While EUA allows a medicinal product to be disseminated quickly, it still requires substantial clinical trial data from the drug/vaccine pharmaceutical company and rigorous review by the FDA of both safety and efficacy data. An EUA request for COVID-19 vaccines can be submitted based on the final or interim analysis of a phase III clinical efficacy trial. Furthermore, regarding safety, the EUA request must also include all safety data from both phase I and II trials, and safety data from phase III trials that have a median follow-up of at least 2 months. In addition, there is the expectation from the FDA that manufacturers will continue their clinical trials after obtaining an EUA to receive full approval.

Current COVID-19 vaccine status

The COVID-19 vaccine landscape has developed at an unprecedented scale and speed. Both SARS-CoV and SARS-CoV-2 use the ACE2 receptor to enter human cells.[54] The initial research approach was to create a whole virus vaccine using inactivated virus. Use of inactivated virus was to promote an immediate immune response in the body to new SARS-CoV-2 infection.[55] A second strategy was to use subunit vaccines, to develop a vaccine that sensitizes the immune system to key subunits of the virus. For SARS-CoV-2, the research narrowed in on the S protein which aids

the virus to bind the ACE2 enzyme receptor and infect cells. A third strategy using nucleic acid (DNA or RNA)-based vaccines offered greater flexibility in terms of antigen manipulation and potential for rapid research and development.[55,56] Scientists are also trying to employ viral vectors to deliver the SARS-CoV-2 antigen gene into the cell as a fourth strategy. These vectors can be replicating or non-replicating.[54,55] Any experimental vaccine derived from the previously mentioned strategies would have to undergo safety and efficacy testing in humans.

According to the WHO, in March 2022 there were over 349 COVID-19 candidate vaccines in research and development pipeline worldwide: 196 candidate vaccines were in preclinical evaluation and 153 in different phases of clinical trials, using different platforms.[57]

Currently, 49 of the most advanced clinical candidates are in Phase II/III or III clinical trials, and data to support licensure are anticipated to be available later this year. Most of the vaccine candidates which are now being tested in clinical trials target S protein and its variants as the primary antigen. In addition, there are candidates that target other or multiple antigens, including candidates that target N protein, attenuated vaccines, inactive vaccines, and peptide vaccines.

Three vaccines initially received emergency authorization for use in the United States. Among them were the COVID-19 vaccines manufactured by Pfizer–BioNTech and Moderna. The two vaccines were developed to use messenger RNA (mRNA) to stimulate an immune response, and their efficacy is measured by the ability to prevent COVID-19 disease as opposed to stopping infection.[58] When introduced into human tissues, the vaccine contains either self-replicating RNA or mRNA, which both cause cells to express the SARS-CoV-2 S protein. This guides a host organism to identify and destroy the corresponding pathogen. The delivery of mRNA is achieved by 'packaging' of the molecule into lipid nanoparticles (LNPs), which protect the RNA strands and aid their penetration into the cells.

Pfizer reported results of their phase III final analysis for their COVID-19 vaccine which showed 95% efficacy from their pivotal trial.[59] Researchers did not find serious safety concerns, and the vaccine was well tolerated following a review of data from 8000 study subjects. On 11 December 2020, the FDA granted an EUA for the Pfizer–BioNTech vaccine, and by the end of December 2020, this vaccine had been approved or authorized in various countries.[60,61] Moderna reported results of the interim analysis of their phase III study, with 94.5% efficacy of their vaccine candidate (mRNA-1273).[62] Among 30,000 study participants who were randomized into either a placebo or a vaccine group, there were 95 cases of symptomatic COVID-19 and there were no reports of serious side effects. The FDA granted an EUA for mRNA-1273 on 18 December 2020.[63]

Regarding specific AEs, according to CDC, severe allergic reactions such as anaphylaxis after COVID-19 vaccination are considered rare and have occurred in approximately 5 people per 1 million vaccinated in the United States.[64] In December 2020, 1,893,360 first doses of Pfizer–BioNTech COVID 19 vaccine administration resulted in 175 cases of severe allergic reaction, of which 21 were anaphylaxis.[65] For the 4,041,396 Moderna COVID-19 vaccine doses administered in December 2020 and January 2021, only 10 cases of anaphylaxis were reported. According to the Moghimi article in *Molecular Therapy*, LNPs were most likely responsible for the allergic reactions.

Following the initial EUA, the FDA granted full approval of the Pfizer–BioNTech vaccine, now marketed as 'Comirnaty', on 23 August 2021 for the prevention of COVID-19 disease in individuals aged 16 years and older. The vaccine, however, continues to be available under EUA for individuals 12 through 15 years of age and for the administration of a third dose in certain immunocompromised individuals.[66] To grant full approval for the Pfizer–BioNTech COVID-19 vaccine, the FDA reviewed updated data from the clinical trial which supported the EUA and included a longer duration of follow-up in a larger clinical trial population. The safety of Comirnaty was evaluated in approximately 22,000 people who received the vaccine and 22,000 people who received a placebo aged 16 years and older. Based on results from the clinical trial, the vaccine was 91% effective in preventing COVID-19 disease.[67] More than half of the clinical trial participants were followed for safety outcomes for at least 4 months after the second dose. Overall, approximately 12,000 recipients have been followed for at least

6 months. In terms of safety profile, the most commonly reported side effects by those clinical trial participants who received Comirnaty were pain, redness, and swelling at the injection site, fatigue, headache, muscle or joint pain, chills, and fever. The vaccine was deemed by the FDA to be effective in preventing COVID-19 and potentially serious outcomes including hospitalization and death.

The full approval for the Moderna COVID-19 vaccine was granted by FDA on 31 January 2022 and will be marketed as Spikevax. The decision was supported by real-world evidence (RWE) from the more than 200 million doses administered in the United States since the FDA cleared this vaccine in December 2020.[68]

The approval of Spikevax is based on the FDA's evaluation and analysis of follow-up safety and effectiveness data from the ongoing randomized, placebo-controlled, blinded clinical trial that supported the original EUA for the Moderna COVID-19 vaccine, issued in December 2020, and information from post-EUA experience to further inform safety and effectiveness.

The updated analyses to determine the effectiveness of Spikevax included 14,287 vaccine recipients and 14,164 placebo recipients aged 18 years and older who did not have evidence of SARS-CoV-2 infection prior to receiving the first dose. The data used for the analyses were accrued before the Omicron variant emerged. These data demonstrated that Spikevax was 93% effective in preventing COVID-19, with 55 cases of COVID-19 occurring in the vaccine group and 744 COVID-19 cases in the placebo group. The vaccine was also 98% effective in preventing severe disease. Similar to mRNA-based vaccine produced by Pfizer, the most commonly reported side effects by clinical trial participants were pain, redness, and swelling at the injection site, fatigue, headache, muscle or joint pain, chills, nausea/vomiting, swollen lymph nodes under the arm, and fever.[69,70] In addition, the FDA conducted a rigorous evaluation of the post-authorization safety surveillance data pertaining to myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of tissue surrounding the heart) following vaccination with the Moderna COVID-19 vaccine. This evaluation determined that the data demonstrate increased risks particularly within 7 days following the second dose, with the observed risk highest in males aged 18 through 24 years. Available data from short-term follow-up suggest that most individuals have had resolution of symptoms. However, some individuals required intensive care support. Information about potential long-term health outcomes is not yet available. The Spikevax Prescribing Information includes a warning about these risks. FDA has determined that the benefits of the vaccine outweigh the risk of myocarditis and pericarditis in individuals 18 years of age and older. The FDA is requiring the company to conduct post-marketing studies to further assess the risks of myocarditis and pericarditis following vaccination with Spikevax. These studies will include an evaluation of long-term outcomes among individuals who develop myocarditis following vaccination with Spikevax. In addition, the company has committed voluntarily to conduct additional post-marketing safety studies, including initiating a pregnancy registry study to evaluate pregnancy and infant outcomes after administration of Spikevax during pregnancy.

A third vaccine manufactured by Johnson & Johnson/Jansen (J&J/Jansen) received EUA on 27 February 2021. It was the first single-dose vaccine and is based on human adenovirus viral vector.[71] The vaccine was reported to be 72% effective in the United States.[72,73] It was not as effective in South Africa in cases against a more transmissible variant of the virus (B.1.351). According to J&J, in their South Africa trial participants, the vaccine was 52–64% effective 2 weeks to a month after vaccination. J&J also reported that it told the FDA that its vaccine performed better in protecting against severe disease in South Africa. J&J's vaccine achieved effectiveness rates of 73.1–81.7% in preventing severe disease 2 weeks to a month after vaccination. In terms of safety profile, thrombosis with thrombocytopenia syndrome (TTS) after J&J/Janssen COVID-19 vaccination is rare. TTS is a rare but serious adverse event that causes blood clots in large blood vessels and low platelets (blood cells that help form clots).[74] As of 24 March 2022, more than 18.5 million doses of the J&J/Janssen COVID-19 vaccine have been given in the United States. CDC and FDA identified 60 confirmed reports of people who got the J&J/Janssen COVID-19 vaccine and later developed TTS. Also, the CDC identified nine deaths that were caused by or were directly attributed to TTS following J&J/Janssen COVID-19 vaccination. Women aged 30–49 years, especially, should be

aware of the increased risk of this rare adverse event, and other vaccination options should be offered to them per current CDC guidelines.

Overall, the Pfizer–BioNTech and Moderna vaccines reported higher effectiveness; however, these results mainly occurred before new variants were known and emerged.[59,62] In addition, regulatory authorities stated the J&J vaccine was sufficiently protective, particularly in cases of severe disease. This protection in severe cases combined with its single-dose regimen and favorable temperature requirements was hoped to make a difference in the pandemic.[71] However, currently in most situations, Pfizer–BioNTech or Moderna COVID-19 vaccines are preferred over the J&J/Janssen COVID-19 vaccine for primary and booster vaccination due to the emergent risk of serious AEs, such as higher rate of blood clots. Many COVID-19 vaccine manufactures such as Moderna and J&J have stated they are working on modifying their vaccines to prove more effective against new COVID-19 variants.[75,76]

Multi-phase distribution plans prioritized higher risk groups, namely, vaccines have been implemented in elderly and healthcare workers across various countries. For example, the US CDC's Advisory Committee on Immunization Practices (ACIP) voted in December 2020 that first doses of the vaccine should go to healthcare workers and residents and staff of nursing homes.[77] In the second phase (phase Ib), per ACIP, it was recommended that vaccines be administered to individuals aged >75 years and non-healthcare frontline essential workers.[78] However, US States have local responsibility for prioritization, distribution, and logistics of vaccinating everyone within their state. The European Union started phased vaccine rollout on 27 December 2020.[79] Each member country is managing distribution; however, across all EU countries, a common focus has been prioritizing healthcare workers, people at high risk of exposure, the elderly, and those with serious health conditions.[80] The vaccination program in the United Kingdom initially prioritized elder care facility residents and staff, followed by healthcare workers and those over 80 years of age.[81] The next phases were based primarily on age, declining from 75 years in 5-year increments.

For each of the vaccines, it is recognized that all potential AEs from the vaccine are not yet known; therefore, phase IV studies for post-marketing surveillance are being conducted by each manufacturer to assess safety profile as these products are being used by the general population.[82,83]

Importance of post-approval safety surveillance for COVID-19 vaccines

Vaccine safety is of highest priority for government agencies and industry partners. Expectations for the accelerated clinical development of COVID-19 vaccines, including evaluations for safety, were outlined in the FDA's June 2020 guidance for industry.[83] In general, the expectations for safety evaluations under accelerated development are the same as for vaccines developed under non-emergency conditions. For instance, standard nonclinical safety studies would be required for a novel COVID-19 vaccine candidate that has no previous nonclinical and clinical data available; they have to be in an environment which is consistent with good laboratory practices regulations and they must be completed, analyzed, and submitted to the FDA prior to initiation of human clinical trials. Complete understanding of the vaccine-induced immune response in animal models is recommended to characterize the possible risk of VAERD.

During the clinical phases of a COVID-19 accelerated vaccine development program, the amount of safety data collected is expected to be the same by the regulatory authorities as for other preventive vaccines for infectious diseases, if developed under a non-emergency timeline. The pre-licensure safety database for a preventive vaccine often is made up of thousands of study subjects vaccinated with the dose-scheme intended for licensure. Properly powered efficacy trials for COVID-19 vaccines are anticipated to be of adequate size to establish an acceptable safety database for both younger adult and elderly populations, those for whom early vaccination might be recommended. A data safety monitoring board may be helpful in evaluating rare yet clinically concerning events such as VAERD.

As with vaccines developed and tested on traditional timelines, the accelerated development of vaccines to battle the COVID-19 pandemic will require robust systems for post-licensure safety surveillance to ensure the rapid identification and mitigation of potential safety risks. The FDA acknowledges the possible limitations of the pre-licensure safety database for a vaccine developed

on an accelerated schedule, such as the safety follow-up period for AEs, which could potentially not be completed for all participants taking part in the clinical trials. It is possible that a large population will be vaccinated in a very short time in a rapid, mass vaccination campaign, and if so, large numbers of coincidental AEs will be reported and vaccine-related adverse reactions that occur infrequently will more quickly become evident. It is essential that such risks are detected early so that mitigation actions can be taken, and that risks are placed into the context of public health benefit to help maintain public trust in vaccination. However, an unprepared pharmacovigilance (PV) system could encounter an overwhelming volume of case reports, resulting in a backlog that would not be rapidly processed given capacity constraints. Sponsors are encouraged to develop a PV plan in advance of vaccine approval, taking into consideration the need for both passive and active elements for enhanced surveillance and reporting, including expedited submission of events of special interest, frequent preparation of aggregate safety summaries, pharmacoepidemiologic studies of events of special interest, and a registry of all exposures during pregnancy. For COVID-19 vaccines, post-marketing safety studies may be required for characterization of important risks.

During a virtual meeting held in May 2020, the Global Advisory Committee on Vaccine Safety (GAVCS), which provides scientific advice to the WHO on vaccine safety issues, addressed PV preparations for the launch of COVID-19 vaccines.[84] Topics discussed included defining potential adverse events of special interest (AESI) in relation to COVID-19 vaccines, establishing background incidence rates in target populations, prioritization of AESI for rapid assessment, and communications plans to achieve public acceptance and update regarding COVID-19 vaccines. In addition, the application of standardized templates for benefit–risk assessment of vaccines and COVID-19 vaccine benefit–risk communication management were also explored. The GACVS noted that COVID-19 vaccine safety surveillance infrastructure and capacity should ideally be in place along with the existing infrastructures that should be reactivated and actively engaged prior to vaccine introduction in all countries and recommended that the WHO work with national teams of the Expanded Program on Immunization to strengthen routine vaccine safety monitoring alongside COVID-19-related activities. The COVAX is a global collaboration which is a vaccine-focused pillar of the Access to COVID-19 Tools (ACT) Accelerator aimed at ensuring equitable global access to COVID-19 diagnostics, treatments, and vaccines, which is working with UNICEF and the WHO to provide technical support for safety monitoring to low-income and lower-middle-income economies to ensure country readiness for COVID-19 vaccine distribution.[85] In the initial clinical studies of COVID-19 vaccines, children and adolescents, pregnant and lactating women, and immunocompromised individuals were not included. The lack of evidence for efficacy and safety in these special populations challenges informed decision making.[86] Since the beginning of the pandemic, substantial information about the use of COVID-19 vaccines in special populations has been collected and has led to recommendations for vaccination in these groups.

Diversity and patient centricity in COVID-19 vaccine development

Although much news about COVID-19 vaccines has been focused on accelerated development and authorization, and distribution after authorization, it is imperative that the individuals who will receive the vaccines remain the top focus. The success of all COVID-19 vaccine clinical trials depends on subject participation, but enrolling subjects who are representatives of the global population in which the vaccine will be used is challenging. As noted earlier in this article, particular racial groups including African Americans, Latin Americans, Native Americans and Asians, and older adults bear more significant impact from COVID-19.[18–21] In addition, while the general risk of COVID-19 in pregnant women is low, severe illness does appear to be increased during pregnancy.[87] Immunosuppression in people due to exogenous (e.g. drugs) or endogenous (e.g. underlying conditions such as cancer) factors is also a heighted risk for severe COVID-19 illness. Diversity of race, ethnicity, age, and pre-existing conditions in clinical trials is necessary to ensure that any authorized vaccine can be trusted to be safe and effective across a diverse set of individuals.

One way of improving diversity in COVID-19 vaccine clinical trials is by conducting trials in multiple countries. In the last decade, most likely due to globalization, clinical trials run in low-middle-income countries (LMICs) have

increased, and it is estimated that ~28% of pivotal trials are coming from the 'rest of world (ROW)' region which consists of Africa, Middle East/Asia/Pacific, Australia/New Zealand, Central/South America, Eastern Europe, and non–European Union.[88] Conducting clinical trials within many countries potentially broadens the safety and efficacy data collected and improves the ability of researchers to accurately interpret the evidence of benefits and risks within various nationalities and social groups. This is critical for determining how to optimally allocate limited supply of vaccines to lessen the burden of COVID-19 on healthcare systems. Lack of standardization in healthcare infrastructure can impact the quality of data generated, however, and it will therefore be imperative for clinical trial sponsors to support sites which may not have adequate capabilities or capacity to conduct vaccine trials.

Although there has been much progress, improving diversity in age and comorbidities of clinical trial participants has been an acknowledged challenge for drug developers for decades. Clinical trial eligibility criteria are designed to exclude subjects for whom participation would not be considered acceptable because their potential benefit is not expected to exceed the risks they might experience. Exclusions for uncontrolled or severe comorbidities are necessary to protect the welfare of individuals with such conditions. In early phase development, little evidence is available on which to base a benefit–risk assessment, and as a result, children and elderly subjects, persons with kidney or liver dysfunction, individuals with immunodeficiency or immunosuppression, and pregnant and lactating women are often excluded from participating. Without data from these groups, translation of trial results to those at greatest risk of severe disease is difficult. Public health officials must rationalize the ability to rapidly develop safe and effective vaccines with the ability to confidently extrapolate results to diverse populations. Many efforts are being taken to encourage inclusive clinical trial practices such as those detailed in the November 2020 FDA guidance for industry, but such approaches may not be practical in a pandemic environment.[89] Effective PV surveillance will be critical to monitoring for vaccine effectiveness and safety risks that may arise within population subgroups as a result of broadened diversity in post-authorization usage.

COVID-19 has also presented an opportunity to strengthen the patient centricity focus that most biopharmaceutical industry companies have been embracing for the past decade. Disruptions to daily life imposed by the pandemic caused changes in the way clinical trials were operationalized.[90] To offset the constraints which limited subjects' ability to safely travel to clinical sites to receive study treatment and be monitored, treatments were delivered directly to them (when possible) and some monitoring visits were conducted virtually. Other patient-friendly modifications to trial design, such as incorporating electronic health record data to augment clinical trial data, employing health aides to obtain biological specimens directly from subjects in their homes, and using wearable devices to monitor vital signs remotely, are being used to make participation less burdensome for volunteers. Although there is much interest in digital and at-home solutions, the power of touch and the importance of consistency cannot be underestimated. Research-related interactions are a source of comfort for many trial participants, providing an opportunity to socialize and build meaningful relationships with physicians and research teams and validating their contribution to the greater good. Just as sponsors and investigators must weigh the potential benefits and risks of an interventional agent for each individual subject, they must also consider the impact of the operational aspects of trial participation on the subject and their caregivers. They should continuously seek feedback to identify burdens and anxieties that can be mitigated through knowledge sharing or planning, never assuming any single solution is 'one-size-fits-all'. Flexibility and choice are critical in patient-centric trial design and execution.

PV systems and signal detection

The reporting, tracking, follow-up, and analysis of AEs during clinical trials and after approval, especially in an increasingly global and connected world, are extensive processes which require robust PV systems. There are currently various PV systems in place run by both global and national organizations. Although this article highlights PV systems coordinated by the WHO, International Organizations of Medicinal Sciences (CIOMS), FDA, CDC, and the EMA, it is important to note that there are many other national and local health agencies which have their own PV monitoring systems.[91–96]

Signal detection for COVID-19 vaccines

While the purpose of this article is not to discuss the monitoring of AEs that will arise as a result of COVID-19 vaccination, it would be remiss if the importance of signal detection was not mentioned. In simplistic terms, a safety signal is an AE that may be caused by a drug/vaccine, and signal detection is the process of identifying these signals.[97] Signal detection is done via various qualitative and quantitative methods often with the use of large safety databases. In addition, signal detection is done both by the manufacturer of a drug/vaccine and by health authorities. With the wide-scale use of all COVID-19 vaccines and the fact that some of the COVID-19 vaccines use mRNA technology, efficient signal detection is going to be extremely important to determine causality of any potential adverse effects. Some key aspects that will be important in COVID-19 signal detection will include appropriate escalation and communication of AEs deemed severe and life-threatening, safety in particular vulnerable populations such as children, as well as further analysis of particular types of AEs that have already been identified such as cardiovascular and thrombotic.[98] Due to the wide-scale use of these vaccines, there is an opportunity for the use of RWE to detect AEs and further characterize the safety profile of COVID-19 vaccines.

Globally focused PV systems

The GACVS, which was established in 1999 under the WHO, advises the WHO on safety issues related to vaccines, enabling prompt and scientifically rigorous responses to vaccine safety concerns of potential global importance.[91] Because vaccines are a group of medicinal products with unique safety considerations, a joint working group focused on vaccine PV was established in 2005 by the CIOMS and the WHO.[92] The purpose of this working group was to propose standardized relevant vaccine for effective vaccine safety monitoring during clinical trials and after licensing. In 2013, the CIOMS Working Group on Vaccine Safety was established to address unmet needs in vaccine PV, especially regarding public–private information exchange.[93] The group's 2017 report, CIOMS Guide to Active Vaccine Safety Surveillance (Guide AVSS), offers a practical approach to aid immunization professionals and decision-makers in determining the best course of action when confronting such challenges.[94]

US-focused PV systems

Created in 1990, the VAERS is a vaccine safety surveillance program managed jointly by CDC and the FDA.[47,95] It is the nation's early alert system for detecting possible safety issues associated with vaccines licensed for use in the United States through the collection of information about AEs that occur after vaccination. Healthcare Practitioners (HCPs), pharmaceutical companies, and any public citizen can make a report to VAERS, via their website, in case of any health issue or adverse effect that occurs after vaccination. The main goals of VAERS are to identify new, unusual, or rare post-vaccination AEs, monitor changes in known side effects, detect potential risk factors, assess the overall safety of newly licensed vaccines, reveal unusual or unexpected patterns in AE reports, and serve as a monitoring system during public health emergency situations. For COVID-19 therapies, the FDA created the Coronavirus Treatment Acceleration Program (CTAP). This program is aimed at moving new therapies to patients as rapidly as possible by using all available methods while determining whether they are helpful or harmful at the same time.

EU-focused PV systems

In a number of European countries, the EMA has the responsibility for coordinating the evaluation and supervision of PV activities for medicinal medications and vaccines.[96] The EMA assists Member States in pharmacovigilance activities by operating and maintaining the framework for safety surveillance of vaccines, including systems such as EudraVigilance, European Pharmacovigilance Issues Tracking Tool (EPITT), and the European Union electronic register of post-authorization studies (EU PAS register), and by providing reports to facilitate the monitoring of EudraVigilance data. The EMA also helps identify and connect relevant networks and research groups in the EU for conducting post-authorization studies. The EMA typically requires up to 210 active days for the evaluation of a medicine, but the review period for COVID-19 products has been accelerated to 150 days or less.

Discussion

There are still many unknowns regarding the COVID-19 pandemic. Will it end? What will the end look like? Or will the COVID-19 pandemic become an ongoing endemic? The likely future

will be shaped by several key considerations. These include the rise of variants, what are the long-term effectiveness and safety of various vaccines, the global COVID-19 vaccine distribution strategy, and the dissemination of information and public education efforts regarding the COVID-19 vaccine and COVID-19 in general.[99–103]

As variants of the initial SARS-COV-2 virus continue to multiply, the result is increased challenges in managing the disease and controlling the pandemic.[99] Each new variant has the potential to present the disease differently. Some of these new variants may increase transmission or increase severity of the disease. Other variants may lead to a milder presentation of the disease. Further studies are needed regarding the individual variants before a conclusive judgment should be made. Another challenge is the effectiveness of the COVID-19 vaccines against the variants.[100,101] Further studies are needed assess the effectiveness of the vaccines against the variants, and if so, to which specific variants they are effective against. Furthermore, more long-term effectiveness and safety data of vaccines are needed.

Another consideration and challenge are the distribution of the COVID-19 vaccines.[102] Factors such as manufacturing, storage, vaccine scheduling and dosing, as well as vaccine prioritization play a role in how successful vaccine distribution is. Adding to this challenge is the need of distribution of the vaccines to low- to medium-income nations. Both distribution and vaccination for all are critical to prevent healthcare inequity and control of the pandemic. Returning to pre-pandemic travel (both business and personal) will not occur without global vaccine distribution. The economic impact of the disruption from COVID-19 is beyond the scope of this article.

Over the longer term, it is crucial COVID-19 vaccines are seen to be safe not only for their acceptance but also for the broad development of confidence in vaccination. The overall safety profile for each vaccine will evolve as more people receive the vaccine, and ongoing safety surveillance identifies less frequent or uncommon serious AEs. In contrast to a therapeutic clinical trial in which safety is weighed against patient benefit, vaccine clinical studies must weigh safety against the risk of infection, not disease outcome. Because vaccines are given to healthy volunteers and, during the pandemic, potentially to everyone after phase III trials and approval, safety is paramount. COVID-19 vaccine AEs should be monitored (reported, tracked, and analyzed) in an ongoing basis. This will include national, regional, and global PV systems as mentioned in this article (e.g. GACVS, VAERS and VAC4EU) for a better risk management of eventual risks that will come up following mass use of the vaccines.[91,95,96]

It is critical the healthcare community, governments, and other organizations (e.g. patient advocacy, local community, and religious leaders) educate the public on the COVID-19 vaccine through a range of communication channels to create awareness of the vaccines' effectiveness and their monitoring.[103] Herd immunity is needed, which means a significant percentage of the population will need to have immunity to the virus, ideally via the vaccine.[104] The public has experienced misinformation via social media on other topics, resulting in increasing distrust which also impacts their willingness to be vaccinated. Therefore, effective and transparent communication of scientifically backed information will be one of the most critical actions in the effort to control this pandemic.[103] Further collaboration among health agencies, pharmaceutical companies, healthcare providers and workers, public health specialists, governments, and patient advocates will be needed to create effective public health campaigns that provide true information while also dispelling misinformation.

Conclusion

Given the magnitude and duration of the current COVID-19 pandemic, the more rapidly successful vaccines are developed, globally the better. Any developed vaccine must demonstrate safety and sustained effectiveness, particularly in higher risk groups, in large randomized clinical studies before introduction to the public. Achieving equity of access will require several producers of vaccines and suppliers to deliver them in a variety of settings.

A major focus surrounding current and potential COVID-19 vaccines has always been the safety of the vaccine. As this article has sought to highlight, safety is one of the most important factors in drug and vaccine development, and there are several measures put in place by both pharmaceutical companies and healthcare agencies to ensure safety. Furthermore, as all the authors of this

article are members of the International Society of Pharmacovigilance, it was imperative that this article highlights and brings awareness to the general public of the specific vaccine safety measures that are currently in practice throughout the lifespan of vaccine development. The hope is that this article educates individuals and allows for informed questions and conversations to occur.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions
Abimbola Cole: Conceptualization; Methodology; Project administration; Writing – original draft; Writing – review & editing.

Peggy Webster: Conceptualization; Methodology; Project administration; Writing – original draft; Writing – review & editing.

Denny Van Liew: Conceptualization; Methodology; Project administration; Writing – original draft; Writing – review & editing

Maribel Salas: Conceptualization; Methodology; Project administration; Writing – original draft; Writing – review & editing.

Omar Aimer: Conceptualization; Methodology; Project administration; Writing – original draft; Writing – review & editing.

Marina A. Malikova: Conceptualization; Methodology; Project administration; Writing – original draft; Writing – review & editing.

Acknowledgements
None.

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests
The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Abimbola Cole was an employee of Takeda Pharmaceuticals when the full manuscript was completed and is now employed by GSK and adjunct faculty at MCPHS University, Peggy Webster was an employee of Takeda Pharmaceuticals at the initiation of this manuscript and is now an employee of GSK, Denny Van Liew is an employee of Red Nucleus, Maribel Salas is an employee of DSI, Omar Aimer is an employee of InnoVigilance, and Marina Malikova is an employee of Boston Medical Center and Boston University. Peggy Webster is GSK stock holder.

Availability of data and materials
Not applicable.

ORCID iDs
Abimbola Cole https://orcid.org/0000-0002-0672-6262

Marina A. Malikova https://orcid.org/0000-0003-1370-187X

References
1. World Health Organization. *Coronavirus (COVID-19) dashboard*. Geneva: WHO, https://covid19.who.int (accessed 8 September 2020 and 16 March 2021).
2. *Symptoms of coronavirus*. Atlanta, GA: Centers for Disease Control and Prevention (CDC), 2020, https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html (accessed 8 September 2020 and 16 March 2021).
3. *Coronavirus disease 2019 (COVID-19): symptoms and causes*. Rochester, MN: Mayo Foundation for Medical Education and Research, https://www.mayoclinic.org/diseases-conditions/coronavirus/symptoms-causes/syc-20479963 (accessed 8 September 2020 and 16 March 2021).
4. Ye Q, Wang B and Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. *J Infect* 2020; 80: 607–613.
5. Zhu N, Zhang D, Wang W, *et al*. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020; 382: 727–733.
6. *Health Department-reported cases of multisystem inflammatory syndrome in children (MIS-C) in the United States*. Atlanta, GA: Centers for Disease Control and Prevention, https://www.cdc.gov/mis-c/cases/index.html (accessed 16 March 2021).

7. Castagnoli R, Votto M, Licari A, *et al*. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review. *JAMA Pediatr* 2020; 174: 882–889.
8. Lu X, Zhang L, Du H, *et al*. SARS-CoV-2 infection in children. *N Engl J Med* 2020; 382: 1663–1665.
9. US Centers for Disease Control Prevention (CDC). Interim clinical guidance for management of patients with confirmed coronavirus disease (COVID-19), https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html (accessed 5 April 2021).
10. Schwartz DA and Graham AL. Potential maternal and infant outcomes from Coronavirus 2019-nCoV (SARS-CoV-2) infecting pregnant women: lessons from SARS, MERS, and other human coronavirus infections. *Viruses* 2020; 12: 194.
11. Engin AB, Engin ED and Engin A. Two important controversial risk factors in SARS-CoV-2 infection: obesity and smoking. *Environ Toxicol Pharmacol* 2020; 78: 103411.
12. Wenham C, Smith J and Morgan R. COVID-19: the gendered impacts of the outbreak. *Lancet* 2020; 395: 846–848.
13. Rabin RC. In Italy, coronavirus takes a higher toll on men. *The New York Times*, 20 March 2020, https://www.nytimes.com/2020/03/20/health/coronavirus-italy-men-risk.html (accessed 11 September 2020).
14. Epidemiology Working Group for NCIP Epidemic Response Chinese Center for Disease Control Prevention. [The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China]. *Zhonghua Liu Xing Bing Xue Za Zhi* 2020; 41: 145–151 (in Chinese).
15. Hu Y, Sun J, Dai Z, *et al*. Prevalence and severity of corona virus disease 2019 (COVID-19): a systematic review and meta-analysis. *J Clin Virol* 2020; 127: 104371.
16. Yuki K, Fujiogi M and Koutsogiannaki S. COVID-19 pathophysiology: a review. *Clin Immunol* 2020; 215: 108427.
17. World Health Organization. *COVID-19 weekly surveillance report*. Geneva: WHO, https://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/weekly-surveillance-report (accessed 11 September 2020).
18. Dorn AV, Cooney RE and Sabin ML. COVID-19 exacerbating inequalities in the US. *Lancet* 2020; 395: 1243–1244.
19. Adams ML, Katz DL and Grandpre J. Population-based estimates of chronic conditions affecting risk for complications from coronavirus disease, United States. *Emerg Infect Dis* 2020; 26: 1831–1833.
20. Laurencin CT and McClinton A. The COVID-19 pandemic: a call to action to identify and address racial and ethnic disparities. *J Racial Ethn Health Disparities* 2020; 7: 398–402.
21. Cuthbertson A. Coronavirus tracked: how Covid-19 deaths in the UK compare by race and ethnicity. *Independent*, 11 June 2020, https://www.independent.co.uk/news/uk/home-news/coronavirus-death-toll-uk-race-white-black-asian-bame-ethnicity-cases-a9557076.html (accessed 11 September 2020).
22. *What we know about Long-term effects of COVID-19*. Geneva: World Health Organization, 2020, https://www.who.int/docs/default-source/coronaviruse/risk-comms-updates/update-36-long-term-symptoms (accessed 15 October 2020).
23. Zhou H, Lu S, Chen J, *et al*. The landscape of cognitive function in recovered COVID-19 patients. *J Psychiatr Res* 2020; 129: 98–102.
24. Ngai JC, Ko FW, Ng SS, *et al*. The long-term impact of severe acute respiratory syndrome on pulmonary function, exercise capacity and health status. *Respirology* 2010; 15: 543–550.
25. *Long-term effects of COVID-19*. Atlanta, GA: Centers for Disease Control and Prevention, 2020. https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects.html (accessed 13 November 2020).
26. Baltimore D. Expression of animal virus genomes. *Bacteriol Rev* 1971; 35: 235–241.
27. Chan JF, Yuan S, Kok KH, *et al*. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet* 2020; 395: 514–523.
28. Andersen KG, Rambaut A, Lipkin WI, *et al*. The proximal origin of SARS-CoV-2. *Nat Med* 2020; 26: 450–452.
29. Zhou P, Yang XL, Wang XG, *et al*. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020; 579: 270–273.
30. Perlman S. Another decade, another coronavirus. *N Engl J Med* 2020; 382: 760–762.

31. Cohen J. Wuhan seafood market may not be source of novel virus spreading globally. *Science*, 26 January 2020, https://www.sciencemag.org/news/2020/01/wuhan-seafood-market-may-not-be-source-novel-virus-spreading-globally (accessed 8 September 2020).

32. Wu C, Liu Y, Yang Y, *et al*. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. *Acta Pharm Sin B* 2020; 10: 766–788.

33. Aronson JK. *Coronaviruses – A general introduction*. Oxford: Centre for Evidence-Based Medicine, 2020, https://www.cebm.net/covid-19/coronaviruses-a-general-introduction (accessed 8 September 2020).

34. Xu X, Chen P, Wang J, *et al*. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. *Sci China Life Sci* 2020; 63: 457–460.

35. Hoffmann M, Kleine-Weber H, Schroeder S, *et al*. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020; 181: 271–280.

36. The Economist. Understanding SARS-CoV-2 and the drugs that might lessen its power. *The Economist*, 12 March 2020. https://www.economist.com/briefing/2020/03/12/understanding-sars-cov-2-and-the-drugs-that-might-lessen-its-power (accessed 7 April 2021).

37. *Guidance for industry: General principles for the development of vaccines to protect against global infectious diseases*. Rockville, MD: U.S. Food and Drug Administration, 2011.

38. Investigational new drug application (IND). 21 CFR 312 Subpart B (2020 April), https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRsearch.cfm?CFRPart=312

39. *The complex journey of a vaccine*. Geneva: International Federation of Pharmaceutical Manufacturers and Associations, 2019, https://www.ifpma.org/resource-centre/infographic-the-complex-journey-of-a-vaccine (accessed 14 October 2020).

40. Verdier F. Non-clinical vaccine safety assessment. *Toxicology* 2002; 174: 37–43.

41. *Principles of epidemiology in public health practice*. 3rd ed. Washington, DC: U.S. Department of Health and Human Services and Centers for Disease Control and Prevention (CDC), 2006, pp. 3–49.

42. Orenstein WA, Bernier RH, Dondero TJ, *et al*. Field evaluation of vaccine efficacy. *Bull World Health Organ* 1985; 63: 1055–1068.

43. *U.S. vaccine safety – Overview, history, and how it works*. Atlanta, GA: Centers for Disease Control and Prevention (CDC), 2020, https://www.cdc.gov/vaccinesafety/ensuringsafety/history/index.html

44. Beasley DWC. The vaccine development pathway. In: Milligan GN and Barrett ADT (eds) *Vaccinology: An essential guide*. 1st ed. Chichester: John Wiley & Sons, Ltd., 2015, pp. 33–42.

45. FDA Guidance for Industry. Development and licensure of vaccines to prevent COVID-19. Guidance for Industry, 2020, https://www.fda.gov/media/139638/download

46. Biologics Licensing (BLA). 21 CFR 601 Subpart C (2020 November), https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=601

47. *About VAERS*. Washington, DC: Department of Health and Human Services, https://vaers.hhs.gov/about.html (accessed 15 March 2021).

48. Lurie N, Saville M, Hatchett R, *et al*. Developing Covid-19 vaccines at pandemic speed. *N Engl J Med* 2020; 382: 1969–1973.

49. *Emergency use authorization for vaccines to prevent COVID-19: Guidance for industry*. Rockville, MD: U.S. Food and Drug Administration, 2020.

50. *Communication from the Commission: EU strategy for COVID-19 vaccines*. Brussels: European Commission, 2020.

51. Loftus P and Hopkins JS. Covid-19 vaccine developers prepare joint pledge on safety, standards. *Wall Street Journal*, 4 September 2020, https://www.wsj.com/articles/covid-19-vaccine-developers-prepare-joint-pledge-on-safety-standards-11599257729 (accessed 5 September 2020).

52. Office of the Commissioner.Emergency Use Authorization. U.S. Food and Drug Administration, 2022, https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization (accessed 11 April 2022).

53. Center for Biologics Evaluation, Research. *Emergency use authorization for vaccines explained*. Washington, DC: U.S. Food and Drug Administration, 2020, https://www.fda.gov/vaccines-blood-biologics/vaccines/emergency-use-authorization-vaccines-explained (accessed 11 April 2022).

54. Thanh Le T, Andreadakis Z, Kumar A, *et al*. The COVID-19 vaccine development landscape. *Nat Rev Drug Discov* 2020; 19: 305–306.

55. Chen WH, Strych U, Hotez PJ, *et al*. The SARS-CoV-2 vaccine pipeline: an overview. *Curr Trop Med Rep* 2020; 7: 61–64.

56. Jackson LA, Anderson EJ, Rouphael NG, *et al*. An mRNA vaccine against SARS-CoV-2 – preliminary report. *N Engl J Med* 2020; 383: 1920–1931.

57. *Draft landscape and tracker of COVID-19 candidate vaccines*. Geneva: World Health Organization, https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines (accessed 13 April 2022).

58. Krammer F. SARS-CoV-2 vaccines in development. *Nature* 2020; 586: 516–527.

59. Hopkins JS. Pfizer's COVID-19 vaccine 95% effective in final results, company to seek approval within days. *MarketWatch*, 18 November 2020, https://www.marketwatch.com/story/pfizers-covid-19-vaccine-95-effective-in-final-results-company-to-seek-approval-within-days-2020-11-18 (accessed 18 November 2020).

60. Thomas K, LaFraniere S, Weiland N, *et al*. F.D.A. clears Pfizer vaccine, and millions of doses will be shipped right away. *The New York Times*, 12 December 2020, https://www.nytimes.com/2020/12/11/health/pfizer-vaccine-authorized.html (accessed 12 December 2020).

61. *Questions and answers: COVID-19 vaccination in the EU*. Brussels: European Commission, 2021, https://ec.europa.eu/commission/presscorner/detail/en/qanda_20_2467 (accessed 21 December 2020).

62. Park A. Moderna's COVID-19 vaccine is 94.5% effective. Here's what that really means. *Time*, 17 November 2020, https://time.com/5912491/moderna-covid-19-vaccine-effectiveness (accessed 17 November 2020).

63. *FDA takes additional action in fight against COVID-19 by issuing emergency use authorization for second COVID-19 vaccine*. Rockville, MD: U.S. Food and Drug Administration, 2020, https://www.fda.gov/news-events/press-announcements/fda-takes-additional-action-fight-against-covid-19-issuing-emergency-use-authorization-second-covid (accessed 18 December 2020).

64. CDC. *Selected adverse events reported after COVID-19 vaccination*. Atlanta, GA: Centers for Disease Control and Prevention, 2022, https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fvaccines%2Fsafety%2FJJUpdate.html (accessed 11 April 2022).

65. Moghimi SM. Allergic reactions and anaphylaxis to LNP-based COVID-19 vaccines. *Mol Ther* 2021; 29: 898–900.

66. Office of the Commissioner. *FDA approves first COVID-19 vaccine*. Washington, DC: U.S. Food and Drug Administration, 2021, https://www.fda.gov/news-events/press-announcements/fda-approves-first-covid-19-vaccine (accessed 11 April 2022).

67. Naik R, Wang X, Cheung A, *et al*. Summary basis for regulatory action. Fda.gov, 2022, https://www.fda.gov/media/151733/download (accessed 11 April 2022).

68. Office of the Commissioner. *Coronavirus (COVID-19) update: FDA takes key action by approving second COVID-19 vaccine*. Washington, DC: U.S. Food and Drug Administration. 2022, https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-takes-key-action-approving-second-covid-19-vaccine (accessed 11 April 2022).

69. Center for Biologics Evaluation, Research. SPIKEVAX. U.S. Food and Drug Administration, 2022, https://www.fda.gov/vaccines-blood-biologics/spikevax (accessed 11 April 2022).

70. Center for Biologics Evaluation, Research. SPIKEVAX. U.S. Food and Drug Administration. 2022, https://www.fda.gov/media/155675/download (accessed 11 April 2022).

71. *FDA issues emergency use authorization for third COVID-19 vaccine*. Rockville, MD: U.S. Food and Drug Administration, 2021, https://www.fda.gov/news-events/press-announcements/fda-issues-emergency-use-authorization-third-covid-19-vaccine (accessed 4 March 2021).

72. Johnson & Johnson. *COVID-19 vaccine authorized by U.S.FDA for emergency use – First single-shot vaccine in fight against global pandemic*. New Brunswick, NJ: Johnson & Johnson, 2021, https://www.jnj.com/johnson-johnson-covid-19-vaccine-authorized-by-u-s-fda-for-emergency-usefirst-single-shot-vaccine-in-fight-against-global-pandemic (accessed 4 March 2021).

73. Steenhuysen J. J&J vaccine adds to COVID-19 armoury, includes South African variant. *Reuters*,

17 March 2021, https://www.reuters.com/article/us-health-coronavirus-vaccines-johnson-j-idUSKBN29Z0F0 (accessed 17 March 2021).

74. CDC. *Information about the J&J/Janssen COVID-19 vaccine*. Atlanta, GA: Centers for Disease Control and Prevention 2022, https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/janssen.html (accessed 14 April 2022).
75. Kuchler H. Moderna develops new vaccine to tackle mutant Covid strain. *Financial Times*, 25 January 2021, https://www.ft.com/content/c0c8f72c-e58e-4319-80c4-0db153ad85db (accessed 4 March 2021).
76. *Moderna announces it has shipped variant-specific vaccine candidate, mRNA-1273.351, to NIH for clinical study*. Cambridge, MA: Moderna, Inc., 2021, https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-it-has-shipped-variant-specific-vaccine (accessed 4 March 2021).
77. Dooling K, McClung N, Chamberland M, *et al.* The Advisory Committee on Immunization Practices' interim recommendation for allocating initial supplies of COVID-19 vaccine – United States, 2020. *MMWR Morb Mortal Wkly Rep* 2020; 69: 1857–1859.
78. Dooling K, Marin M, Wallace M, *et al.* The Advisory Committee on Immunization Practices' updated interim recommendation for allocation of COVID-19 vaccine – United States, December 2020. *MMWR Morb Mortal Wkly Rep* 2021; 69: 1657–1660.
79. Europe rolls out vaccines in bid to leave pandemic behind. *Reuters*, 2020, https://www.reuters.com/article/us-health-coronavirus-europe-vaccines-idUSKBN291003 (3 April 2021).
80. *Overview of COVID-19 vaccination strategies and vaccine deployment plans in the EU/EEA and the UK*. Stockholm: European Centre for Disease Prevention and Control, 2020.
81. *Joint Committee on Vaccination and Immunisation: advice on priority groups for COVID-19 vaccination, 30 December 2020*. London: Department of Health and Social Care, Government of the United Kingdom, 2021. https://www.gov.uk/government/publications/priority-groups-for-coronavirus-covid-19-vaccination-advice-from-the-jcvi-30-december-2020/joint-committee-on-vaccination-and-immunisation-advice-on-priority-groups-for-covid-19-vaccination-30-december-2020 (accessed 2 January 2021).
82. *Vaccine Development – 101*. Rockville, MD: Center for Biologics Evaluation and Research, U.S. Food and Drug Administration, 2020, https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/vaccine-development-101 (accessed 3 January 2021).
83. *Development and licensure of vaccines to prevent COVID-19: Guidance for industry*. Rockville, MD: U.S. Food and Drug Administration, 2020.
84. World Health Organization. Global Advisory Committee on Vaccine Safety, 27-28 May 2020. *Weekly Epidemiol Record* 2020; 95: 325–336.
85. *The country readiness and delivery workstream*. Geneva: World Health Organization, https://www.who.int/initiatives/act-accelerator/covax/covid-19-vaccine-country-readiness-and-delivery/act-accelerator-country-readiness-and-delivery-for-covid-19-vaccines (accessed 7 January 2021).
86. Kantarcioglu B, Iqbal O, Lewis J, *et al.* An update on the status of vaccine development for SARS-CoV-2 including variants. Practical considerations for COVID-19 special populations. *Clin Appl Thromb Hemost* 2022; 28: 1–40.
87. *Breastfeeding and caring for newborns*. Atlanta, GA: Centers for Disease Control and Prevention, 2021, https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/pregnancy-breastfeeding.html (accessed 7 January 2021).
88. Grenham A and Villafana T. Vaccine development and trials in low and lower-middle income countries: key issues, advances and future opportunities. *Hum Vaccin Immunother* 2017; 13: 2192–2199.
89. *Enhancing the diversity of clinical trial populations – eligibility criteria, enrollment practices, and trial designs: Guidance for industry*. Rockville, MD: U.S. Food and Drug Administration, 2020.
90. *Conduct of clinical trials of medical products during the COVID-19 public health emergency: Guidance for industry, investigators, and institutional review boards*. Rockville, MD: U.S. Food and Drug Administration, 2020.
91. *WHO Pharmaceuticals Newsletter No. 4*. Geneva: World Health Organization, 2020.
92. *Definition and application of terms for vaccine pharmacovigilance: Report of CIOMS/WHO working group on vaccine pharmacovigilance*. Geneva: Council for International Organizations of Medical Science (CIOMS), 2012.

93. *Global vaccine safety blueprint*. Geneva: World Health Organization, 2012.

94. *CIOMS guide to active vaccine safety surveillance: Report of CIOMS working group on vaccine safety*. Geneva: Council for International Organizations of Medical Sciences (CIOMS), 2017.

95. *Vaccine adverse event reporting system (VAERS): Vaccine safety monitoring*. Atlanta, GA: Centers for Disease Control and Prevention, 2020, https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vaers/index.html (accessed 12 March 2021).

96. Guideline on good pharmacovigilance practices (GVP) – product- or population-specific considerations I: Vaccines for prophylaxis against infectious diseases. Amsterdam: European Medicines Agency and Heads of Medicines Agencies, EMA/488220/2012 Corr, 2013.

97. Uppsala Monitoring Centre. What is a signal? https://who-umc.org/signal-work/what-is-a-signal/ (accessed 11 April 2022).

98. Shrestha S, Khatri J, Shakya S, *et al*. Adverse events related to COVID-19 vaccines: the need to strengthen pharmacovigilance monitoring systems. *Drugs Ther Perspect* 2021; 37: 376–382.

99. *About variants of the virus that causes COVID-19*. Atlanta, GA: Centers for Disease Control and Prevention, 2021, https://www.cdc.gov/coronavirus/2019-ncov/transmission/variant.html (accessed 10 March 2021).

100. Castaneda R and Vaidya M. *New SARS-CoV-2 variants push Covid-19 vaccine long-term durability questions to back seat*. London: Clinical Trials Arena, 2021, https://www.clinicaltrialsarena.com/comment/new-sars-cov-2-variants-push-covid-19-vaccine-long-term-durability (accessed 10 March 2021).

101. Moore JP. Approaches for optimal use of different COVID-19 vaccines: issues of viral variants and vaccine efficacy. *JAMA* 2021; 325: 1251–1252.

102. Wouters OJ, Shadlen KC, Salcher-Konrad M, *et al*. Challenges in ensuring global access to COVID-19 vaccines: production, affordability, allocation, and deployment. *Lancet* 2021; 397: 1023–1034.

103. Rothwell J and Desai S. *How misinformation is distorting COVID policies and behaviors*. Washington, DC: The Brookings Institution, 2020, https://www.brookings.edu/research/how-misinformation-is-distorting-covid-policies-and-behaviors (accessed 10 March 2021).

104. *Coronavirus disease (COVID-19): herd immunity, lockdowns and COVID-19*.Geneva: World Health Organization, 2020, https://www.who.int/news-room/q-a-detail/herd-immunity-lockdowns-and-covid-19 (accessed 10 March 2021).