SARS-CoV-2 Vaccines: Where Are We Now?

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The best and safest way to control the coronavirus disease 2019 (COVID-19) pandemic is by using vaccination to generate widespread immunity. The urgent need to develop safe and effective COVID-19 vaccines was met with unprecedented speed and action from the global community. There are now 289 vaccines in development pipeline. More remarkably, there are 20 publicly available vaccines, and more than 3.3 billion doses of COVID-19 vaccines have been administered across 180 countries. This is just the beginning of our fight against the pandemic. Even at the current vaccination rate, it could take years to vaccinate the world’s population; many high-income countries are focusing on their needs, whereas the poorer nations are waiting for vaccines. There is still much that we do not understand about immunity to this new disease, and we will have to contend with the emerging variants. In

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this commentary, we describe the current status of COVID-19 vaccine development and provide insights into how the development and approvals happened so quickly. We discuss the clinical trial data that led to rapid emergency use authorization and the many challenges of global rollout. We also comment on some of the key unanswered questions and future directions for COVID-19 vaccine development and deployment. © 2021 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2021;9:3535-43)

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As the world acknowledged that it was facing a pandemic, the urgent need to develop safe and effective coronavirus disease 2019 (COVID-19) vaccines became paramount. This led to remarkable and unprecedented action from the global scientific and regulatory community in the development of multiple COVID-19 vaccines. Herein, we discuss the current status of global COVID-19 vaccine development and regulatory pipelines, the emerging and efficacy and effectiveness data, the logistics and challenges of global rollout, and future challenges.

COVID-19 VACCINE PLATFORMS AND MECHANISMS OF ACTION

As of July 8, 2021, there are 184 COVID-19 vaccine candidates in preclinical development and 105 in human clinical trials (Table I). The platform technologies being developed range from the traditional, such as whole live-attenuated and inactivated virus, protein subunit vaccines and virus-like particles (VLPs), through to novel technologies never before used for licensed human vaccines, including nucleic acid (mRNA, DNA), replicating and nonreplicating viral and bacterial vectors, and modified antigen presenting cells and T cells (Figure 1, Table I). Protein subunit vaccines are the most common approach representing one-third of candidates, but viral vectors, nucleic acid, inactivated virus, and VLP approaches are all well represented among those in clinical trials (Table I). The majority in clinical trials (65%) require a 2-dose schedule (ranging from 2 to 12 weeks apart) and are given via the intramuscular route (76%). The single-dose (14%), intranasal (7%), and oral (3%) vaccine candidates are particularly exciting developments from a logistic point of view.

All candidates currently in clinical trials are designed to elicit an immune response to the spike protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is the surface molecule responsible for binding of virus to the human host-cell angiotensin-converting enzyme 2 receptor. However, some emerging candidates are based on other viral proteins such as membrane and nucleoprotein. Although no immunological correlate of protection against SARS-CoV-2 has yet been identified, the major focus has been on the induction of neutralizing antibodies to spike protein that likely play a major protective role. Various T-cell subsets are thought to be important for controlling disease progress rather than preventing infection. These include CD8+ cytotoxic T cells to kill virally infected cells, proinflammatory T helper (Th)1 and Th17 T cells, CD4+ follicular helper and Th2 T cells that provide help for antibody production, and anti-inflammatory regulatory T cells.

EXISTING VACCINE TECHNOLOGIES

There are pros and cons to each of the platforms for vaccine development (Table II). The traditional methods are all tried and tested using well-established technology and regulatory pipelines. Live-attenuated viral vaccines are the most long-standing methodology in which the virus is modified so as not to elicit virus-associated disease, but still cause an attenuated form of the disease. They are highly immunogenic and many require only a single dose to elicit long-lasting broad immunity. Drawbacks include the fact that they can cause disseminated disease in those with immunocompromise and are often contraindicated for use in pregnancy (Table II). Inactivated COVID-19 vaccines are made by β-propiolactone inactivation and combined with an aluminum hydroxide or alternative adjuvant. They elicit broad immunity to a range of viral proteins and can be used in the immunocompromised and pregnant women. However, they are less immunogenic than live-attenuated vaccines and require more than 1 dose for adequate immunity (Table II).

Protein and peptide subunit vaccines use either whole protein or specific regions of the protein containing key B- and T-cell epitopes combined with adjuvant that are taken up by antigen presenting cells (APCs), and processed and presented to B cells and T cells. They are relatively stable and highly safe vaccines. The protein conformation is essential to ensure that the correct epitopes are recognized. Peptide-based vaccines have the disadvantage of being human leukocyte antigen (HLA) restricted, which could compromise their suitability across HLA diverse populations (Table II).

VLP vaccines, such as the human papilloma virus vaccine, use an expression system to produce protein that self-assembles into particles that are injected and taken up by APCs, and processed and presented to B cells and T cells to elicit an immune response. The speed, ease, and cost of manufacturing these vaccines depend on the expression system used. They are highly immunogenic and safe, but the proteins often require considerable purification and the particles can be unstable; thus large-scale production can be challenging (Table II).
**NOVEL VACCINE TECHNOLOGIES**

The most prominent novel platforms are the viral vector and nucleic acid vaccines. Vectors are used as a vehicle to deliver the gene of interest into the host nucleus where it uses host machinery to be transcribed and expressed to stimulate an immune response. The genetic material delivered by the viral vector is not incorporated into the host DNA. The viral vector vaccines can be either nonreplicating (replication-deficient) or replicating, thus mimicking natural infection. The most popular nonreplicating viral vector used for COVID-19 vaccines is adenovirus, usually human adenoviruses, although the AstraZeneca vaccine uses a chimpanzee adenovirus (ChAd). Other nonreplicating vectors in COVID-19 vaccine development include Modified Vaccinia Ankara and influenza virus. The replicating viral vectors, for example, influenza virus and vesicular stomatitis virus, produce new viral particles in the human cells they infect, which then infect new cells that will make the vaccine antigen. Replicating and nonreplicating bacterial vectors are also being developed for COVID-19 vaccines using much the same concepts as viral vector vaccines.

The mRNA vaccines, in development for over a decade, transport RNA packaged in nanoparticles into the cellular cytoplasm where it takes over the host machinery to make the encoded protein target. They can either be nonreplicating or self-amplifying, the latter of which carry the genetic code to allow intracellular RNA replication. DNA vaccines deliver DNA into the cell where it is transcribed into RNA leading to protein expression. The DNA can either be delivered as a naked plasmid or used to coat nanoparticles such as gold particles that are taken up by APCs.

Cell-based vaccination involves administering genetically modified T cells or APCs to stimulate an immune response against the target. For example, a synthetic minigene encoding multiple SARS-CoV-2 proteins has been inserted into dendritic cells (DCs) in one approach, and another uses autologous DCs loaded with SARS-CoV-2 antigens. Modified APCs are being tested in combination with viral vector vaccines in several ongoing clinical trials. This approach is expensive and low-yield and therefore is not practical for large-scale manufacture and deployment (Table II).

**EFFICACY FROM CLINICAL TRIALS**

It is remarkable that a little over 12 months after the declaration of the pandemic by the World Health Organization (WHO), phase 3 efficacy results are published or in press-release for a number of vaccines. Nineteen vaccines have regulatory approval (most preliminary or emergency use only) at country level and are publicly available (Table III), and more than 3 billion doses of COVID-19 vaccines have been administered globally. International licensing requirements included data from ≥1 well-designed phase 3 clinical trial demonstrating an efficacy of ≥50% versus placebo with a confidence interval (CI) lower bound of ≥30%, and sufficient COVID-19 infections to assess efficacy and the potential safety signal of vaccine enhanced respiratory disease. It is important to note that some of the candidates, despite being used in some countries, have not met these requirements.

**PHASE 3 CLINICAL TRIAL EFFICACY RESULTS**

**RNA vaccines**

Two mRNA vaccines targeting COVID-19 (BNT162b2, Pfizer and mRNA-1273, Moderna) were brought from bench to completed clinical trials and marketing approval by December 2020—truly an example of vaccine development at "pandemic speed." The BNT162b2 trial included over 43,000 participants ≥16 years who received 2 doses of vaccine or placebo 21 days apart. Vaccine efficacy was remarkably high, with 95.0% protection (95% CI: 90.3%-97.6%) against symptomatic virologically confirmed COVID-19 at least 7 days after the second dose (Table III). Importantly, efficacy was equivalent by age, body mass index, and coexisting conditions. The mRNA-1273 trial included around 30,000 participants ≥18 years who received vaccine or placebo in 2 doses 28 days apart and demonstrated a similar efficacy of 94.1% (95% CI: 89.3%-96.8%) (Table III). The number of cases of severe disease was low in the mRNA vaccine trials but nevertheless supported good protective efficacy, with 1 severe case in BNT162b2 recipients versus 9 in placebo recipients and zero cases in mRNA-1273 recipients as compared with 30 in the placebo group. Efficacy was not reported for the small number of subjects with stable HIV infection enrolled in the BNT162b2 trial. In vitro studies...
demonstrate that the Pfizer vaccine–induced antibodies have decreased ability to neutralize the South African beta (B.1.351) variant of SARS-CoV-2 but retained capacity to neutralize the UK alpha (B.1.1.7) and Brazilian gamma (P.1) variants of concern (VOC) and the newly emergent Indian delta (B.1.167.2) VOC and kappa (B.1.167.1) variant of interest. Encouragingly, a recent study in Qatar showed 89.5% (95% CI: 85.9-92.3) and 75% (95% CI: 70.5-78.9) protection against documented infection with alpha and beta strains, respectively, after 2 doses of the Pfizer vaccine. Protection against severe, critical, or fatal disease with any strain was 97.4% (95% CI: 92.2-99.5). A UK study found 93.4% (95% CI: 90.4-95.5) protection against symptomatic alpha strain infection after 2 doses of BNT162b1 and 87.9% (95% CI: 78.2-93.2) protection against the delta strain. Two doses of mRNA-1273 elicited cross-reactive nAb responses to alpha, beta, epsilon, and iota variants that persisted for 6 months.

**Viral vector vaccines**

The ChAdOx1 vaccine, manufactured by AstraZeneca, was the first COVID-19 candidate to commence clinical trials in April 2020. Preliminary results of trials in Brazil and the United Kingdom enrolling almost 12,000 subjects ≥18 years showed an efficacy of 70.4% (95% CI: 54.8-80.6) against symptomatic infection 14 days after dose 2. Further combined analysis of 4 clinical trials involving almost 25,000 people showed that the efficacy increased with the greater dosing interval from 55.1% (95% CI: 33.0-69.9) with an interval of <6 weeks to 81.3% (95% CI: 60.3-91.2) with an interval of 12 weeks. The AstraZeneca vaccine had well-maintained efficacy against the alpha UK variant (74.6% efficacy against polymerase chain reaction [PCR]-positive infection 14 days after dose 2) but provided only minimal protection of 10.9% (95% CI: −76.8 to 54.8) against mild-to-moderate infection with the B.1.135 South African variant in HIV-negative subjects. The small cohort of HIV-positive individuals enrolled in the South African study was not included in interim efficacy analyses. Protection against moderate-severe disease, hospitalization, or death could also not be assessed in this study because of the relatively small size (n = 2026) and younger age (average 31 years) of the cohort. In another UK study, 2 doses of AstraZeneca vaccine provided 66.1% (95% CI: 54-75) protection against symptomatic infection.
infection with the alpha variant and 59.8% (95% CI: 28.9-77.3) protection against the delta variant. Of note, a single dose of AstraZeneca provided only 32.9% (95% CI: 19.3-44.3) protection against the delta variant in this study, highlighting the importance of completing 2 doses. Encouragingly, protection against hospitalization was 86% (95% CI: 53-96) against the alpha strain and 92% (95% CI: 75-97) against the delta variant after 2 doses, and even 1 dose provided >70% protection against both variants.

Three other human adenoviral vector COVID-19 vaccines have reported efficacy results. The Russian Gamaleya Institute adenoviral (Ad)26/Ad5 prime-boost vaccine trial including approximately 22,000 participants assigned 2:1 vaccine and placebo with 21 days between doses reported an efficacy of 91.6% (95% CI: 85.6%-95.2%) from day 21, the day dose 2 was administered (Table III); however, concerns have been raised over lack of transparency and data discrepancies in this trial. The Janssen Ad26 viral vector vaccine (Ad26.COV2.S) recently reported their multicountry trial including almost 45,000 participants using a 1-dose schedule. Importantly, almost 20,000 were ≥60 years and SARS-CoV-2 variant strains were circulating in South Africa and Brazil during the trial. Efficacy from 14 days against moderate-to-severe disease was 66.9% (95% CI: 59.0-73.4) but when restricted to severe/critical disease with onset ≥28 days increased to 85.4% (95% CI: 54.2-96.9) and was similar for the ancestral and variant strains.

### Table II. Pros and cons of the most common COVID-19 vaccine platforms in development

| Vaccine platform mechanism of action | Pros | Cons |
|--------------------------------------|------|------|
| Protein/peptide subunit              |      |      |
| Protein/peptide + adjuvant taken up by APC to stimulate an immune response | Traditional methodology with well-tested regulatory pipeline, Relatively stable, Good safety profile and often fewer AEs, Cheap and easy to produce | Not very immunogenic, Require adjuvant and multiple doses, Protein conformation critical, Peptide vaccines are HLA-restricted |
| IV                                   |      |      |
| Whole virus or parts of virus + adjuvant taken up by APC to stimulate an immune response | Traditional methodology with well-tested regulatory pipeline, Good safety profile, Strong Ab response | Not very immunogenic, Require adjuvant and multiple doses |
| LAV                                  |      |      |
| Elicits a mild form of the disease but attenuated so as to not cause full-blown infection | Traditional methodology with well-tested regulatory pipeline, Highly immunogenic providing long-lasting immunity from a single dose | Take a long time to make and handling safety concerns, Cannot be used in pregnancy or the immunocompromised, The attenuated virus may revert to wild-type |
| VLP                                  |      |      |
| Constructed from the protein of interest using an expression system that self-assembles into particles that are taken up by APC to stimulate an immune response | Relatively easy and rapid to make and scale up, Highly immunogenic, Considered safe vaccines | Often unstable, Purification necessary, Large-scale production can be challenging |
| DNA                                  |      |      |
| DNA encoding the antigen of interest (either naked or coating particles such as gold particles) enters the host-cell nucleus and uses cell machinery to transcribe and express the protein leading to an immune response | Relatively easy and rapid to make and scale up, Considered safe vaccines | Often require special delivery devices to gain cell entry, eg, gene gun, electroporation device, Not very immunogenic, Usually require an adjuvant and multiple doses, Long-term DNA persistence and theoretical risk of integration into host DNA |
| mRNA                                 |      |      |
| mRNA encoding the antigen of interest packaged in lipid or other nanoparticles enters cytoplasm and uses cell machinery to transcribe and express the protein leading to an immune response | Relatively easy and rapid to make and scale up, Highly immunogenic (both antibodies and T cells), Robust innate immune response, Considered safe vaccines | RNA highly unstable and often require ultracold temperature storage and transport, High reactivity profile (particularly due to stimulation of innate defenses) |
| nRVV                                 |      |      |
| Use a replication-deficient viral vector to transport the gene of interest into the cell leading to transcription and immune response | Versatile platform with multiple vector options, Highly immunogenic (Abs and T cells), Single dose sometimes adequate, Considered safe vaccines, Can be delivered orally and intranasally | Complex manufacturing process takes time to scale-up production, Anti-vector immunity from prior exposure can hamper the immune response, Considered GMOs that may harm human/environment |
| rRVV                                 |      |      |
| As for nRVV but produce new viral particles in the human cells that they infect, which infect new cells | Versatile platform with multiple vector options, Highly immunogenic (Abs and T cells), Single dose sometimes adequate, Considered safe vaccines, Can be delivered orally and intranasally | Complex manufacturing process takes time to scale-up production, Cannot be used in pregnant/immunocompromised, May revert to wild-type, Anti-vector immunity from prior exposure can hamper the immune response, Considered GMOs |

*Ab*, Antibody; *AE*, adverse event; *APC*, antigen presenting cell; *GMO*, genetically modified organism; *HLA*, human leukocyte antigen; *IV*, inactivated virus; *LAV*, live-attenuated virus; *nRVV*, nonreplicating viral vector; *rRVV*, replicating viral vector; *VLP*, virus-like particle.
Of note, this primary endpoint differs from the other 2 adeno-virus vaccines, which used symptomatic infection as the primary endpoint. An Ad5 vaccine, manufactured by CanSino in China, has reported phase 2 results\(^7\)\(^9\) and has unpublished claims of 65.7% efficacy ≥14 days after dose 1, justifying provisional authorization for use in China (Table III).

### Protein vaccines

The US manufacturer Novavax candidate is based on the prefusion spike protein using nanoparticle technology and a saponin-based Matrix-M adjuvant. More than 15,000 participants were enrolled in a UK trial, including 27.9% ≥65 years, demonstrating an efficacy of 89.7% (95% CI: 80.2-94.6) against PCR-confirmed symptomatic COVID-19 7 days after dose 2.\(^{11}\) Efficacy in South Africa, among 4400 enrolled, was 60.1% (95% CI: 19.9-80.1) for COVID-19 of any severity after dose 2 among HIV-negative participants in which 93% of cases were due to the beta variant strain. Efficacy declined to 49.4% (95% CI: 6.1-72.8) when HIV-negative and HIV-positive participants were included.\(^{28}\)

Four other protein-based vaccines are licensed for human use despite a lack of published phase 3 efficacy data. These are Anhui’s ZF2001 vaccine called ZIFIVAX, which is licensed in China and Uzbekistan; 2 vaccines developed and licensed in Cuba called Abdala (or CIGB-66) and Soberana 02 (or FINLAY-FR-2); and Russia’s EpiVacCorona peptide-based vaccine licensed in Russia, Belarus, and Turkmenistan.

### Whole inactivated virus vaccines

Two Chinese vaccines based on whole inactivated SARS-CoV-2 have market authorization. A phase 3 trial of the Sinovac candidate called CoronaVac conducted in 12,396 Brazilian health care workers, where the gamma variant was dominant at the time, showed an efficacy of 50.7% (95% CI: 36.0-62.0) against symptomatic COVID-19 and 83.7% (95% CI: 58.0-93.7) efficacy for cases with severity score ≥3 with all 6 severe cases in the placebo group.\(^{14}\) Phase 3 trials in Turkey and Indonesia reported 84% (95% CI: 65-92) and 65% (95% CI: 20-85) efficacy against symptomatic COVID-19, respectively. As of late June, more than 600 million individuals have been vaccinated with CoronaVac. Sinopharm has developed 2 inactivated COVID-19 vaccines called BBIBP-CorV (developed by the Beijing Institute of Biological Products) and WIBP-CoV (developed by the Wuhan Institute of Biological Products). A large multicountry phase 3 trial of BBIBP-CorV showed that it provided 78.1% (96% CI: 64.8-86.3) protection against symptomatic infection from 14 days after dose 2 and 79% protection against hospitalization as compared with an aluminum hydroxide—only control.\(^{13}\) It has full approval for use in China, Bahrain, and the United Arab Emirates (UAE), and more than 200 million doses have been supplied. The UAE program has largely relied on BBIBP-CorV, but a recent spike in COVID-19 cases led to the decision to offer Pfizer vaccine boosters 6 months after the 2 doses of BBIBP-CorV. WIBP-CoV is licensed in China and the UAE, and the same multicountry trial as discussed

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**Table III.** Preliminary efficacy results from phase 3 trials and approval status of the 9 frontrunner COVID-19 vaccines

| Manufacturer | Platform | No. of doses | 1 Efficacy endpoint (reference in superscript where applicable) | Efficacy % (95% CI) | Approval status |
|--------------|----------|--------------|---------------------------------------------------------------|---------------------|-----------------|
| Pfizer       | mRNA     | 2 doses      | PCR+ symptomatic COVID-19 ≥7 days after dose 2\(^1\)\(^{11}\) | 95 (90.3-97.6)      | Approved in 113 countries |
| Moderna mRNA-1273 | mRNA     | 2 doses      | Symptomatic COVID-19 ≥14 days after dose 2\(^8\) | 94.1 (89.3-96.8) | Approved in 77 countries |
| AstraZeneca  | nrVV     | 2 doses      | PCR+ symptomatic COVID-19 ≥15 days after dose 2\(^9\) | 54.9 (32.7-69.7)\(^+\) | Approved in 172 countries |
| Janssen Ad26.COV2.S | nrVV     | 1 dose       | Moderate or severe COVID-19 ≥14 days after dose 1\(^1\)\(^{10}\) | 66.9 (59-73.4) | Approved in 79 countries |
| Gamaleya     | nrVV     | 2 doses      | PCR+ COVID-19 ≥21 days after dose 1\(^{11}\) | 91.6 (85.6-92.2) | Approved in 74 countries |
| CanSino      | nrVV     | 1 dose       | Symptomatic COVID-19 ≥14 days after dose 1 | 65.7\(^+\)\(^\dagger\) | Approved in 9 countries |
| Novavax NVX-CoV-2373 | Protein | 2 doses      | PCR+ symptomatic COVID-19 ≥7 days after dose 2\(^1\)\(^{12}\) | 89.7 (80.2-94.6) | Not approved |
| Sinopharm    | IV       | 2 doses      | Symptomatic COVID-19 ≥14 days after dose 2\(^1\)\(^{13}\) | 78.1 (64.8-86.3) | Approved in 77 countries |
| BBIBP-CorV   | IV       | 2 doses      | PCR+ symptomatic COVID-19 ≥14 days after dose 2\(^1\)\(^{14}\) | 50-7 (36-0-62-0)\(^\dagger\) | Approved 49 countries |
| NovacV       | IV       | 2 doses      | Symptomatic COVID-19 ≥14 days after dose 2\(^1\)\(^{14}\) | 50-7 (36-0-62-0)\(^\dagger\) | Approved 49 countries |

Ad, Adenovirus; ChAd, chimpanzee adenovirus; IV, inactivated vaccine; nrVV, nonreplicating viral vector; PCR-, SARS-CoV-2 detected on nasopharyngeal swab by polymerase chain reaction.

Only leading COVID-19 vaccine candidates with published phase 3 trial results are listed here. There are 20 vaccines with regulatory approval (most provisional or emergency use only) in at least 1 country but not all have released phase 3 trial results. Approved vaccines not listed in the table include 7 inactivated virus vaccines (Sinopharm Wuhan’s WIBP-CorV licensed in 5 countries including China; Minhai Biotechnology’s vaccine approved in China; Chinese Academy of Medical Sciences Vaccine approved in China; Bharat Biotech’s BBV152 [called Covaxin] approved in 20 countries; Russian Academy of Sciences Covivac [KovIvac] approved in Russia; Kazakhstan RBSP’s QozCovid-1 [called QazVac] approved in Kazakhstan; Shifa Pharmd Industrial Co’s COVIran Barakat approved in Iran) and 4 protein-based vaccines (Anhui’s ZF2001 [called ZIFIVAX] approved in China and Uzbekistan; Cuba’s CIGB-66 [called Abdala] licensed in Cuba and Venezuela; Instituto Finlay de Vacunas’ FINLAY-FR-2 [called Soberana 02] approved in Cuba and Iran; and Russia’s EpiVacCorona peptide-based vaccine approved in Russia, Belarus, and Turkmenistan). The Novavax protein-based vaccine is a leading candidate but has not yet been granted approval for use in any country.

*Efficacy depends on dosing interval with greater efficacy with increasing interval—4-week (above) and 12-week (below) dosing results shown.
†Results unpublished and figures based on media reports from trials in various countries.
above found 72.8% (95% CI: 58.1-82.4) efficacy against symptomatic infection and 100% against severe disease for BBIBP-CorV and WIBP-CorV combined.13

Another four inactivated vaccines are being deployed at a country-wide level, despite the fact that phase 3 efficacy data have not been released. These are Bharat Biotech’s BBV152 vaccine called Covaxin licensed in 20 countries, QazCovid-in or QazVac developed and licensed in Kazakhstan, Chinese Academy of Medical Sciences COVID-19 Vaccine licensed in China, and Covivac approved in Russia.

IMPACT ON DISEASE TRANSMISSION AND REAL-WORLD EFFECTIVENESS DATA

Emerging real-world data show impressive effectiveness of COVID-19 vaccines against symptomatic infection, hospitalization, and death from COVID-19. A Scottish prospective study in 5.4 million people, in which just over 1.3 million had received their first dose, showed 88% (95% CI: 75-94) protection for the AstraZeneca vaccine and 91% (95% CI: 85-94) protection for the Pfizer vaccine against hospitalization 28 to 34 days after vaccination.27 A large UK case-control study involving >7.5 million adults aged ≥70 years showed 73% (95% CI: 60-81) effectiveness against hospitalization >28 days after 1 dose of the AstraZeneca vaccine and 93% (95% CI: 89-95) 7 days after 2 doses of the Pfizer vaccine in those ≥80 years.30 The corresponding effectiveness estimates in the 70- to 79-year age group was 84% (95% CI: 74-89) 28 days after 1 dose of AstraZeneca and 81% (95% CI: 73-87) for Pfizer. A US study showed 88.7% (95% CI: 68.4-97.1) effectiveness in reducing infection at least 36 days after receiving dose 1 of either Pfizer or Moderna vaccines, and another US study estimated 94% (95% CI: 49-99) effectiveness against hospitalization among those ≥65 years after full vaccination with Moderna or Pfizer vaccines.31 The Israeli real-world data similarly show high levels of protection ≥7 days after 2 doses of Pfizer vaccine against asymptomatic infection of 92%, symptomatic infection of 94% (95% CI: 87-98), hospitalization of 87% (95% CI: 55-100), and severe disease of 92% (95% CI: 75-100).32 Post-licensure studies also show reduced severity of infection in突破性 cases, including against delta variant infection, among vaccinated individuals.33

A number of studies have shown that COVID-19 vaccines reduce asymptomatic infection and thus the likelihood of disease transmission. Two doses of the Pfizer vaccine provide efficacy against asymptomatic infection of >85% in several studies,32,34 whereas the AstraZeneca vaccine seems less effective, for example, 22.8% (95% CI: −63.3 to 63.5) for a 12-week dosing interval.23 Other studies similarly report reduced asymptomatic infection after immunization with mRNA-based vaccines of 80% (95% CI: 63-88) in patients undergoing preprocedural screening28 and 4-fold reduction among UK health care workers who had received a single dose of BNT162b2 more than 12 days prior.36 A UK study investigating onward transmission to household contacts of Pfizer or AstraZeneca vaccinated health care workers with breakthrough infections compared with transmission from unvaccinated individuals suggested a 30% (95% CI: 22-37) reduction in transmission.37 This may equate to around 60% transmission reduction because approximately half of the infections were likely acquired outside of the household; however, the relative effects of the 2 vaccines in this study cannot be determined. An Israeli study showed that rates of adult vaccination with BNT162b2 were associated with a subsequent decline in COVID-19 rates among unvaccinated children <16 years of age, supporting an effect on transmission.38 There are currently no data available regarding the impact on transmission for other COVID-19 vaccines.

RAPID REGULATORY APPROVAL PATHWAYS FOR COVID-19 VACCINES

International regulatory bodies played a pivotal role in the SARS-CoV-2 pandemic response through oversight and facilitation of clinical studies leading to emergency use authorization (EUA).39 The US Food and Drug Administration (FDA) can issue an EUA in the absence of adequate, approved, available alternatives.40 Unprecedented collaboration and transparency between regulatory bodies, clinical investigators, and industry led to monumental shortening of the typical 10- to 15-year vaccine development and review cycle without compromising long-standing standards for new vaccine development.41 Government pre-purchase contracts provided the important vaccine development and manufacturing incentives, whereas regulatory bodies opened unprecedented lines of communication, progressing a model of rolling reviews to facilitate actionable data.42

The United Kingdom’s Medicines and Healthcare products Regulatory Agency was the first to authorize the emergency use of a COVID-19 vaccine on December 8, 2020. The FDA approved its first EUA 3 days later. Clear FDA issued guidance for industry contributed to the design of pivotal clinical trials. Specific and regularly updated guidance sets expectations for comprehensive safety and efficacy data to support a favorable benefit-risk assessment, data demonstrating manufacturing quality and consistency, and plans for ongoing vaccine safety and efficacy.40 The October 2020 update set a minimum of 2 months of observation to assess for immediate and early and delayed adverse event signals before EUA consideration.40 FDA strong recommendations for enhanced clinical trial population diversity and adaptive trial design progressively incorporating at risk populations continue to serve as unmet needs.39,42

PROGRAMMATIC AND POLICY ISSUES FOR GLOBAL MASS VACCINATION

Mass vaccination, which has been pursued by some countries such as Israel, may achieve herd immunity, which is the cessation of sustained community transmission and protection of unvaccinated people when vaccination rates are high enough. The required level of vaccination is determined by the efficacy of the vaccine and the basic reproductive number (R0) of the infection. The required population level immunity can be calculated by the formula H = 1 − (1/R0), where H is the herd immunity. For SARS-CoV-2, to interrupt community transmission with a vaccine of 90% efficacy would require approximately 66% of the population to be vaccinated.43 This efficacy must be against all infections, rather than symptomatic infection only, which is a common endpoint in COVID-19 vaccine clinical trials.25 A key determinant of herd immunity, therefore, is whether vaccines can stop transmission by preventing both symptomatic and asymptomatic infection. The high Pfizer vaccine efficacy of >85% discussed above35,36 suggests that herd immunity may be possible with this vaccine. However, the relatively poorer efficacy of the AstraZeneca vaccine against asymptomatic infection of 23% casts doubt as to its ability to
stop transmission. A study of Pfizer vaccine found very low viral loads in people who became infected after vaccination, suggesting a lower likelihood of disease transmission. More real-world observation in highly vaccinated populations will determine if herd immunity is achieved in countries with high vaccination uptake. Israel was the first country to achieve high vaccine coverage, and in doing so, prevented spread of the B.1.17 variant. However, the resurgence of infections in the Seychelles, which achieved 2-dose vaccination of over 60% of the population using the Sinopharm and AstraZeneca vaccines, serves as a note of caution. The resurgence may be due to the herd immunity threshold not being reached or vaccines lacking adequate efficacy. Duration of immunity is a key consideration but can be addressed with booster doses of vaccination.

Global mass vaccination on this scale has not been attempted since the eradication of smallpox, which took 20 years to achieve. The requirements for mass vaccination include adequate vaccine supply, vaccinators and infrastructure, community outreach, as well as equity in vaccine distribution and a communication strategy to address vaccine hesitancy. Vaccine supply has been a limitation for many countries, with over half the supply distributed in high-income countries and only a handful of countries with vaccine manufacturing capacity. It is estimated that at the current rate it may take almost 5 years to vaccinate the world’s population. The resurgence of SARS-CoV-2 in India threatens the whole region because all South Asia is relying on India, which has manufacturing capacity, for vaccine supply.

Multiple wealthy countries pre-purchased COVID-19 vaccines before the release of efficacy data, often with agreements sufficient to vaccinate their populations many times over. They also developed prioritization advice with the support of their respective national immunization technical advisory groups, focused on those with the highest risk of exposure or mortality and morbidity from infection, with the understanding that supplies would initially be limited and that it would not be logistically possible to vaccinate the whole population immediately. Today, there continues to be great controversy over distribution to at-risk populations, including marginalized and socioeconomically disadvantaged groups.

As the majority of doses available worldwide have been purchased by wealthier nations, international access inequities remain of growing concern, particularly in underdeveloped nations. The COVID-19 Vaccines Global Access Facility led by the Coalition for Epidemic Preparedness Innovations, Global Alliance for Vaccines and Immunization, the WHO, and United Nations Children’s Fund is actively addressing the issue with a goal to distribute 2 billion doses to the most vulnerable by the end of 2021. However, this initiative can only provide a fraction of the required supply to low-income countries and cannot overcome inequities in vaccine distribution. Modeling shows that high coverage with high-efficacy vaccines are the route to health and economic recovery, and that low coverage or low-efficacy vaccines will result in long-term circulation of SARS-CoV-2 and repeated epidemics. As such it is likely that we will see hot spots of COVID-19 in the world for several years to come. Vaccine passports are likely to become a requirement for travel to and from many countries, in the same way as yellow fever vaccination is required, which may further increase inequity by making travel and mobility more accessible to people from high-income countries.

**KNOWLEDGE GAPS AND FUTURE DIRECTIONS**

The ongoing pivotal trials of COVID-19 vaccines that led to emergency use need to be completed to address all safety and efficacy endpoints and enable full licensure. A comprehensive strategy will be important to ensure vaccination and protection for the whole world. Immediate challenges include the logistics of manufacturing billions of doses of vaccines, support to supply poorer nations, and the logistics of global vaccine delivery including cold chain and equitable distribution. Ongoing scrutiny for rare adverse event signals will be essential, in particular to ensure public confidence and vaccine uptake.

It would be enormously helpful to determine the correlates of protection against SARS-CoV-2, particularly if COVID-19 cases decline and efficacy cannot be determined by disease prevention. Unanswered questions include vaccine efficacy against disease transmission, duration of protection, and whether heterologous prime-boost schedules (ie, the use of mixed schedules with different vaccines) can be used. SARS-CoV-2 variants will continue to emerge, which will require close international monitoring and potentially vaccination boosters against emerging VOC. The possibility of developing a pan-beta coronavirus vaccine that could protect against future emergent pandemic strains looks promising.

**CONCLUSION**

COVID-19 vaccine development and licensure has happened at pandemic speed in what must be one of the greatest public health achievements in history. However, the identification of several highly efficacious vaccines is just the beginning of the journey. There is still much to learn about vaccine-induced immunity, and the next-generation vaccines are likely to be better than the first. An ongoing COVID-19 vaccine strategy will be required to ensure global protection against this virus and allow worldwide travel to resume. However, this goal can be approached with great optimism given the high levels of protection afforded by these first-generation vaccines and the unprecedented global collaboration that has taken us to where we are now.

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