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Review

The success of SARS-CoV-2 vaccines and challenges ahead

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SUMMARY

The rapid and remarkably successful development, manufacture, and deployment of several effective severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines is now tempered by three key challenges. First, reducing virus transmission will require prevention of asymptomatic and mild infections in addition to severe symptomatic infections. Second, the emergence of variants of concern with mutations in the S protein's receptor binding domain increases the likelihood that vaccines will have to be updated because some of these mutations render variants less optimally targeted by current vaccines. This will require coordinated global SARS-CoV-2 surveillance to link genotypes to phenotypes, potentially using the WHO's global influenza surveillance program as a guide. Third, concerns about the longevity of vaccine-induced immunity highlight the potential need for re-vaccination, depending on the extent to which the virus has been controlled and whether re-vaccination can target those at greatest risk of severe illness. Fortunately, as I discuss in this review, these challenges can be addressed.

INTRODUCTION

The World Health Organization (WHO) articulated a target product profile (TPP) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines through a consultative process (https://cdn.who.int/media/docs/default-source/blue-print/who-target-product-profiles-for-covid-19-vaccines.pdf?sfvrsn=1d5da7ca_5&download=true) that served as a guide for vaccine developers. The strategic goal WHO articulated was to develop and license vaccines for outbreak settings and/or for the long-term protection of those at high, ongoing risk of coronavirus disease 2019 (COVID-19). The preferred and minimal desired characteristics of vaccines were listed in the TPP. These key vaccine characteristics include: (1) that vaccines target all ages of a population; (2) in terms of safety and reactogenicity, that they have a highly favorable benefit/risk profile with only mild, transient adverse events; (3) that in terms of efficacy assessed versus disease, severe disease and/or shedding/transmission, vaccines produce at least 70% efficacy on a population basis, with consistent results in older adults; (4) that vaccines can be given as a single dose with yearly or less-frequent booster doses providing long term protection; (5) that protection lasts for at least one year; (6) that non-parenteral delivery routes are developed for better outbreak control; (7) that vaccines are developed as a thermostable product that can be stored at higher temperatures; and (8) that the production of multi-dose vaccines for use in vaccination campaigns can be scaled at a cost that allows their broad use, including in low- and middle-income countries.

The development, manufacture, and deployment of several SARS-CoV-2 vaccines that exceeded the TPP goals, within 12–15 months of the first reports of this novel virus, are truly remarkable achievements and a testament to scientific innovation and to public-private partnerships. The rapid and highly successful response was possible, in part, because of prior academic and industry research on related zoonotic coronaviruses that caused SARS and Middle East respiratory syndrome (MERS), and also because of investment in the development of vaccine platforms that could be rapidly deployed in response to newly recognized pathogens by organizations, such as the Coalition for Epidemic Preparedness and Innovation. Another adaptation was the conduct of vaccine evaluation in overlapping, rather than in sequential, phases and the manufacture of vaccines while clinical trials were still ongoing, despite the inherent risk that the effort and expense would be wasted if the clinical trial results did not support further development of the vaccine (Krammer, 2020; Lurie et al., 2020). Even when the COVID-19 pandemic is behind us, lessons learned from this experience will serve us well in responding to future pandemics.

The story of the success of SARS-CoV-2 vaccines and of the challenges that lie ahead is still evolving as the virus continues to circulate in much of the world and as vaccines are rolled out across nations. There are hundreds of excellent primary publications and reviews on different aspects of SARS-CoV-2; this review focuses on a selection of issues, specifically the goal of vaccines (preventing severe illness and death and reducing transmission), variants of concern and of interest and their control (including monitoring and responding to new variants), the duration of immunity (including immune memory), the need for booster doses or re-vaccination, and the potential for immunologic imprinting or original antigenic sin (where the antibody response will be preferentially directed against the first strain to which the person was exposed).

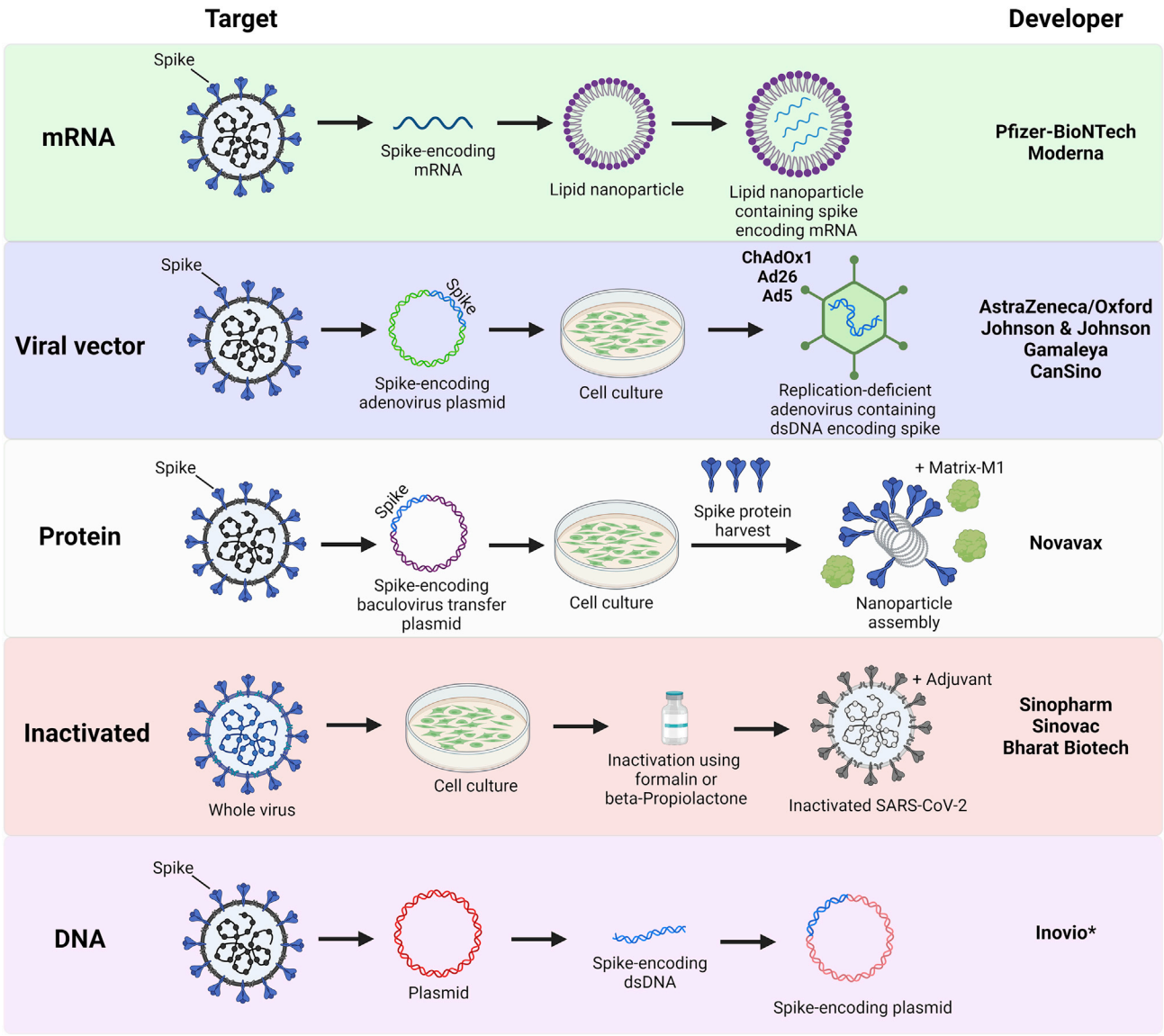

Figure 1. COVID-19 vaccine platforms
A schematic of the platforms, targets, vaccine developers, and the principles underlying different COVID-19 vaccines. The asterisk indicates a vaccine that has yet to receive emergency use authorization. Figure generated by Dr. Matthew Gartner using BioRender.

THE INITIAL FOCUS AND SUCCESS OF SARS-CoV-2 VACCINES

Vaccines based on several different platforms (Figure 1), including mRNA (Baden et al., 2021; Polack et al., 2020) and viral vectors (Logunov et al., 2021; Ramasamy et al., 2021; Sadoff et al., 2021; Voysey et al., 2021b) that express the Spike (S) protein or inactivated whole virus (Al Kaabi et al., 2021; Ella et al., 2021a; Sadoff et al., 2021; Wu et al., 2021b; Xia et al., 2021; Zhang et al., 2021), have received emergency use authorization after phase 3 clinical trials. Purified S protein vaccines are in advanced development (Keech et al., 2020). The focus on S protein as a vaccine target was based on substantial research and preclinical vaccine development for the two zoonotic coronaviruses that preceded SARS-CoV-2: SARS-CoV in 2002–2003 and MERS-CoV in 2012 (Buchholz et al., 2004; Subbarao, 2020b; Subbarao et al., 2004; Zhou et al., 2018). However, very few SARS-CoV and MERS-CoV vaccine candidates progressed to clinical trials (Folegatti et al., 2020; Koch et al., 2020; Lin et al., 2007; Martin et al., 2008; Modjarrad et al., 2019; Pallesen et al., 2017) and none were licensed for use in humans. Therefore, clinical experience with coronavirus vaccines was lacking.

The COVID-19 pandemic spread rapidly around the world, causing more than 172 million cases and 3.7 million deaths as of early June 2021 (https://covid19.who.int, accessed June 5, 2021). Infection fatality risk (IFR) has been difficult to estimate accurately because a large proportion of SARS-CoV-2 infections

are asymptomatic or mild (Oran and Topol, 2021), because cases and deaths are under-reported from areas with limited testing capacity (Mwananyanda et al., 2021), and because there is a high degree of heterogeneity in the methodology of seroprevalence studies (Chen et al., 2021) and estimates (Levin et al., 2020). A systematic review of 113 studies and a meta-analysis of 27 studies identified an exponential relationship between age and IFR for COVID-19 and placed the IFR at 1.4% at age 65, 4.6% at age 75, and 15% at age 85 (Levin et al., 2020), whereas a separate estimate from seroprevalence data placed the global IFR at 0.15%–0.2% overall, and 0.03%–0.04% in those < 70 years of age (Ioannidis, 2020; 2021). Severe illness requiring hospitalization and intensive care places a huge burden on healthcare systems. Therefore, the initial focus of the SARS-CoV-2 vaccines was to prevent symptomatic, often severe, illness. Phase 3 clinical trials for the different SARS-CoV-2 vaccines were generally powered to assess the effectiveness of the vaccines to prevent symptomatic illness (primary outcomes); the prevention of COVID-19-associated hospitalization and death were important secondary outcomes (Baden et al., 2021; Polack et al., 2020; Voysey et al., 2021a).

Vaccine manufacturers published their clinical trial protocols and announced their interim results by press release, followed in many cases by peer-reviewed publications. Table 1 summarizes the published data on primary and secondary outcomes from phase 3 clinical trials of SARS-CoV-2 vaccines (available as of early-June 2021). The details of how these outcomes were defined are important for interpreting the trial data and for comparing vaccines (Rapaka et al., 2021). Many of the SARS-CoV-2 vaccines performed exceptionally well, and all exceeded the minimal desired vaccine efficacy (VE) of 50% (https://cdn.who.int/media/docs/default-source/blue-print/who-target-product-profiles-for-covid-19-vaccines.pdf?sfvrsn=1d5da7ca_5&download=true). A range of SARS-CoV-2 vaccines have now been rolled out around the world and more will follow. Observational data from several countries indicate that the performance of the vaccines in ''real life'' is very consistent with what was reported from the phase 3 clinical trials (Table 2), demonstrating that the vaccines are effective in protecting individuals from symptomatic COVID-19, hospitalization, and death (Abu-Raddad et al., 2021; Bernal et al., 2021b; Dagan et al., 2021; Thompson et al., 2021; Vasileiou et al., 2021).

MOVING THE GOAL POSTS: PREVENTING TRANSMISSION

Although the initial focus of SARS-CoV-2 vaccines was appropriately on preventing symptomatic, often severe illness, given that vaccines that achieve this goal would reduce COVID-19 hospitalizations and deaths, attention is now shifting to whether vaccines can also reduce virus transmission. Vaccines can reduce virus transmission in three different ways: (1) some vaccines can effectively prevent mild or asymptomatic infections that can be a source of viral transmission; (2) where infection does occur in a vaccinated individual, it is plausible that the resulting viral load will remain below a threshold at which efficient person-to-person transmission occurs (Levine-Tiefenbrun et al., 2021); and (3) at a population level, current vaccines could drive the burden of infection low enough to reduce or stop community spread of the virus. That said, all available vaccines might not be equally capable of preventing virus transmission.

We now know that up to 40% of SARS-CoV-2 transmission is linked to asymptomatic or pre-symptomatic cases (Oran and Topol, 2021). Therefore, in order to reduce SARS-CoV-2 transmission, a vaccine will have to prevent asymptomatic and mild infections. This is a tall order for a few reasons. First, the cost and complexity of clinical trials are greatly increased if they include asymptomatic and mild infections as outcomes of interest because virologic samples have to be collected from asymptomatic study participants. Few clinical trials have included such analyses (Voysey et al., 2021a). Second, the modeling of neutralizing antibody titers and vaccine effectiveness data suggest that the neutralizing antibody titer that is needed to prevent severe illness is lower than that needed to prevent infection (Khoury et al., 2021). Although we do not yet know what the target titer is to prevent infection, it is estimated to be higher than the titer needed to prevent severe illness (Khoury et al., 2021). Third, we do not yet know which arm(s) of the immune system will confer protection from asymptomatic and mild infection. Experience with other respiratory viruses suggests that mucosal immune responses play an important role in controlling virus shedding and onward transmission (Wright et al., 2019). Immunoglobulin G (IgG) at mucosal surfaces can be derived by transudate from parenterally administered vaccines (Spiekermann et al., 2002), whereas secretory IgA is elicited by the local mucosal delivery of vaccines (Clements et al., 1986; Renegar and Small, 1991). Data on the ability of the currently licensed vaccines to elicit mucosal IgG to reduce transmission of SARS-CoV-2 is awaited with interest.

VARIANTS OF INTEREST AND CONCERN

The vaccines that are available now are based on the first SARS-CoV-2 genomic sequence, Wuhan-1, that was shared internationally by scientists in China (Wu et al., 2020), or they are based on genetically closely related viruses from other locations affected by the initial global spread of the virus (Corbett et al., 2020; Ella et al., 2021b; Mercado et al., 2020; van Doremalen et al., 2020; Vogel et al., 2021; Wang et al., 2020). These vaccines were developed in record time, using overlapping pre-clinical and clinical phases of development, and with the inherent risks of manufacturing vaccines while trials were ongoing (Krammer, 2020; Lurie et al., 2020). As discussed above and in Table 1, these vaccines were highly effective in clinical trials, and in observational studiesTable 2, against the prevalent circulating viruses that were genetically similar to the Wuhan-1 virus or that had an amino acid substitution D614G (Korber et al., 2020). However, over the last 4–6 months, SARS-CoV-2 variants that have additional mutations throughout their genome, and crucially in the S protein's receptor binding domain (RBD), have emerged in different parts of the world. Mutations in the RBD are of particular significance because receptor binding is a critical first step in virus infection and the vast majority (~90%) of neutralizing antibodies are directed against the RBD (Piccoli et al., 2020). Mutations that interfere with either of these functions can have a profound biological effect (Greaney et al., 2021): some RBD mutations, e.g., N501Y, enhance the virus' binding affinity for the angiotensin converting enzyme 2 (ACE2)

Table 1. Primary and secondary outcomes from interim reports of phase 3 clinical trials of SARS-CoV-2 vaccines

Vaccine	Platform	Primary outcome		Secondary outcome(s)		Comments	Reference and Clinicaltrials.gov identifier
		Definition	Vaccine efficacy/ effectiveness (95% CI)	Definition	Result (95% CI)		
Moderna mRNA1273	mRNA	RT-PCR confirmed symptomatic COVID-19 (≥2 systemic or at least 1 respiratory symptom) ≥ 14 days after dose 2	94.1 (89.3–96.8); p < 0.001	severe COVID-19 COVID-19 after 1 dose	could not be estimated 95.2 (91.2–97.4)	N = 30,420 assigned 1:1 vaccine (V): placebo (P) cases (11 V versus 185 P); severe (0 versus 30)	Baden et al., 2021; NCT04470427
Pfizer BioNTech 167b2	mRNA	RT-PCR confirmed COVID-19 with ≥1 symptom (fever, cough, shortness of breath, chills, muscle pain, loss of taste or smell, sore throat, vomiting or diarrhea)	95.0 (90.3–97.6)	severe COVID-19: confirmed COVID-19 + 1 of the following: respiratory failure, shock, acute renal, hepatic or neurologic dysfunction, ICU admission or death	not estimated	N = 43,448 assigned 1:1 vaccine (V): placebo (P) cases (8 V versus 162 P); severe (1 versus 9)	Polack et al., 2020; NCT04368728
AstraZeneca AZ1222	chimpanzee adenovirus vectored	virologically confirmed COVID-19 with at least 1 symptom (fever, cough, shortness of breath, anosmia or ageusia) ≥ 14 days after dose 2	63.1 (51.8–71.7)	COVID-19 ≥21 days after dose 1	76.0 (59.3–85.9)	Pooled interim analysis of 17,178 participants from 4 trials; cases (74 V versus 197 P); hospitalised (0 V versus 15 P)	Voysey et al., 2021b; NCT04324606, NCT04400838, and NCT04444674
Gamaleya Sputnik V	Ad5+Ad26	RT-PCR confirmed COVID-19 ≥21 days after dose 1 (the day of dose 2)	91.6 (85.6–95.2)	severe COVID-19	100 (94.4–100)	preliminary analysis on 16,427 participants	Logunov et al., 2021; NCT04530396
Janssen Ad26.COV2.S Single dose	Ad26	centrally confirmed moderate to severe-critical COVID-19	66.9 (59–73.4) ≥14 days after and 66.1 (55–74.8) ≥28 days after administration	severe-critical COVID-19	76.7 (54.6–89.1) ≥14 days after and 85.4 (54.2–96.9) ≥28 days after administration	N = 39,321 assigned 1:1 vaccine (V): placebo (P). moderate to severe-critical cases (116 V versus 348 P ≥14 days after and 66 V versus 193 P ≥28 days after administration); severe-critical cases (14 V versus 60 P ≥14 days after and 5 V and 34 P ≥28 days after administration)	Sadoff et al., 2021; NCT04505722
China National Biotec Group Company Limited WIV04 (V1) or HB02 (V2)	inactivated vaccines	laboratory-confirmed COVID-19 ≥14 days after dose 2)	V1:72.8 (58.1–82.4), p < 0.001 V2: 78.1 (64.8–86.3), p < 0.001	severe COVID-19 and/or death	only 2 cases of severe disease occurred	N = 40,382 assigned 1:1:1 vaccine 1(V1): placebo (P). cases 26 V1, 21 V2 and 95 P. participants were mainly young, healthy men	Al Kaabi et al., 2021; NCT04510207

Data are as of early June 2021.

Table 2. Vaccine effectiveness (VE) from observational studies

Vaccine	Platform	Location	# doses	Outcome	VE (%)	95% CI	Comments	Reference
Pfizer BioNTech	mRNA	Israel	1 2	documented infection symptomatic COVID-19 hospitalization severe disease documented infection symptomatic COVID-19 hospitalization severe disease	46 57 74 62 92 94 87 92	40–51 50–63 56–86 39–80 88–95 87–98 55–100 75–100	nationwide mass vaccination program; widespread circulation of the alpha (B.1.1.7) variant	Dagan et al., 2021
Pfizer BioNTech AstraZeneca	mRNA adenovirus vectored	Scotland	1	hospitalization	85 94	76–91 73–99	28–34 days after vaccination; widespread circulation of the alpha (B.1.1.7) variant	Vasileiou et al., 2021
Pfizer BioNTech AstraZeneca	mRNA adenovirus vectored	England	1 2 1	symptomatic COVID-19 symptomatic COVID-19 symptomatic COVID-19	60–70 85–90 60–75		test negative design; odds ratios at different intervals; widespread circulation of the alpha (B.1.1.7) variant	Bernal et al., 2021b
Pfizer BioNTech and Moderna	mRNA	USA		RT-PCR confirmed infection in fully immunized in partially immunized	90 80	68–97 59–90		Thompson et al., 2021
Pfizer BioNTech	mRNA	Qatar	2	test negative design: any documented infection with B.1.1.7 B.1.351 severe critical or fatal disease cohort study: B.1.1.7 B.1.351	89.5 75 97.4 87 72.1	85.9–92.3 70.5–78.9 92.2–99.5 81.8–90.7 66.4–77.8	N = 16,354; widespread circulation of the alpha and beta (B.1.1.7 and B.1.351) variants	(Abu-Raddad et al., 2021)

Data are as of early June 2021.

receptor (Tian et al., 2021); others, e.g., E484K, permit escape from neutralizing antibody (Graham et al., 2021; Jangra et al., 2021; Rees-Spear et al., 2021; Weisblum et al., 2020; Wibmer et al., 2021); and some change the shape of the S protein (Hoffmann et al., 2021).

The WHO has defined Variants of Interest (VOIs) and Variants of Concern (VOCs) (COVID-19 Weekly Epidemiological Update 25, February 2021). A SARS-CoV-2 isolate is a VOI if it is suspected to change disease severity or transmissibility; antigenicity or virulence; or if the utility of diagnostic tests, vaccines, therapeutics or public health and social measures are reduced and such variants have been identified to cause multiple COVID-19 cases or clusters in multiple countries. A VOI is a VOC if it has been demonstrated to be associated with an increase in transmissibility or with a change in COVID-19 epidemiology, such as an increase in virulence, change in clinical disease presentation, or with a decrease in the effectiveness of public health and social measures, available diagnostics, vaccines or therapeutics. VOIs and VOCs can also be designated by the WHO SARS-CoV-2 Virus Evolution Working Group (COVID-19 Weekly Epidemiological Update, 25 February 2021).

Among the VOCs, those with mutations in neutralizing antibody epitopes present the greatest challenge for vaccine effectiveness (VE) because vaccine-induced antibodies will be less effective in neutralizing the infectivity of such viruses. Data are now emerging on the ability of post-vaccination sera, obtained from recipients of currently licensed vaccines, to neutralize VOCs (Collier et al., 2021; Muik et al., 2021). For some vaccines, VOC-specific VE data are available because the VOCs emerged while phase 3 trials were being conducted and viral samples from trial participants in both the vaccine and placebo arms (Sadoff et al., 2021; Shinde et al., 2021), were sequenced. In addition, observational data from countries experiencing the widespread circulation of VOCs have also provided an estimate of VE against the variants, although these data are less precise than those obtained from phase 3 trials (Abu-Raddad et al., 2021; Dagan et al., 2021; Lumley et al., 2021; Pouwels et al., 2021; Pritchard et al., 2021; Vasileiou et al., 2021). There is also emerging evidence that current vaccines can prevent the rapid rise of some VOCs (Munitz et al., 2021) and reduce the risk of onward transmission in families (https://khub.net/documents/135939561/390853656/Impact+of+vaccination+on+household+transmission+of+SARS-COV-2+in+England.pdf/35bf4bb1-6ade-d3eb-a39e-9c9b25a8122a?t=1619551571214).

To address the complex naming convention for the variants, on the basis of lineages defined by the Global Initiative on Sharing All Influenza Data (GISAID), Pango, and Nextstrain platforms, the WHO has proposed a simplified nomenclature using the Greek alphabet, which will be updated as needed (https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/). As of early June 2021, four VOCs (alpha, beta, gamma, and delta, corresponding to B.1.1.7, B.1.351, P.1, and B.1.617.2, respectively) and six VOIs (epsilon, zeta, eta, theta, iota, and kappa, corresponding to B.1.427/B.1.429, P.2, B.1.525, P.3, B.1.526, and B.1.617.1, respectively) have been defined.

The information available to date indicates that there is only a minimal reduction in the ability of serum antibodies induced by

the Pfizer BioNTech 167b2 vaccine to neutralize the alpha (B.1.1.7) variant (Collier et al., 2021; Kuzmina et al., 2021; Muik et al., 2021; Shen et al., 2021) and a minimal reduction in vaccine effectiveness (Abu-Raddad et al., 2021). With the beta (B.351) variant, a 3-fold (Liu et al., 2021a), 6.8-fold (Kuzmina et al., 2021), and 14-fold (Planas et al., 2021) reduction in neutralizing antibody and a ~20%–40% reduction in vaccine effectiveness have been reported for the Pfizer BioNTech 167b2 vaccine (Abu-Raddad et al., 2021). For the Moderna mRNA1273 vaccine, a minimal reduction in neutralizing antibody against the alpha (B.1.1.7) variant (Wu et al., 2021a) and a 3.5 fold (Edara et al., 2021) or 6-fold (Wu et al., 2021a) reduction against the beta (B.1.351) variant has been reported. The effectiveness of the AstraZeneca AZ1222 vaccine was evaluated in South Africa when the beta (B.1.351) variant was circulating; there was only 10.4% effectiveness against mild-to-moderate disease (Madhi et al., 2021). However, the effectiveness of this vaccine in protecting from severe disease could not be evaluated because there were no cases of severe disease in the study participants. During the phase 3 study of the Janssen Ad26.COV2.S vaccine in South Africa, viruses sequenced from 94.5% of 91 cases belonged to the beta (B.1.351) lineage. The VE of the Janssen vaccine in South Africa against moderate to severe-critical COVID-19 was 52% and 73.1% against severe-critical disease, respectively. These figures were 14% and 3%, respectively, lower than the VE obtained from worldwide data collated for the phase 3 study (Sadoff et al., 2021). In a post hoc analysis, the Novavax vaccine was found to be 51% effective in protecting against infection from the beta (B.1.351) variant in HIV-negative participants and was 43% effective in the combined group of HIV-negative and HIV-positive participants in South Africa. These rates were about 6%–9% lower than the corresponding VE estimates against infection caused by non-beta and beta (B.1.351) variants altogether (49.4% in all participants and 60.1% in HIV-negative participants) (Shinde et al., 2021). These VE estimates were significantly lower than those reported (96%) in a Novavax company press release. Thus, the alpha (B.1.1.7) variant does not appear to have a significant effect on VE whereas the beta (B1.351) variant significantly reduces VE. A recent pre-print of VE estimates from a test-negative design study from the UK reported a modest reduction in VE against symptomatic COVID-19 with the delta (B.1.617.2) variant after two doses of the Pfizer BioNTech BNT162b2 mRNA vaccine (87.9%) or AZ1222 adenovirus vectored vaccine (59.8%), although VE after a single dose of either vaccine was substantially lower (33.5% and 32.9%, respectively) (Bernal et al., 2021a). These data highlight the need to protect vulnerable groups with two doses of vaccine. Data on VE against the gamma (P.1) variant are not yet available. It is possible that, as was seen against the Wuhan-1 virus, protection from severe disease caused by variants might be higher than protection from mild to moderate disease.

MONITORING AND RESPONDING TO NEW VARIANTS

At the outset of the COVID-19 vaccine development efforts, a single dominant genotype of SARS-CoV-2 was circulating globally. It was reasonable to hope that the vaccine strain would not require updating because coronaviruses have a lower mutation frequency than do many other RNA virus families, having evolved a unique protein (ExoN) that has a proof-reading function (Denison et al., 2011). However, since the last quarter of 2020, variant viruses (VOIs and VOCs) have emerged in many parts of the world as a result of the high burden of infection and the adaptation of the spike protein to human ACE2 under immune pressure (Cerutti et al., 2021; Choi et al., 2020; Kemp et al., 2021). *In vitro* data, including neutralizing antibody assays using post-infection and post-vaccination sera, and VE data from ongoing clinical trials and observational studies indicate that vaccines based on the original Wuhan-1 strain might not provide optimal protection from some variant viruses, such as the beta (B.1.351) and potentially the gamma (P.1) strains (Fontanet et al., 2021). These findings raise the very real possibility that the virus strain in COVID-19 vaccines will have to be updated. However, neutralizing antibodies induced by infection with some SARS-CoV-2 variants might be able to cross-react with other strains; antibodies induced by beta (B.1.351) variant cross-neutralized alpha (and gamma) variant viruses (Moyo-Gwete et al., 2021). It is not yet clear how often such updates will be needed in the future; decisions of this nature will have to be supported by coordinated, global virologic surveillance that must include the sequencing of viruses from breakthrough infections.

To tackle the challenge that new variants pose for global vaccination programs, we need to address four key priorities in our global response to VOCs, which should be coordinated by the WHO: (1) we need to establish programs to determine the efficacy of available vaccines against variants; (2) strategies to determine whether and when modified or new variant-specific or cross-protective vaccines are needed; (3) global action to reduce the likelihood of emergence of VOCs; and (4) coordinated international research and response to new variants (Krause et al., 2021).

The WHO has a very successful global surveillance program in place for influenza, called the Global Influenza Surveillance and Response System (GISRS), which can serve as a model for coronavirus surveillance. Among vaccine-preventable diseases, influenza is unusual in that the vaccine composition is updated annually to keep pace with antigenic drift. Under GISRS, National Influenza Centres monitor influenza viruses within their countries, share epidemiologic information with the WHO, and send representative strains or samples to one of five WHO Collaborating Centres for Influenza for further antigenic and genetic characterization and antiviral susceptibility testing. The GISRS Collaborating Centres and Essential Regulatory Laboratories review the global data, select and then recommend strains to be included in the tri- or quadrivalent seasonal influenza vaccines. These recommendations are made twice a year, in September and February, for vaccines to be used in the next winter in the southern or northern hemisphere, respectively.

Through the COVID-19 pandemic, SARS-CoV-2 genetic sequence data have been generated and shared freely and in real time on the GISAID platform, which was developed for the global sharing of influenza virus sequences. As of mid-May 2021, 1.2 million whole-genome sequences have been uploaded to GISAID. However, the distribution of sequence data on GISAID does not reflect global virus activity accurately because sequencing efforts are not uniform. The emergence of VOCs and associated second and third "waves" of disease will

Table 3. Mutations reported in VOCs

Name(s)	Alpha (B.1.1.7)	Beta (B.1.351 or 501Y.V2)	Gamma (P.1 or B.1.1.28.1)	Delta (B.1.617.2)
first identified in	UK	South Africa	Brazil	India
key RBD mutation(s)	N501Y	K417N, E484K, and N501Y	K417T, E484K, and N501Y	L452R and P681R
no. of identifying SNPs	17	8	16	9
associated (possible) phenotypes	increase in transmissibility and severity of illness	increase in transmissibility	not yet known	increase in transmissibility
effect on public health measures	interferes with some diagnostic tests	reduced effectiveness of some monoclonal antibody cocktails and vaccines	reduced effectiveness of some monoclonal antibody cocktails and vaccines	reduced effectiveness of a single dose of vaccine

Global Report Investigating Novel Coronavirus Haplotypes https://cov-lineages.org/index.html, accessed March 7, 2021; https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/variant-info.html, accessed May 11, 2021; (https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/)
Data are as of early June 2021.

reinforce the importance of sequencing the viral genome. At this time, each of the 4 VOCs designated by WHO (alpha, beta, gamma, and delta) has one or more mutations in the RBD of the S protein (Table 3). The fact that some of the same amino acid residue(s), e.g., 484 and 417, have mutated in different VOCs indicates that these residues are being selected for independently in viruses in different parts of the world in convergent evolution. This is also commonly observed in influenza viruses; the same amino acid substitution is often seen in the hemagglutinin gene of viruses isolated in disparate locations.

The critical piece in influenza virus surveillance that is not yet fully developed for SARS-CoV-2 global surveillance is the link between genotype and phenotype. The antigenic characterization of influenza viruses complements genetic sequence data and establishes which amino acid sequence changes cause significant alterations in antigenic reactivity that could warrant the updating of vaccines. Post-infection ferret antisera and post-vaccination human sera are used to identify viruses that are antigenically different from the previous vaccine strain. In typical influenza seasons, 3,000 to 6,000 viruses are antigenically characterized by the Collaborating Centres of WHO GISRS. A change in the vaccine composition is considered if an antigenic variant is responsible for disease outbreaks in disparate locations, especially in different countries. A similar approach could be used for SARS-CoV-2, with several labs sharing a panel of human monoclonal antibodies that have been mapped to different epitopes on the spike protein (Barnes et al., 2020; Dejnirattisai et al., 2021; Liu et al., 2021b; Piccoli et al., 2020; Pymm et al., 2021; Weisblum et al., 2020), as well as post-infection and post-vaccination human sera to support the antigenic characterization of circulating viruses, VOIs, and VOCs. Assays, shared reagents, and the criteria for considering whether a strain requires a COVID-19 vaccine to be updated all need to be defined.

HOW LONG WILL IMMUNITY TO SARS-CoV-2 LAST?

An important and unresolved question is how long protection from COVID-19 vaccines will last. A series of elegant studies in non-human primates have demonstrated that primary SARS-CoV-2 infection elicits neutralizing antibodies and cellular immune responses and that animals are protected from re-challenge (McMahan et al., 2021), with neutralizing antibodies correlating with protection (McMahan et al., 2021). In the absence of neutralizing antibodies, $CD8^+$ T cells confer protection. These data mirror what was learned about SARS-CoV in the early 2000s (Channappanavar et al., 2014; Chen and Subbarao, 2007). One study has also reported that neutralizing antibodies from a prior infection correlated significantly with protection from SARS-CoV-2 re-infection in an outbreak on a fishing vessel (Addetia et al., 2020). Altogether, these data support the focus on neutralizing antibody responses in patients who have recovered from COVID-19.

Several studies of the kinetics of the immune response to natural SARS-CoV-2 infection have demonstrated that antibody titers in patients who were severely ill are higher than in those who had a mild or asymptomatic infection and that antibody titers decline in all patients 3–6 months after infection (Beaudoin-Bussières et al., 2020; Crawford et al., 2021; Dan et al., 2021; Guthmiller et al., 2021; Laing et al., 2020; Legros et al., 2021; Okba et al., 2020; Seow et al., 2020; Wheatley et al., 2021; Zohar et al., 2020). The decline in antibody titers occurs in two phases: an initial rapid decline followed by a slower decay (Wheatley et al., 2021). If the initial post-infection titers are low or modest, they are undetectable a few months later, whereas an initial high titer response remains detectable even after the two-phase decline.

Immune memory involves antibodies, memory B cells, memory $CD4^+$ and memory $CD8^+$ T cells. Although studies have shown that serum antibody responses decline after vaccination or infection, SARS-CoV-2 infection has been found to establish robust, long-term humoral immune memory, and both bone marrow plasma cells and memory B cells were detected 7–9 months after infection (Turner et al., 2021). In a comprehensive study of blood samples collected 6–8 months after infection, B cell memory to SARS-CoV-2 was robust and inferred to be long lasting (Dan et al., 2021). Memory B cells increased between 1 and 8 months after infection (Dan et al., 2021). Circulating SARS-CoV-2 $CD4^+$ and $CD8^+$ memory T cells were detected at 1 month after infection in 40% and 70% of subjects, respectively, and they declined with a half-life of 3–5 months. The majority of SARS-CoV-2-specific $CD8^+$ memory cells were terminally differentiated effector memory cells (T_{EMRA}). Substantial amounts of circulating memory T follicular helper cells (cT_{FH}) were observed in the majority of COVID-19 cases at early time points, with a durability of $\geq$6 months after infection (Dan et al., 2021). At 5–8 months after infection, despite there being heterogeneity in

the pattern of immune memory, 95% of subjects studied were positive for at least three SARS-CoV-2 immune memory responses (Dan et al., 2021). Thus, robust and durable SARS-CoV-2-specific $CD4^+$ and $CD8^+$ T cell responses were detected in recovered COVID-19 cases, although their contribution to protection is not yet clear.

Because all of the currently licensed vaccines elicit immune responses to the spike protein, it is reasonable to anticipate that post-vaccination neutralizing antibody responses will follow the patterns seen in post-infection follow-up. It should be noted that the Spike protein is the only SARS-CoV-2 target in mRNA and in adenovirus-vectored vaccines, whereas additional viral proteins, such as the nucleoprotein, are present in inactivated whole-virus vaccines. Although formal proof of an immune correlate of protection in humans is not yet available, neutralizing antibody titers correlate very well with efficacy, as reported in the clinical trials of several vaccines (Khoury et al., 2021). An analysis of neutralizing antibody responses and of the efficacy of seven vaccines in convalescent cohorts has revealed that the neutralizing antibody titer for 50% protection against SARS-CoV-2 infection was 20.2% of the average titer in convalescent sera (95% confidence interval 14.4%–28.4%), and the titer for 50% protection against severe disease was 3% of the average titer in convalescent sera ($p = 0.0004$) (Khoury et al., 2021). When the decline of post-vaccination antibody titers over 250 days was modeled, a significant loss in protection from infection was predicted, but protection from severe disease was anticipated to persist (Khoury et al., 2021). Several studies are now underway to assess the longevity of vaccine-induced antibody responses against the vaccine strain and VOCs. By contrast, many other (non-COVID-19) licensed vaccines confer very long-lasting protection after vaccination in early childhood (Amanna et al., 2007; Slifka et al., 1998) that is conferred by long-lived plasma cells that produce circulating antibodies and a boost in antibody titers provided by memory B cells upon re-exposure or re-infection.

The significance of the decline in post-infection or post-vaccination SARS-CoV-2 neutralizing antibody titers for lasting protection after the pandemic ends is yet to be understood. Infections with "common cold" human coronaviruses do not confer lifelong immunity. A recent paper suggests that the Spike protein of human coronavirus 229E accumulates mutations associated with antigenic evolution (Eguia et al., 2021). On the other hand, in the absence of re-exposure, immune response to infection by the closely related SARS-CoV was detectable 11–17 years later (Le Bert et al., 2020; Liu et al., 2017).

BOOSTER VACCINATION AND IMPRINTING

Although the pandemic is still in progress, there are two reasons to consider, and plan for, booster vaccine doses or re-vaccination programs: a decline in post-vaccination antibody titers in the face of continuing, large outbreaks of disease; and the emergence of VOCs that are not well neutralized by antibodies elicited by vaccines encoding the Wuhan-1 virus Spike protein. Indeed, reports are emerging of breakthrough infections in fully vaccinated individuals; sequence analysis will reveal whether these infections are caused by variant viruses, as shown in a recent report (Hacisuleyman et al., 2021). In such cases, cross-reactive antibodies should ameliorate the severity of illness.

The strategies that are being discussed and evaluated to address these challenges include the following: the administration of an additional dose of the same vaccine to boost antibody titers, the creation of new vaccines that encode the Spike protein of a VOC, and the creation of bi-valent vaccines that include the original Wuhan-1 Spike plus the Spike of a new VOC.

These strategies raise several issues to consider, some that apply across all vaccines, others that are vaccine platform specific or specific to new VOC vaccines. A question that is relevant to all vaccines concerns who should be re-vaccinated and when. This will be a public health decision guided by a number of factors, including the risk of infection, the population at greatest risk of severe illness (or infection), neutralizing antibody titers in the population, the availability of vaccines, and data on what can be achieved by re-vaccination.

Although re-infections have been reported, symptomatic re-infections in previously infected individuals occur at a lower rate than primary infections (Dimeglio et al., 2021; Leidi et al., 2021), consistent with the demonstration of immune memory after infection (Dan et al., 2021; Turner et al., 2021). In a study of young, healthy US Marines, seropositive individuals had about one-fifth the risk of re-infection and 10-fold reduced viral loads compared with seronegative individuals (Letizia et al., 2021). Re-infection in seropositive individuals was more likely to occur when lower amounts of baseline SARS-CoV-2 antibody were observed (Letizia et al., 2021). Recent studies have demonstrated that a single dose of mRNA vaccine in previously infected seropositive individuals enhanced both T and B cell responses (Reynolds et al., 2021) and boosted antibody titers by up to 1,000-fold (Stamatatos et al., 2021) or to levels similar to those achieved after two doses of vaccine in seronegative individuals. These findings indicate that a single dose of vaccine can boost immunity in primed populations (Krammer et al., 2021; Saadat et al., 2021).

However, vaccine-platform-specific concerns have been identified, such as whether vector immunity will limit the immunogenicity of subsequent doses of adenovirus-vectored vaccines, and whether the adverse events associated with booster doses of mRNA vaccines will limit their acceptance. Another issue concerns individuals who have been immunized with a Wuhan-1 vaccine and what their immune response will be to a vaccine that targets a new VOC, because of the concept of immunologic imprinting or original antigenic sin. This phenomenon has been well-described in the context of influenza, and is seen when an individual who has had a prior infection or vaccination is infected or vaccinated with a new strain: their antibody response will be preferentially directed against the original, infecting strain. This occurs because antibodies to epitopes that are conserved between the original and new strains are recalled at the expense of new antibodies generated against epitopes that are unique to the new strain. With influenza vaccines, the consequences of imprinting depend on the extent of diversity between the antigens. Whether this will happen with COVID-19 vaccines, and the effect it might have on the antibody response to VOCs, remain to be seen and will require antigenic characterization of viruses. Studies can be conducted in animal models and in clinical trials to address this question.

In practical terms, will the neutralizing antibody titer to a new VOC vaccine be lower in people (or animals) who have previously received a Wuhan-1 vaccine than in previously unvaccinated people (or animals)?

THE PATH(S) FORWARD

In the 16 months since the world was first notified about the emergence of SARS-CoV-2, progress in understanding the biology of, and our immune response to, the virus, and in the development, evaluation, and deployment of vaccines, has been unprecedented. However, the scientific and public health community and the public have also had to adjust to new information, such as rare but consequential adverse events associated with some vaccines and the emergence of variant viruses (reviewed in Andreano and Rappuoli, 2021). It is clear that variant viruses with antigenic changes can emerge simultaneously in several locations and spread. Therefore, unlike measles (for which the same vaccine strain has been effective for 50 years), the possibility that SARS-CoV-2 vaccines will need to be updated is being considered. Time will tell whether SARS-CoV-2 vaccines will require occasional updates or annual updates, as are needed for influenza. It is possible that vaccine updates will be needed only until the pandemic is brought under control, although we don't yet know what the post-pandemic epidemiologic pattern of SARS-CoV-2 will be. If SARS-CoV-2 settles into a pattern of seasonal or sporadic infections, in which most infections are mild and a small proportion are severe and require hospitalization, one can envision a targeted vaccination program to protect those at greatest risk of severe illness. The availability of effective treatments for severe COVID-19 will also be very important for the management of post-pandemic SARS-CoV-2 (Neuzil, 2021).

The COVID-19 pandemic has revealed massive inequities in health care and in vaccine access that must be confronted to ensure health for all (Fontanet et al., 2021; Koff et al., 2021; Subbarao, 2020a; Wouters et al., 2021), but these topics are beyond the scope of this review. At the request of the World Health Assembly, the WHO appointed an Independent Panel for Pandemic Preparedness and Response. Their review entitled "COVID-19: Make it the last pandemic" commends the rapid development of effective vaccines but calls for the more equitable and strategic distribution of vaccines to curtail the pandemic (Sirleaf and Clark, 2021).

Although the roll-out of effective vaccines can bring an end to the COVID-19 pandemic, SARS-CoV-2 will likely become endemic. Important adjuncts to vaccines are the awareness that SARS-CoV-2 spreads efficiently by aerosol in closed spaces, the use of public health measures, and effective therapeutics against SARS-CoV-2 and against other zoonotic coronaviruses that could emerge to cause future outbreaks or pandemics.

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