CORONAVIRUS

Development and deployment of COVID-19 vaccines for those most vulnerable

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Development of safe and effective COVID-19 vaccines is a global priority and the best hope for ending the COVID-19 pandemic. Remarkably, in less than 1 year, vaccines have been developed and shown to be efficacious and are already being deployed worldwide. Yet, many challenges remain. Immune senescence and comorbidities in aging populations and immune dysregulation in populations living in low-resource settings may impede vaccine effectiveness. Distribution of vaccines among these populations where vaccine access is historically low remains challenging. In this Review, we address these challenges and provide strategies for ensuring that vaccines are developed and deployed for those most vulnerable.

INTRODUCTION

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in late 2019 resulted in the ongoing coronavirus disease 2019 (COVID-19) pandemic. This pandemic has resulted in more than 90 million cases and 1.9 million deaths worldwide so far, with catastrophic socioeconomic and global health consequences. SARS-CoV-2 now represents the greatest threat to human health since the 1918 influenza pandemic that killed more than 50 million people worldwide. Development and deployment of safe and effective vaccines against COVID-19 are a global priority.

The World Health Organization (WHO) established a Target Product Profile for COVID-19 vaccines, with the preferred vaccine demonstrating at least 70% efficacy (1). SARS-CoV-2 infection produces a broad spectrum of disease symptoms, from asymptomatic to severe, with greatest morbidity and mortality among aging adults with comorbidities (2).

Historically, vaccine development is a high risk, costly, and time-consuming enterprise, in which over 90% of candidates fail, and those that are successful often take more than a decade from design to licensure. Today, with unprecedented financial commitments coupled with vaccine platforms developed over the past several years and building upon a foundation of coronavirus research and vaccine discovery associated with prior severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) outbreaks, several COVID-19 vaccines are in advanced clinical development (3, 4).

Development and deployment of COVID-19 vaccines that are safe and effective for those most vulnerable face many challenges (Table 1). Vaccines are often less effective in aging populations because of immune senescence and comorbidities (5). Moreover, deployment of vaccines in these populations, where the track record for vaccine uptake is historically low, requires new strategies. Similarly, populations in low- and middle-income countries (LMICs) suffer from concomitant infections, malnutrition, microbiome dysbiosis, and environmental enteropathy leading to immune dysregulation that may suppress immune responses to vaccines and also face comparable deployment challenges (6). In this Review, we address these challenges and provide strategies for ensuring that vaccines are developed and deployed for those most vulnerable to expedite an end to the COVID-19 pandemic.

TARGET POPULATION CONSIDERATIONS

Target population selection for COVID-19 vaccines for those most vulnerable aims for direct protection of at-risk populations, as well as herd immunity to indirectly protect those at risk (7). COVID-19 is an emergent disease of aging, with the case fatality rate increasing with age and comorbidities associated with age (8). Challenges for vaccine developers and policy-makers are as follows: (i) inducing protective immune responses in elderly populations against a new pathogen; (ii) assessing vaccine safety and efficacy in the elderly with mitigation measures remaining in effect; (iii) determining what data support expanding vaccination to all ages to ensure herd immunity; and (iv) successfully distributing vaccines to elderly populations with historically low uptake.

Inducing safe and effective immune responses to a new pathogen in elderly populations without preexisting immunity is a key

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Table 1. Challenges and opportunities for development and deployment of COVID-19 vaccines for aging and LMIC populations.

Challenge	Opportunity
Less effective responses to vaccines	Increase dose
	Adjuvants
	Prime-boost regimens
	Anti-inflammatory drugs
Determine efficacy of vaccines in aging populations with comorbidities	Include sufficient numbers of participants >age 65 and in nursing homes in efficacy trials
Determine efficacy of vaccines in LMIC populations with concomitant infections	Include sufficient numbers of participants with concomitant infections (HIV, TB, and parasites) in efficacy trials
Effective uptake of vaccines in aging populations	Efficacy trials in aging populations
	Demonstration project with licensed vaccines, e.g., influenza
	Marketing and education campaigns with transparent communication
Effective uptake of vaccines in LMIC populations	Efficacy trials in LMIC populations
	Demonstration projects with licensed vaccines, e.g., influenza
	Marketing and education campaigns with transparent communication
Prevent future coronavirus pandemics for those most vulnerable	Identify correlates of protection for COVID-19 vaccines
	Make samples available for comparison of vaccine platforms
	Conduct additional trials to identify predictive signatures of effective immunity
	Increase surveillance of zoonotic coronaviruses
	Provide resources toward pan and universal coronavirus vaccine development

challenge. Immune senescence, a progressive deterioration of innate and adaptive immune responses, coupled with comorbidities leads to decreased effectiveness of vaccines in the elderly (9–12). Aging is associated with an increase in baseline inflammation manifested as high concentrations of serum C-reactive protein, interleukin-6 (IL-6), and IL-8 (9). Age-related declines in vaccine effectiveness also reflect decreased antibody responses, dysfunction in the generation of pro- and anti-inflammatory mediators, and declines in effective cellular immunity (13). In addition, the approved vaccines currently targeting elderly adults—e.g., those for influenza, pneumococcal disease, herpes zoster, and tetanus-diphtheria—rely, to some extent, on boosting preexisting immune responses (14). Primary immune responses to a new pathogen, like SARS-CoV-2, may be even more challenging to induce in the elderly than recall

responses, and it remains to be determined whether preexisting cross-reactive immunity to other coronaviruses will affect COVID-19 vaccine responses in this age group. Vaccination strategies to address immune senescence include increasing immunogenicity with higher antigen doses (15), use of more potent adjuvants (16) and protein conjugate vaccines (17), development of multidose regimens (18), and potentially using agents that suppress inflammation (Table 1) (19, 20). Including elderly populations with comorbidities at sufficient numbers in COVID-19 vaccine trials will provide important data to help determine which segments of this population may benefit from vaccination.

Assessing vaccine safety and efficacy in elderly populations may be particularly challenging. If mitigation measures persist, then the elderly will remain largely in isolation that may make their inclusion in vaccine efficacy trials impractical because of limited exposure to SARS-CoV-2. Whereas SARS-CoV-2 transmission may persist in groups such as nursing home residents because of close exposure to staff living in the community, this population includes higher rates of frailty, dementia, and other comorbidities, thereby increasing the complexity of clinical trial participation and vaccine safety evaluation.

Vaccinating children may help to protect older populations, as shown previously for influenza (21). In the United States, the all-causes death rate for the very elderly ≥85 years old is 183-fold compared to ages 15 to 24 years, is 60-fold for ages 75 to 84 years, and is 24-fold for ages 65 to 74 years (22). These are precisely the age groups where data show reduced vaccine efficacy for other infectious diseases such as influenza (13). Given evidence of asymptomatic viral transmission (23) and the potential that COVID-19 vaccines will be less effective in the elderly (24), including children and young adults in the COVID-19 vaccine target population with the goal of achieving herd immunity and long-term suppression of transmission may be required and may eventually be the most successful strategy. Vaccine developers will need to consider whether to aim for this broad target population at the outset of development. This may require longer timelines to include children in clinical trials or to assess these populations later in vaccine development, depending on the evolving epidemiology of SARS-CoV-2. Identification of immune correlates of protection could facilitate bridging studies in younger populations. Modeling the impact of vaccination of different age groups on overall morbidity and mortality over time can help to inform target population strategies (25).

Identification of target populations in LMICs will depend on the evolving epidemiology of SARS-CoV-2. LMIC populations are likely to bear a disproportionate burden of COVID-19 due to compromised nutritional status; less access to preventive medical care, critical care, and ventilators; poor sanitation; and lack of personal space (26). The current low level of COVID-19 cases in some LMICs is likely masked by low surveillance capacity (27). It may also be due to lower population mean age compared to the United States and Europe as well as host genetic and immunological factors and other environmental factors (28). Improving SARS-CoV-2 surveillance to identify new hotspots in LMICs and participation of these countries in vaccine clinical development programs will generate important comparative efficacy data, facilitate vaccine confidence, and enhance vaccine uptake in these populations.

COVID-19 vaccines may perform less effectively in some LMIC populations. For example, an activated immune microenvironment before vaccination (with biomarkers consistent with some

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inflammatory signatures seen in aging populations) altered cellular and humoral immune responses to the yellow fever 17D vaccine and impeded efficacy in an African cohort (*29*). Moreover, oral vaccines, such as those for rotavirus, cholera, and polio, have shown impaired efficacy in LMIC populations (*30*). Gastrointestinal microbiome changes due to chronic intestinal infections found in some LMIC settings have been linked to immune dysregulation and may be related to lower vaccine efficacy. Chronic schistosomiasis and other comorbidities can stimulate polarized T helper cell type 2 responses and suppress vaccine-induced immunity (*31*). Thus, how COVID-19 vaccines perform across LMIC populations may in part be due to the vaccine regimen as well as population-specific issues in immune dysfunction. Last, women of reproductive age are an important global target population due to their role as frontline health care workers. However, women in LMICs may spend more lifetime years either pregnant or breastfeeding and, consequently, are more likely to be excluded from initial COVID-19 vaccine trials (*32*). As a result, approval for vaccination of pregnant and breastfeeding women may be delayed.

COVID-19 VACCINE DEVELOPMENT
SARS-CoV-2 pathogenesis and host immunity
Studies on SARS-CoV-2 pathogenesis and host immunity provide important insights relevant to ensuring effectiveness of COVID-19 vaccines in vulnerable populations. SARS-CoV-1 emerged in 2002 causing ~8000 infections and ~800 deaths during the SARS epidemic. The genus group 2b coronavirus (CoV), subgenus *Sarbecovirus*, includes SARS-CoV-1 and a large number of closely related clade I SARS-like bat coronaviruses identified between 2013 and 2017, which use human angiotensin-converting enzyme 2 (hACE2) receptors to gain entry to host cells. These viruses replicate efficiently in primary human cell cultures leading to the prediction that they would emerge in human populations. SARS-CoV-2, a clade III strain, emerged in late 2019, and its closest relatives include the bat coronavirus strain RaTG13 and related pangolin coronaviruses (*33*), which are 96 and 88% identical in genome sequence, respectively, strongly suggesting a bat origin (Fig. 1) (*34*). The SARS-CoV-2 genome is about 30 kb in length and is organized in a similar way to the genomes of many other sarbecoviruses. The first 20 kb encodes two large open reading frames (ORFs), which encode 16 replicase protein subunits. An assortment of structural proteins, e.g., spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins and accessory ORFs, are encoded downstream of the replicase (Fig. 2).

The SARS-CoV-2 spike glycoprotein (S) mediates virus docking and entry into susceptible host cells by binding to the hACE2 receptor (*34*) and is the major antigenic target for vaccine development. Whereas the correlates of protection for SARS-CoV-2 are currently undefined, most vaccine developers are focusing on the S glycoprotein because it is the major target for neutralizing antibodies (*35*). The S glycoprotein comprises an N-terminal domain S1 that contains the receptor binding domain (RBD) required for cell entry and a C-terminal domain S2 that is required for virus-cell fusion and plasma membrane penetration. SARS-CoV-2 infection induces antibodies to both S1 and S2 subunits, and cross-reactive humoral immunity generated by seasonal human coronaviruses targeting S2 has also been observed (*36*). Whereas antibodies to both S1 and S2 may be required for protection, recent studies analyzing the specificity and kinetics of neutralizing antibodies in more than 600 SARS-CoV-2–infected individuals revealed that antibodies against RBD are immunodominant and the target of 90% of the virus-neutralizing activity present in SARS-CoV-2 immune sera (*37*). Several neutralizing monoclonal antibodies targeting S have been identified by sorting single plasmablasts and memory B cells from the blood of convalescent patients with COVID-19; these antibodies prevent SARS-CoV-2 infection in animal models, strengthening the case for targeting S in COVID-19 vaccines (*38–40*). In addition, non-neutralizing antibodies may assist in viral clearance through mechanisms such as antibody-dependent cellular cytotoxicity and other Fc-mediated immune cell effector functions (*41*).

Although SARS-CoV-2 does not appear to be mutating as rapidly as HIV and influenza virus, mutations in the S glycoprotein have occurred since its original emergence in Wuhan, China, and the mutation D614G now appears to be the dominant mutation in SARS-CoV-2 circulating in Europe and the United States (*42*). It appears that the D614G mutation confers on the virus a greater fitness and potential for infectivity, but this makes the virus more vulnerable to neutralizing antibodies and does not appear to be a major obstacle for vaccine development (*43*). Other variants have also been identified, and as vaccines are deployed, there is a potential for selective pressure to induce additional mutations, and these will need to be closely monitored (*44–46*). Most recently, new variants have emerged in the United Kingdom and South Africa that appear to be more easily transmitted, and studies of these new variants are ongoing.

The kinetics and duration of SARS-CoV-2–specific antibody responses after exposure to SARS-CoV-2 or vaccination are of importance for long-term protection of the population, the trajectory of the current pandemic, and the potential for effective vaccine intervention strategies. In COVID-19, there are few antibodies detected against the S glycoprotein or N protein before day 10 after infection, which is consistent with other human coronaviruses (*47, 48*). From days 10 to 15 after infection, immunoglobulin M (IgM), IgG, and IgA against SARS-CoV-2 S and N proteins all increase as measured by enzyme-linked immunosorbent assay (ELISA) (*49*). The association between antibody responses and disease severity remains unclear and is reviewed elsewhere (*50, 51*).

It has been a year since SARS-CoV-2 emerged and 9 months since vaccine trials began. It is still too early to draw conclusions regarding potential durability of experimental COVID-19 vaccines. In general, infection with seasonal circulating human coronaviruses occurs in a winter seasonal pattern, and reinfection may occur when specific antibody responses wane after 1 to 2 years (*51, 52*). Recent data suggest that robust neutralizing antibody responses to SARS-CoV-2 infection persist for months (*53*) and immunological memory for greater than 6 months (*54*). Ongoing vaccine efficacy trials will monitor vaccinated participants for years to determine durability of protection and adverse events. Cohort studies of SARS-CoV-2–infected participants will also monitor immune responses over time. Both efforts will be important in defining parameters for eventual population-based herd immunity.

The role of cellular immunity in conferring or augmenting protective immunity remains undefined, as does whether additional SARS-CoV-2 antigens beyond S will be needed in COVID-19 vaccines to confer long-lived protective immunity. Studies using human leukocyte antigen class I and II peptide pools showed that 100% of convalescent patients with COVID-19 had circulating
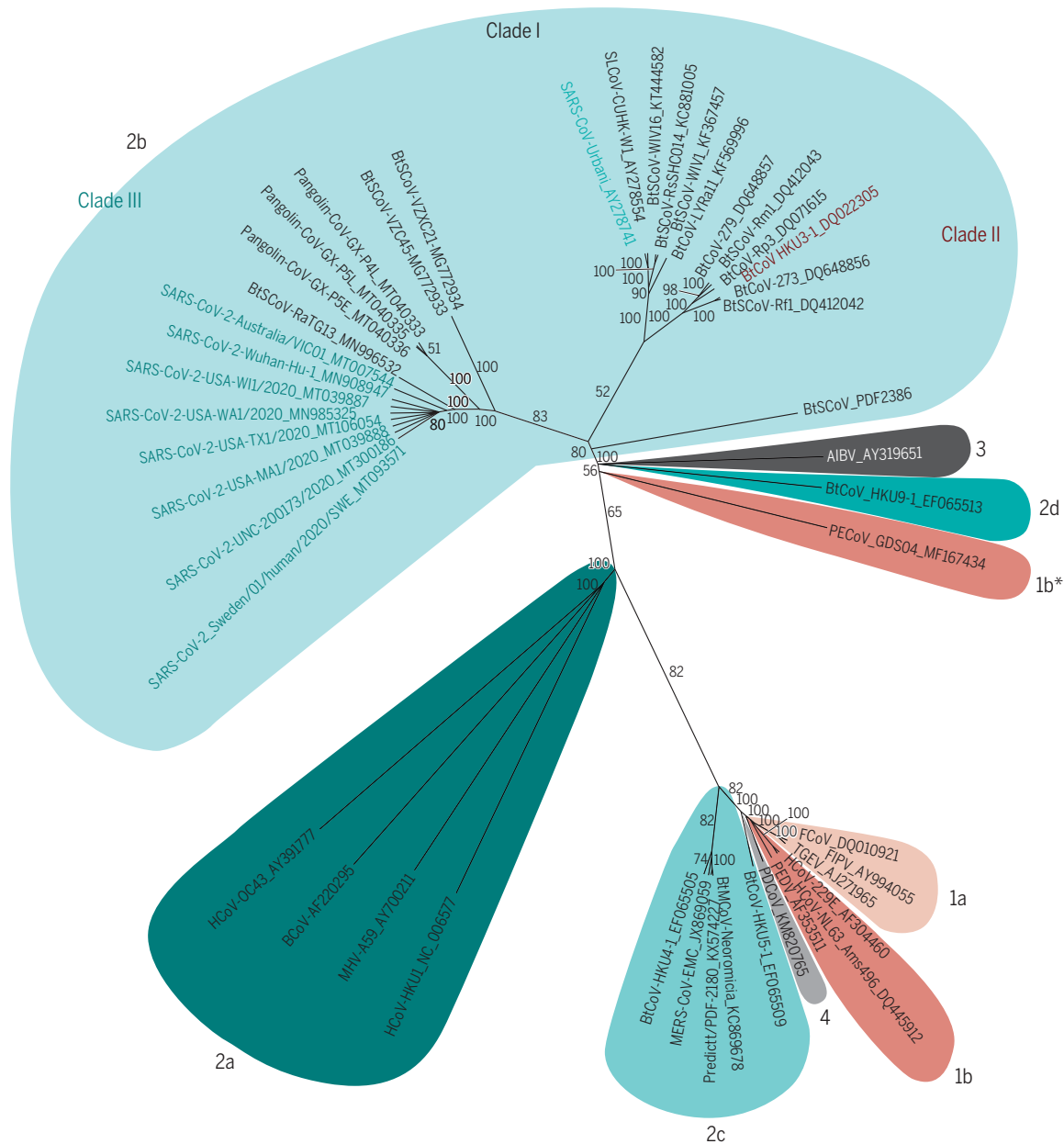
Fig. 1. Phylogeny of coronaviruses. The spike (S) protein gene sequences of selected coronaviruses were aligned and phylogenetically compared. Coronavirus genera are grouped by classic subgroup designations (1a and 1b, 2a to 2d, 3, and 4). Porcine epidemic coronavirus (PECoV) is designated as 1b* because of its distinctive grouping compared with more conserved proteins within subgroup 1b. Branches in each tree are labeled with consensus support values (%). Gene sequences from GenBank were aligned using free end gaps with the Blosum62 cost matrix, and the tree was constructed using the neighbor-joining method based on multiple sequence alignments in Geneious Prime (www.geneious.com). Numbers after the underscores in each sequence correspond to the GenBank accession number. Abbreviations in the radial phylogram refer to animal species where the coronaviruses were identified: BtCoV and BtSCoV, bat; BCoV, bovine; FCoV, feline; HCoV, human; MHV, murine; PEDV and TGEV, swine.

SARS-CoV-2–specific CD4 T cells, and 70% had circulating SARS-CoV-2–specific CD8 T cells. Notably, 40 to 60% of unexposed participants had SARS-CoV-2–reactive T cells, suggesting cross-reactivity from prior exposure to other human coronaviruses (*55, 56*).

COVID-19 vaccines may have specific safety challenges that may lengthen the timelines for vaccine development (*57*). Severe COVID-19 disease is characterized by pneumonia, lymphopenia, multiorgan involvement, and a robust cytokine storm. A subset of these patients progresses to acute respiratory distress syndrome

suggesting potential immunopathology by antibody and cellular arms of the immune system (*58*). Whereas there is some suggestion of antibody-dependent enhancement in animal models of SARS, this has not been observed to date in clinical trials of vaccines for SARS, MERS, or COVID-19 (*59*).

New systems biology technologies and tools are currently being applied to understand mechanisms of effective immunity as well as predictive signatures for protective immunity in COVID-19. They may help to identify biomarkers for beneficial versus pathological
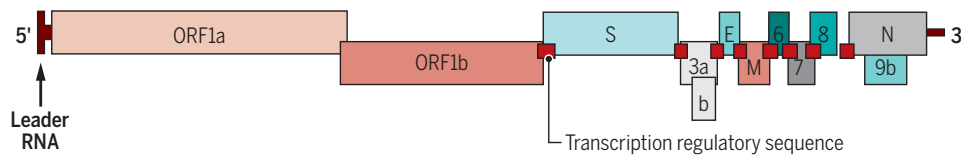
Fig. 2. SARS-CoV-2 genome organization. The SARS-CoV-2 genome is a single-stranded, positive-polarity RNA that is about 29,800 nucleotides in length. ORF1 is divided into two ORFs designated ORF1a and ORF1b that encode the viral replicase protein subunits 1 to 16. The structural genes encode S, E, M, and N proteins, and the remaining ORFs encode functions that may not be required for efficient virus replication but may be crucial for blocking the host innate immune response.

immune responses generated by COVID-19 vaccines, potentially accelerating vaccine development for those most vulnerable (*60, 61*). For example, a systems biological assessment of immunity in patients with mild versus severe COVID-19 detected increases in inflammatory mediators that correlated with disease severity (*62*). Moreover, recent studies revealed dysfunctional type 1 interferon responses including the generation of autoantibodies against type I interferons in patients with life-threatening COVID-19 pneumonia (*63, 64*). Understanding innate, humoral, and cellular immune responses elicited by SARS-CoV-2 infection, particularly those responsible for recovery in patients with COVID-19, will shed light on correlates of protective immunity.

Vaccine platforms

Given the urgency and global health priority for developing safe and effective COVID-19 vaccines, an unprecedented worldwide effort is ongoing, which is reviewed elsewhere (*65, 66*). Structural modeling of the S glycoprotein has led to inclusion of prefusion-stabilized S in many experimental COVID-19 vaccines (*67*), with the focus on generating potent and durable neutralizing antibody responses. Additional antigens are included in some vaccine candidates to generate potent and durable cellular immune responses, which may be required for enhancing immunity in aging or LMIC populations.

Multiple vaccine platforms are in development for COVID-19 vaccines, including attenuated and inactivated virus, recombinant subunit and virus-like particles (VLPs), synthetic peptides, and nucleic acid vaccines (Table 2). Two mRNA-based vaccines, developed by Pfizer/BioNTech and Moderna, have already been authorized for emergency use and validate the capacity of mRNA vaccine platforms for rapid development. Conversely, mRNA-based vaccines require freezers or ultracold freezers for storage, which may impede deployment in low-resource settings. In contrast, adenoviral vector and recombinant protein vaccines currently advancing in clinical development can be stored at refrigerated temperatures, allowing for cold-chain management with existing infrastructure. Some adenoviral vectors, such as human adenovirus 5, may be limited by preexisting host immunity to the vector, which may be overcome by heterologous prime-boost regimens. Vaccine platforms where large-scale manufacturing processes have already been developed and validated, e.g., Janssen's human adenovirus 26 platform used to develop an Ebola vaccine, may offer advantages for moving rapidly from demonstration of vaccine efficacy to large-scale deployment.

Because of the potential for elderly populations and those living in LMICs to respond less effectively to COVID-19 vaccines, strategies need to be implemented early in vaccine development programs to optimize effectiveness of vaccines in these vulnerable populations. This potentially includes development of high-dose regimens, combining vaccines in prime-boost regimens, immune modulation by agents that suppress inflammation, and utilization of adjuvants to increase immunogenicity (Table 1). A high-dose inactivated influenza virus vaccine improved antibody responses to influenza virus among adults 65 years of age or older (*68*). Similarly, the herpes zoster virus subunit vaccine, containing recombinant varicella zoster virus glycoprotein E and the AS01B adjuvant, reduced the risk of shingles and postherpetic neuralgia among adults 70 years of age or older (*69*). GlaxoSmithKline, Seqirus, and Dynavax, developers of the AS03, MF-59, and CpG adjuvants, respectively, that are used in licensed vaccines, have made their adjuvants available to other vaccine developers for use in COVID-19 vaccine development.

Animal models

There are a number of animal models of COVID-19 under development, including small animals and nonhuman primates, and these have been reviewed elsewhere (*70, 71*). The ideal animal model would reproduce human COVID-19 disease; however, to date, no model completely mimics SARS-CoV-2 pathogenesis in humans (Table 3). Age-related models would be quite useful to explore the impact of age on vaccine-induced immune responses along with mechanisms of immune senescence. Such models are now in early development, and preliminary data suggest that SARS-CoV-2 causes more severe interstitial pneumonia in older monkeys than in younger monkeys (*72*). Similarly, animal models to mimic the impact of concomitant infections applicable to those occurring in LMIC populations would be useful. Small animals including Syrian hamsters and transgenic mice present the most severe symptoms of SARS-CoV-2 infection, such as weight loss (*73, 74*), and may be useful models for screening vaccine candidates for prevention of disease. Meanwhile ferrets, cats, and hamsters offer the potential for assessing SARS-CoV-2 transmission (*75*).

Most COVID-19 vaccine developers have prioritized nonhuman primates for assessment of protection by their vaccines against challenge with SARS-CoV-2. The primary limitation for studying vaccine-mediated protection against SARS-CoV-2 and other highly pathogenic human coronaviruses in nonhuman primates is that monkeys generally lack the more moderate-to-severe clinical presentation and outcomes of COVID-19 disease seen in humans (*71*).

Nonhuman primates have also been used to assess whether primary SARS-CoV-2 infection prevents reinfection. Data thus far indicate that SARS-CoV-2 infection induces protective immunity against rechallenge in rhesus macaques (*76, 77*). Correlates of protection using adoptive transfer methods showed that purified IgG from convalescent rhesus macaques protected naïve recipient macaques against SARS-CoV-2 challenge in a dose-dependent fashion (*78*).

CLINICAL DEVELOPMENT

Clinical development of experimental COVID-19 vaccines has been accomplished with unprecedented speed, rigorous attention to safety, and primary efficacy endpoints focused on prevention of

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Table 2. COVID-19 vaccines in late-stage development.

Platform	Developer	Regulatory status	Issues for development and deployment
mRNA	Pfizer/BioNTech	Approved	95% efficacy (*81*); storage at −70°C
mRNA	Moderna	Approved	94% efficacy (*86*); storage at −20°C; stable at 2° to 8°C for 30 days
mRNA	CureVac	Phase 3	Stable 3 months at 2° to 8°C (*120*)
Viral vector	AstraZeneca/Oxford (Chimp Adeno)	Approved	62% efficacy (*89*); stable at 2° to 8°C for 6 months
Viral vector	Janssen (Ad26)	Phase 3	Assessing single-dose versus two-dose regimens (*90*); storage at −20°C; stable at 2° to 8°C for 3 months
Viral vector	CanSino (Ad5)	Phase 3	Antiviral vector immunity may limit effectiveness (*91*)
Viral vector	Gamaleya (Ad26 + Ad5)	Phase 3	Heterologous prime-boost (*121*); storage at −20°C
Protein-VLP	Novavax	Phase 3	Matrix-M1 adjuvant (*95*); stable at 2° to 8°C
Protein-VLP	Medicago	Phase 2/3	AS03 or CpG adjuvant (*122*)
Protein	Clover Biopharma	Phase 2/3	AS03 adjuvant
Inactivated virus	Sinovac	Phase 3	Modest induction of neutralizing antibodies (*92*); no data in participants >60 years; storage at 2° to 8°C
Inactivated virus	Sinopharm	Phase 3	No data in participants >60 years (*93*)
Inactivated virus	Bharat Biotech	Phase 3	Algel-IMDG adjuvant (*123*)
DNA	Innovio	Phase 2/3	Storage for a year at room temperature; electroporation of skin

symptomatic COVID-19 disease. In this section, we briefly highlight safety and efficacy considerations and review the leading vaccine candidates, addressing issues specific to aging and LMIC populations.

Safety considerations

Despite the urgent need for COVID-19 vaccines, careful accrual of safety data is still required before and during widespread use of these vaccines. Introducing a vaccine without adequate safety characterization could lead to harm. This scenario would damage public support for future COVID-19 vaccines and put the acceptability of other life-saving vaccines at risk. This risk may be particularly relevant for LMIC populations where expanded vaccination coverage over the past three decades has correlated with decreased childhood mortality (*79*) and where concerted global investment has been necessary to drive down vaccine-preventable diseases such as polio. Whereas childhood vaccine safety profiles tend to be comparable across regions, less is known about adult vaccination safety profiles in LMIC populations, which may have higher rates of tuberculosis (TB), cytomegalovirus infection, hepatitis B, HIV infection, and chronic parasitic infections.

Efficacy considerations

Two large platforms have been developed for efficacy testing to accelerate development of COVID-19 vaccines. The Accelerating COVID-19 Therapeutic Interventions and Vaccines public-private

partnership led by the U.S. National Institutes of Health uses multiple harmonized two-arm clinical trials running in parallel with common elements such as trial endpoints, safety monitoring boards, independent statistical analysis, and clinical networks (*65*). The development of standardized assays and central laboratories to conduct such assays will be key for comparative analyses and studies on immune correlates of protection. The WHO Solidarity Vaccine Trial includes multiple arms with different vaccine candidates and a common placebo group. The protocol can accommodate multiple vaccine candidates over time, using adaptive design features, with efficiencies such as use of a shared control group, data systems, and assays (*80*). Both platforms are currently focusing on adults, including the elderly, in regions at high risk for SARS-CoV-2 infection. LMICs are included, with studies ongoing or planned for Brazil and South Africa, and with other countries under consideration including India and other South American countries.

Pfizer/BioNTech mRNA-based vaccine

Pfizer/BioNTech has developed a lipid nanoparticle (LNP)–formulated, nucleoside-modified mRNA-based vaccine termed BNT162b2, which encodes the S glycoprotein captured in its prefusion conformation. This vaccine has demonstrated safety and 95% efficacy in preventing COVID-19 disease in a phase 3 clinical trial of more than 40,000 participants, with similar efficacy achieved across sex, race, ethnicity, and presence of coexisting conditions (*81*). The

Table 3. Animal models in COVID-19 vaccine development.

Model	Advantages	Disadvantages	Key references
Mouse	Ease of use	SARS-CoV-2 does not replicate in wild-type mice	(*71, 73, 124–127*)
	Availability of immunological reagents		
	hACE2 transgenic mice	Challenges to mimic immune dysfunction in elderly and LMIC populations	
	Mouse-adapted models		
Golden Syrian hamsters	High levels of virus replication	Scarcity of immunological reagents	(*71, 74, 128–132*)
	Upper and lower respiratory tract infection	Unclear how useful for assessing age-related responses	
	Transmission studies feasible		
Cat	Domestic and wild cats are susceptible to SARS-CoV-2 infection	Scarcity of immunological reagents	(*71, 75*)
	Naturally susceptible to airborne and droplet infection for efficient transmission	Challenges to mimic immune dysfunction in elderly and LMIC populations	
Ferret	Susceptible to SARS-CoV-2 infection	Scarcity of immunological reagents	(*71, 75, 133, 134*)
	Can model transmission	Infected adult ferrets mimic mild COVID-19 in humans	
	Useful age-related model for respiratory infections		
Nonhuman primates	Closest preclinical model to human physiology	Expensive model to establish and maintain	(*71, 135–137*)
	SARS-CoV-2 infection causes mild to moderate illness with pneumonia and seroconversion	Studies often have limited sample numbers	
	Strong reagent availability and knowledge base, including reference genome	No severe clinical sequelae or outcomes	
	Amenable to aging and vaccine studies		

vaccine was not tested in pregnant or lactating women. Two 30-μg doses of BNT162b2 were administered intramuscularly 21 days apart and were compared to placebo. Safety over a median of 2 months was similar to that of other viral vaccines, and participants will be followed for 2 years. Of the 10 cases of severe COVID-19 in trial participants, 9 occurred in the placebo group. Preliminary data reported did not address whether vaccination prevented asymptomatic infection, nor did it address durability of protection or immune correlates. Immunogenicity data from phase 1 trials of this vaccine revealed that geometric mean titer (GMT) of neutralizing antibodies in older adults aged 65 to 85 years were 41% of titers observed in younger adults aged 18 to 55 years, which may affect the durability of protection in aging populations (*82*). Most recently, the Pfizer/BioNTech COVID-19 vaccine has received emergency use authorization (EUA) from the U.S. Food and Drug Administration (FDA) and regulatory agencies in the United Kingdom and European Union.

Moderna mRNA-based vaccine

Moderna, in collaboration with the U.S. National Institute for Allergy and Infectious Diseases (NIAID), developed an mRNA-based vaccine termed mRNA-1273 encoding a stabilized prefusion S protein of SARS-CoV-2 encased in LNPs. This was the first experimental COVID-19 vaccine to enter clinical trials in March 2020 (*83*). In initial safety and immunogenicity trials, GMT for neutralizing antibodies were 63.8% lower in aging adults >71 years compared to younger adults (*84*). Durability of responses to two vaccinations of 100 μg of mRNA-1273 was assessed out to 90 days after the second

vaccination (*85*). Using a live-virus plaque-reduction neutralization testing assay, the 80% inhibitory dilution GMT in participants aged 56 to 70 years declined from 878 on day 43 to 269 on day 119. In participants aged >71 years, the GMT declined from 317 on day 43 to 165 on day 119. Moderna recently reported results from its 30,000-person phase 3 trial, demonstrating safety and achieving 94.1% efficacy, with 30 severe cases of COVID-19 all occurring in the placebo group (*86*). Most recently, the Moderna COVID-19 vaccine was granted EUA by the FDA, United Kingdom, and other regulatory agencies.

AstraZeneca/University of Oxford adenovirus vector–based vaccine

The University of Oxford together with AstraZeneca have developed a chimpanzee adenovirus vector–based vaccine termed chAdOx1 nCoV-19 encoding the SARS-CoV-2 S protein. In phase 1/2 trials, the vaccine was initially assessed in healthy participants aged 18 to 55 years as single- and two-dose regimens, with the two-dose regimen providing moderate induction of neutralizing antibody responses and cell-mediated immune responses as measured by interferon-γ enzyme-linked immunospot (ELISpot) assay (*87*). Further study of this vaccine in 560 volunteers, stratified by age groups 18 to 55, 56 to 70, and >70 years, showed median neutralizing antibody titers of 193, 144, and 161 and median T cell responses at 14 days after immunization of 1187, 797, and 977 spot-forming cells, respectively, per million peripheral blood mononuclear cells (*88*). Interim analysis of phase 2/3 efficacy trials in participants 18 to 55 years conducted

across Brazil, South Africa, and the United Kingdom showed the chAdOx1 nCoV-19 vaccine to have an acceptable safety profile and 62.1% efficacy in participants who received the two-dose regimen of 5×10^{10} viral particles (*89*). A subset of participants in the U.K. trial received a half dose (2.5×10^{10}) for the first vaccination and a full dose for the second vaccination. In this subset of participants, the vaccine efficacy was 90%. Most recently, the AstraZeneca/University of Oxford COVID-19 vaccine was granted EUA by the United Kingdom and other regulatory agencies.

Janssen adenovirus vector–based vaccine

Janssen's Ad26.COV2.S vaccine, a nonreplicating human adenovirus 26 vector expressing the stabilized prefusion S protein of SARS-CoV-2, was administered at doses of 5×10^{10} or 1×10^{11} viral particles per vaccination, either as a single-dose or as a two-dose schedule separated by 56 days in healthy adults aged 18 to 55 years and >65 years (*90*). In preliminary analyses of the single-dose regimen, the vaccine was safe and immunogenic, eliciting neutralizing antibody responses and $CD4^+$ T helper cell and $CD8^+$ T cell immune responses. At the 1×10^{11} dose, GMT of neutralizing antibody responses in vaccine recipients, measured by a replicating virus neutralization assay at 50% inhibitory concentration, were reduced about 50% for adults >65 years compared with younger adults (243 versus 127, respectively). However, in those participants vaccinated with 5×10^{10} viral particles, the dose selected for further development, no differences were observed between older adults and younger adults (GMT 196 versus 214, respectively). A large-scale, multicountry phase 3 trial of the investigational Janssen Ad26.COV2.S COVID-19 single-dose vaccine candidate is now fully enrolled with about 45,000 participants, with interim analyses planned for the end of January 2021. A separate phase 3 clinical trial of the vaccine exploring safety and efficacy of a two-dose regimen of 5×10^{10} viral particles is ongoing.

CanSino adenovirus vector–based vaccine

CanSino's adenovirus 5 vector–based COVID-19 vaccine (Ad5-nCoV) was administered as a single immunization in participants 18 years or older. It was shown to be safe and induced relatively modest neutralizing antibody and cellular immune responses. Increasing age (>55 years) and high preexisting adenovirus 5 immunity were found to reduce immune responses to the vaccine in this phase 1/2 clinical trial (*91*). CanSino launched a phase 3 trial of the Ad5-nCoV vaccine with results expected in the first quarter of 2021.

Sinovac inactivated vaccine

Sinovac has developed an inactivated COVID-19 vaccine in an alum adjuvant that was administered to 600 adults aged 18 to 59 years in a two-dose regimen on days 0 and 14 or days 0 and 28. The vaccine was shown to be safe and immunogenic as measured by induction of neutralizing antibodies. Data collected during the trial demonstrated a 30 to 40% reduction of neutralizing antibody titers between young adults (18 to 29 years) and older adults (50 to 59 years) (*92*). Neutralizing antibody titers ranged from 23·8 to 65·4 GMT depending on the vaccination schedule and were lower than those of convalescent patients who previously had COVID-19. Sinovac advanced their inactivated COVID-19 vaccine to phase 3 trials, which are ongoing. The Sinovac vaccine has been reported to be 50.4% efficacious in Brazilian clinical trials.

Sinopharm inactivated vaccine

Sinopharm, in association with the China National Biotec Group, has also developed an inactivated COVID-19 vaccine, using β-propriolactone as the inactivating agent and alum as adjuvant. Phase 1/2 trials testing different dosages and regimens of the vaccine, with 96 participants in phase 1 and 224 in phase 2, demonstrated safety and immunogenicity in participants 18 to 59 years, with neutralizing antibody titers comparable to those observed with other leading COVID-19 vaccines (*93*). This experimental vaccine is currently in phase 3 clinical trials.

Novavax recombinant VLP–based vaccine

Novavax's vaccine, NVX-CoV2373, is a recombinant SARS-CoV-2 nanoparticle vaccine composed of trimeric full-length SARS-CoV-2 S glycoprotein and the saponin-based adjuvant Matrix-M1. The S protein component of the vaccine is expressed in a baculovirus insect cell expression system forming VLPs. Structural analysis of the S protein from this candidate vaccine using cryo–electron microscopy and site-specific glycan analysis revealed the structural integrity of the full-length S protein, locked in the antigenically preferred prefusion conformation (*94*). In phase 1/2 clinical trials of two intramuscular injections at days 0 and 21 in adults aged 18 to 59 years, NVX-CoV2373 appeared to be safe, and the two-dose 5-μg adjuvanted regimen elicited robust neutralizing antibody responses by day 35 that exceeded neutralizing antibody responses in COVID-19 convalescent serum. However, data in older adults are not yet available (*95*). Novavax completed enrollment of 15,000 participants in a phase 3 clinical trial being conducted in the United Kingdom, including 25% of participants over age 65 years, to determine safety and efficacy of NVX-CoV2373, with interim data expected in Q1 of 2021. An additional phase 3 trial was recently launched in the United States and Mexico and aims to enroll about 30,000 people.

Several COVID-19 vaccines have shown reduced immunogenicity in older adults, similar to what is observed with the influenza vaccine and other vaccines (*96*). In the case of influenza vaccine, a quantitative review of 31 vaccine antibody response studies conducted from 1986 to 2002 compared antibody responses to influenza vaccine in groups of elderly versus younger adults. The adjusted odds ratio of responses in elderly versus young adults ranged from 0.24 to 0.59 in terms of seroconversion, and this correlated with decreased efficacy of influenza vaccines in the elderly (*96*). Whereas the preliminary efficacy data from Pfizer/BioNTech and Moderna are encouraging, it remains unknown whether durability or effectiveness under field conditions will be negatively affected in aging and LMIC populations.

Data from clinical trials with other vaccines suggest that immune responses to vaccination are lower in LMIC populations and may be modulated by comorbidities such as concomitant parasitic infections. Using the yellow fever 17D vaccine, investigators demonstrated substantially reduced neutralizing antibody and $CD8^+$ T cell responses in Ugandan vaccinees when compared to Swiss vaccinees (*29*). At baseline, Ugandan volunteers had an altered immune microenvironment, with higher frequencies of exhausted and activated natural killer cells, differentiated T and B cell subsets and proinflammatory monocytes that may be responsible for diminished immune responses. A phase 1 study of an investigational HIV vaccine, using a DNA plasmid prime and an alum-adjuvanted protein boost, found that infection with the helminth parasite *Schistosoma mansoni* may modulate antibody responses induced by vaccination (*97*),

consistent with preclinical studies (*31*). Ugandan adults with *S. mansoni* infection had reduced antibody binding responses by ELISA and neutralizing antibody responses to the vaccine compared to *S. mansoni*–negative vaccinees from the same community.

To ensure that COVID-19 vaccines are safe and effective for LMIC populations, strategies to address potential reduced or variable efficacy, such as boosting using heterologous prime-boost regimens or treating coinfections, may be needed. Beyond the leading COVID-19 vaccine candidates described here, there are several other experimental COVID-19 vaccines advancing toward efficacy trials, which may offer additional benefit to those most vulnerable in terms of development and deployment (Table 2).

PARTNERING FOR SCALE AND ACCESS

Recent experience with rapid development of vaccines for Ebola virus, Zika virus, and the H1N1 influenza virus (which emerged in 2009 as a reassortment between two swine influenza lineages containing a hemagglutinin surface protein H1 from the 1918 pandemic virus and neuraminidase N1) provides valuable lessons for meeting the urgent need to manufacture and distribute billions of doses of COVID-19 vaccines during the pandemic. Key priorities include the alignment and coordination of activities for end-to-end development including large-scale manufacturing capabilities, fill/finish processes, and provisions for ensuring the availability of critical reagents and supplies to provide vaccine products in vials for distribution and delivery (*66, 98, 99*). For COVID-19 vaccines, coordination of these activities plays a central role given the likely need for several different vaccine products simultaneously and the use of vaccine manufacturing capabilities worldwide to meet the demand for billions of doses.

In April 2020, the WHO launched the Access to COVID-19 Tools (ACT) Accelerator initiative to support the rapid development, production, and equitable global access to COVID-19 vaccines and health technologies (*100*). COVAX, the vaccine component of the ACT Accelerator, was established to provide end-to-end coordination of a diverse portfolio of COVID-19 vaccine candidates, under the leadership of the Coalition for Epidemic Preparedness Innovations (CEPI), the Vaccine Alliance (Gavi), and WHO, in collaboration with public and private sector manufacturers and funders. The goal of the COVAX program is to ensure the production and equitable distribution of at least 2 billion doses of COVID-19 vaccines in CEPI's R&D portfolio by the end of 2021, reaching at least 20% of the population of participating countries. High-risk groups such as health care workers, the elderly, and other adults with underlying conditions are prioritized for first-round vaccinations in the COVAX program (*101*). In the United States, the federal government established Operation Warp Speed, an interagency public-private partnership to oversee the development, manufacturing, and distribution of 300 million doses of multiple COVID-19 vaccines (*102*).

During the 2009–2010 influenza virus pandemic, a new vaccine against the H1N1 strain was generated within 6 months after the onset of the pandemic; however, developed countries purchased most of the available vaccine (*103*). Some developed countries made pledges to donate or buy vaccine for LMICs, but efforts to secure vaccine for their own populations came first, leaving little excess to share (*103*). This created a marked disparity between wealthy and poorer countries with regard to vaccine distribution. Underlying reasons for inequitable distribution of vaccines include cost, the fact that vaccine manufacturing capacity resides mostly in developed countries, and the lack of infrastructure for vaccine distribution in many underresourced areas (*104*).

Public-private partnerships aimed at ensuring equitable access to vaccines during international public health emergencies can effectively address these issues, for example, by coordinating sustained funding for all stages of development, sharing the risks and benefits of vaccine development among development partners, and facilitating technology transfer to expand manufacturing capabilities (*3, 105–107*). The COVAX program notably includes a mechanism, coordinated by Gavi, for pooling risks and resources, particularly from high-income and upper middle-income countries, to provide advance marketing commitments to secure COVID-19 vaccines for LMICs (*108*). In addition, Gavi and the Bill & Melinda Gates Foundation are collaborating with the Serum Institute of India to produce up to 100 million doses of licensed and WHO-prequalified COVID-19 vaccines in the first half of 2021, priced at a maximum of U.S. $3 per dose, for up to 92 countries included in Gavi's COVAX advance marketing commitments (*109*).

Without global collaborations such as these to promote equitable access to COVID-19 vaccines for vulnerable populations and LMICs, the same scenario that occurred in 2009–2010 will likely play out again in the COVID-19 pandemic (*110*). Key steps to promote equitable vaccine distribution include the following. First, an internationally agreed-upon framework, such as the COVAX program, is critical for supporting equitable vaccine distribution. The framework must have broad buy-in and support from a wide range of key stakeholders, including governments, funders, vaccine manufacturers, and intergovernmental organizations such as WHO and UNICEF (*111, 112*). Second, funding support will be essential to promote availability and affordability of COVID-19 vaccines for LMICs. Public-private partnerships, such as the Gavi COVAX initiative, are critical to address these essential funding needs. Last, efforts to access and strengthen vaccine distribution networks in LMICs should be undertaken immediately to ensure that once vaccines are available, they can reach those in need. Whereas there have been tremendous advances over the past two decades in uptake of WHO-recommended routine immunizations in children (*113*), progress has lagged for adults, the elderly, and those living in LMICs. Forty-one percent of WHO member states are still lacking adult vaccination programs for seasonal influenza vaccines (*114*). Demonstration projects for deployment of vaccines to such populations will increase vaccine confidence and improve logistics for vaccine distribution, thus facilitating future uptake of COVID-19 vaccines in these vulnerable populations (*115*).

FUTURE DIRECTIONS

Building on a foundation of basic science, capitalizing on vaccine platforms developed in response to prior epidemics, marshaling the resources to enable high-risk manufacturing before demonstration of vaccine efficacy, and harnessing global collaborative efforts across public and private sectors have enabled the unprecedented development of COVID-19 vaccines in less than 1 year. Yet, the COVID-19 pandemic, which already affects billions of people across the globe and will likely kill millions before lastly being brought under control, has highlighted the vulnerability of aging and LMIC populations to disease, the global inequities in tackling diseases in LMICs, and how unprepared the world remains for

prevention of future pandemics. According to the United Nations, projections indicate that by 2050, there will be a marked increase in the number of people over the age of 65, with population growth accelerating fastest in LMICs (*116*). This global aging will create enormous public health challenges worldwide, markedly increasing our vulnerability to infectious diseases and the burden of noncommunicable diseases (*5*).

Recent technological advances in biomedical, engineering, and computer sciences offer the potential for implementing a new global research agenda focused on understanding effective immunity in aging and LMIC populations and to decipher the mechanisms of immune senescence and immune dysregulation that are the primary drivers of increased vulnerability to diseases in such populations. These tools will also enable greater understanding of why some people respond more effectively to infections such as SARS-CoV-2 than do others and, similarly, why some respond better to vaccines. Defining these mechanisms of effective immunity will be critical for protecting vulnerable populations against future infectious disease outbreaks.

The COVID-19 pandemic also has enabled a unique opportunity for the coordination of efforts to compare vaccine platforms containing the same antigen, the SARS-CoV-2 S protein, which could yield important insights about principles of effective immunity applicable for prevention and control of new and emerging diseases (*61*, *117*). Relatedly, the pandemic has reinforced the need to prepare for pathogens that have not yet emerged, which will likely cause the greatest morbidity and mortality in aging and LMIC populations. Enhancing resources for surveillance of zoonotic pathogens in bats, birds, pigs, and other intermediate species from which emerging viruses frequently cross over to humans will be critical for successfully preventing and controlling future pandemics. Harnessing technologies such as artificial intelligence and deep learning, together with supercomputing and structural modeling, may facilitate new strategies for development of universal vaccines for coronaviruses (*38*, *118*).

Many challenges remain for controlling and ending the COVID-19 pandemic and to ensure that those most vulnerable are protected. Identification of correlates of protection will facilitate bridging studies for next-generation vaccines. Durability of protection in aging and LMIC populations will need to be monitored closely. Demonstration projects with licensed vaccines in those most vulnerable could facilitate deployment of COVID-19 vaccines. Such projects could build on programs such as the Partnership for Influenza Vaccine Introduction (*119*) that supports influenza vaccine program development in LMICs through public-private partnerships and could include clinical trials to further define the spectrum of immunity to COVID-19 vaccines in such populations. Last, transparency, education, and commitment from political and public health leaders at global, national, state, and local levels will be required to ensure greater vaccine confidence and uptake to achieve requisite levels of herd immunity worldwide. Accelerated progress will require continued scientific advancement, open exchange of data, and innovative mechanisms to enhance global collaboration.

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