A RESEARCH AND DEVELOPMENT (R&D) ROADMAP

FOR

BROADLY PROTECTIVE CORONAVIRUS

VACCINES

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PREAMBLE

The Center for Infectious Disease Research and Policy (CIDRAP) at the University of Minnesota, with support from the Bill & Melinda Gates Foundation and The Rockefeller Foundation, created this research and development (R&D) roadmap for broadly protective coronavirus vaccines (referred to as the Coronavirus Vaccines Roadmap [CVR]) to serve as a strategic planning tool to facilitate R&D, coordinate funding, and promote stakeholder engagement, with the ultimate goal of generating broadly protective vaccines against species and strains of the *Coronaviridae* virus family.

Primary audiences for this roadmap include academic basic and translational scientists, clinical researchers, funders, public health policymakers, government officials, industry scientists, business leaders, regulators, and advocacy specialists.

Rationale

Over the past two decades, three novel pathogenic coronaviruses have emerged from animal reservoirs to cause human epidemics or pandemics. Severe acute respiratory syndrome coronavirus (SARS-CoV or SARS-CoV-1; herein referred to as SARS-CoV-1) emerged in 2003, followed by Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 and SARS-CoV-2 in 2019. Coronaviruses can be highly lethal to humans, as illustrated by the 35% case-fatality ratio (CFR) for MERS-CoV and the 10% CFR for SARS-CoV-1. Fortunately, neither MERS-CoV nor SARS-CoV-1 have been shown to spread efficiently between humans. SARS-CoV-2 has a much lower CFR, but because of its high transmissibility, has caused to date over 600 million confirmed cases and 6.5 million deaths worldwide. The emergence of future coronaviruses with pandemic potential, that are both highly pathogenic *and* highly transmissible, represents a real and present threat that underscores the critical need for a coordinated R&D initiative to develop broadly protective coronavirus vaccines. Additionally, the limited durability and immunologic protection conferred by available SARS-CoV-2 vaccines and natural infection further highlight the crucial need for a new, proactive approach to develop vaccines that provide greater durability and target continually emerging variants.

Advancing a global R&D agenda for broadly protective coronavirus vaccines is a large and complex endeavor that will require ongoing investment, communication, and coordination among researchers; representatives from governments, industry, multilateral and nongovernmental organizations; regulators; and public health policymakers. The purpose of this roadmap is to provide a framework and timeline to align coordination, leadership, and investment to achieve these ambitious goals.

A critical overarching goal of R&D efforts for broadly protective coronavirus vaccines is to develop vaccines that are available and appropriate for use worldwide. The speed of bringing initial SARS-CoV-2 vaccines to market was a major and spectacular accomplishment; however, multiple factors resulted in gross inequities in access to vaccines in remote and low-resource settings. Disparities were fueled by products whose cold-chain and technical requirements

limited their use, protection of national interests in the face of limited supply, and global inequities in technical and public health capacity, financing, technology transfer, and manufacturing capabilities. Future vaccine development must ensure that global equity is a core principle of R&D, and that programs anticipate and resolve issues that may undermine this objective. Going forward, early and continuous engagement at the community, national, regional, and international levels will be essential to accomplish equitable distribution and uptake of future coronavirus vaccines.

Roadmap scope and structure

This document is aimed primarily at developing new, broadly protective coronavirus vaccines that are suitable for use in all countries and will protect against existing coronaviruses known to cause serious disease in humans (including new SARS-CoV-2 variants of concern), and any other pre-emergent coronaviruses that could spill over from zoonotic reservoirs to humans in the future.

Recent efforts to develop R&D roadmaps in other fields, such as medical countermeasure development for WHO priority diseases (WHO R&D Blueprint Initiative, Modjarrad 2016) and the Influenza Vaccines R&D Roadmap, informed the structure of the CVR, which is organized into five topic areas:

- Virology applicable to vaccine R&D
- Immunology and immune correlates of protection
- Vaccinology
- Animal and human infection models for coronavirus research
- Policy and financing

Each section of this roadmap contains an overview of key issues, barriers, and knowledge gaps germane to that topic area. Building on those issues, high-level strategic goals within the five topic areas are identified, followed by associated actions (milestones) required to achieve them. The milestones include target dates for completion and reflect SMART (Specific, Measurable, Achievable, Realistic/Relevant, and Time-sensitive) criteria, to the degree feasible. In some instances, milestones are aspirational in that they reflect an important area of research and include somewhat optimistic timelines to help move the area forward. Each topic area also includes a list of additional research priorities. These lists are not meant to be comprehensive, but rather are intended to illustrate additional areas of interest for future research. Items listed under this heading generally fall into one of the following categories: (1) the item is not of high enough priority to be included in the goals and milestones, (2) the nature of the research or activity does not lend itself to an initial target date for completion (recognizing that research for many of the milestones in the CVR will continue to be further refined over time even after the initial target is met), or (3) the research or activity is relatively nonspecific and not amenable to milestone criteria.

This document focuses specifically on issues related to an R&D agenda; a number of issues, although critical to the advancement of vaccine development, distribution, and uptake, are

beyond the scope of this roadmap. Examples include policy and practices related to current SARS-CoV-2 vaccines (such as dosing schedules, frequency of boosters); routine surveillance of coronaviruses in human and animal populations; vaccine hesitancy issues; public health prevention and control measures; implementation of vaccination programs; and pandemic preparedness (e.g., creating vaccine stockpiles and pandemic plans).

Roadmap development process

The CVR development process has engaged a wide range of stakeholders across scientific disciplines, public and private sectors, and international communities to build consensus around R&D priorities and identify strategies for addressing them. The process includes identifying and reviewing relevant scientific literature, discussing scientific challenges and knowledge gaps with a range of subject-matter experts (SMEs) from different fields, conducting in-depth reviews of draft roadmap documents, and offering a widely-publicized public comment period for written feedback.

Advising CIDRAP's core team throughout the project is a small steering group of senior leaders from the Bill & Melinda Gates Foundation; The Rockefeller Foundation; the Wellcome Trust; the US National Institute of Allergy and Infectious Diseases (NIAID); the Coalition for Epidemic Preparedness Innovations (CEPI); several academic institutions (including University of Iowa [USA], University of North Carolina [USA], Icahn School of Medicine at Mount Sinai [USA], and University of Witwatersrand [South Africa]); and Biologics Consulting, a US-based consulting firm with expertise in regulatory issues. In addition to this steering group, we have established a global CVR development taskforce of approximately 40 SMEs, who offer a wide range of knowledge and experience in vaccine development. This taskforce is charged with providing expert input and commentary on the CVR through detailed online discussions and document review.

This version of the CVR is being posted for public comment from October 24 to November 18, 2022. Feedback from the public comment period will be incorporated into the roadmap with anticipated finalizing and publishing of the CVR in February 2023.

Roadmap vision

To accelerate the development of durable, broadly protective coronavirus vaccines that: (1) are suitable for use in all regions of the globe, including low- and middle-income countries (LMICs), (2) can reduce severe illness and death (and potentially prevent infection) from coronaviruses (both those known to infect humans and pre-emergent viruses), and (3) will mitigate the impact of future coronavirus pandemics worldwide.

INTRODUCTION

Classification of coronaviruses

Coronaviruses are enveloped positive-sense, single-stranded RNA viruses that include four genera: alphacoronaviruses, betacoronaviruses, gammacoronaviruses, and deltacoronaviruses. All four genera contain viruses that infect animal species (mainly mammals or birds). Only alphacoronaviruses and betacornaviruses are generally known to infect humans; however, zoonotic spread of porcine deltacoronavirus to humans has recently been described (Lednicky 2021).

- Within the alphacoronavirus genus, two viruses cause illness in humans—human coronavirus 229E and human coronavirus NL63. Both cause mild upper respiratory tract infections consistent with a clinical presentation of the "common cold."
- Within the betacoronavirus genus, five viruses have been identified that cause human illness. These include severe acute respiratory syndrome coronaviruses 1 and 2 (SARS-CoV-1 and SARS-CoV-2), Middle East respiratory syndrome coronavirus (MERS-CoV), and two viruses that cause mild upper respiratory tract infections (human coronavirus HKU1 and human coronavirus OC43).
- Gammacoronaviruses to date are not known to infect humans.
- Most deltacoronaviruses also do not infect humans; however, porcine deltacoronavirus strains (Hu-PDCoV) have recently been identified in plasma samples from several Haitian children with acute undifferentiated febrile illness, suggesting that zoonotic spread of deltacoronaviruses to humans can occur (Lednicky 2021).

Betacoronaviruses are of greatest concern from a public health perspective, since this genus includes the three viruses that to date have caused severe illness and death in humans (SARS-CoV-1, SARS-CoV-2, and MERS-CoV). Betacoronaviruses include five different subgenera: embecoviruses (group 2a), sarbecoviruses (group 2b), merbecoviruses (group 2c), and hibcoviruses and nobicoviruses (group 2d) (Zhu 2020). Human coronavirus HKU1 and human coronavirus OC43 are in the embecovirus subgenus, SARS-CoV-1 and SARS-CoV-2 are in the sarbecovirus subgenus, and MERS-CoV is in the merbecovirus subgenus. The other subgenera (hibcoviruses and nobicoviruses) contain viruses that to date have only been found in animals other than humans and few efforts have been made to characterize these group 2d viruses; the potential for viruses in this group to cause human disease remains unknown.

Historic occurrence of highly pathogenic betacoronaviruses in humans

SARS-CoV-1

In November 2002, an outbreak of atypical pneumonia occurred in Guangdong Province, China, and additional outbreaks were recognized in that region in early 2003 (Pieris 2003). In February and March 2003, similar outbreaks occurred in Hong Kong, Singapore, and Toronto. SARS-CoV-1 was identified as the causative agent for these outbreaks in March of that year. Over the next few months, the virus spread to 26 different countries on five continents, with just over 8,000 cases identified and 774 deaths (Pieris 2003), yielding a CFR of about 10% among

identified cases. Most cases were associated with outbreaks in healthcare settings, although some were associated with "super-spreader events." In 2004, a second independent spillover of SARS-CoV-1 occurred in China, but only four cases were identified (Wang 2005). Fortunately, the virus was not highly transmissible between humans and no additional outbreaks of SARS-CoV-1 have been identified since 2004. The virus has not been found in the animal reservoir since that time. Several vaccines targeting SARS-CoV-1 were developed and tested in preclinical models and a few phase 1 clinical trials were initiated; however, no SARS-CoV-1 vaccines have advanced beyond that point (Li 2020).

MERS-CoV

MERS-CoV was first identified in 2012 in a patient from the Kingdom of Saudi Arabia who died of atypical pneumonia (Zaki 2012). Since then, cases have continued to occur at a low incidence rate, primarily in the Middle East and particularly in Saudi Arabia. Cases have been identified in 27 countries across the Middle East, North Africa, Europe, North America, and Asia. By mid-2022, just over 2,600 cases had been identified globally, with a CFR of about 35% among reported cases (ECDC 2022). Human-to-human transmission, while it occurs, is neither efficient nor sustained, so cases have not spread widely. As with SARS-CoV-1, vaccines have been developed and assessed in preclinical models and several phase 1/2 trials are ongoing (Li 2020).

SARS-CoV-2

SARS-CoV 2, the causative agent of the current pandemic, first emerged in Wuhan, China, in late 2019 and rapidly spread around the globe; WHO officially declared a COVID-19 pandemic on March 11, 2020 (Cucinotta 2020). As of October 2022, more than 600 million cases had been identified worldwide, with more than 6.5 million documented deaths. The CFR is about 1% among reported cases; however, the public-health impact of this virus has been much greater, owing to the high transmissibility of the virus and the continued emergence of different variants of concern (VOCs) with increased transmissibility and the ability to at least partially evade antibody-induced immune protection from previous infection or vaccination. SARS-CoV-2 vaccines were fast-tracked for development at the start of the pandemic and vaccines first became available in August 2021 (FDA 2021). The pandemic is ongoing at this time.

The persistent threat of coronaviruses

Many emerging pathogens originate in wild animal reservoirs, with factors such as land-use changes, disruption of natural ecosystems, increased urbanization, climate change, and wildlife trade and consumption leading to increased interactions between humans and wild animals (Cunningham 2017, Irving 2021). As the human population increases, the potential for "spill-over" events from zoonotic reservoirs to humans also increases; therefore, we can expect that additional novel viruses will emerge in the future.

Bats are a primary reservoir for several emerging viral pathogens, including Ebola, Nipah, Marburg, and Hendra viruses. Both SARS-CoV-1 and MERS-CoV likely originated in bats, and then later adapted to palm civets (SARS-CoV-1) and dromedary camels (MERS-CoV) (El Sayed

2021). The source of SARS-CoV-2 has yet to be definitively determined; however, bats, with other animal hosts potentially playing intermediate roles, remain the most likely possibility. Over 500 coronaviruses have been identified in various bat species (Chen 2014) and some researchers have estimated that more than 3,000 coronaviruses can be found in bats (Anthony 2017); horseshoe bats are thought to be a primary reservoir for SARS-related coronaviruses in Russia and China (Hu 2017, Alkhovsky 2022). Additionally, bats are considered to be the major evolutionary reservoir and ecological driver of coronavirus diversity globally (Anthony 2017). Given that coronaviruses can evolve rapidly, we can expect that pathogenic coronaviruses will emerge from the bat reservoir or some intermediate host in the future (El Sayed 2021).

Sarbecoviruses often undergo recombination, which can have evolutionary advantages. For example, researchers have postulated that the emergence of SARS-CoV-1 resulted from a recombination event within an animal host that allowed the virus to bind to the human angiotensin converting enzyme 2 (hACE2) receptor site on epithelial cells, which is the primary target for viral entry (Wells 2021). The ability of sarbecoviruses to infect multiple host species in addition to bats creates opportunities for coinfection, mutation, and recombination, which can result in the emergence of novel sarbecoviruses with pandemic potential (Wells 2021, Ren 2008).

Recent research demonstrates that SARS-CoV-2 can infect multiple different animal species in natural settings, including dogs, domestic cats, large wild cats (tigers, lions, etc.), gorillas, ferrets, mink, and white-tailed deer (Sharun 2021). Based on the presence of ACE2 receptors in host species, other animals may also be at risk of infection. Given the potential of the virus to jump species, the possibility exists for SARS-CoV-2 to undergo recombination with other coronaviruses, thereby generating a novel virus with renewed pandemic potential.

Coronaviruses have the potential to be highly pathogenic in humans, as illustrated by the approximately 35% CFR for MERS-CoV and the 10% CFR for SARS-CoV-1. Fortunately, MERS-CoV and SARS-CoV-1 do not spread efficiently between humans; however, we cannot rule out the possibility that a highly pathogenic *and* highly transmissible coronavirus could emerge from a bat or intermediate host in the future. Given the ongoing threat posed by coronaviruses, broadly protective vaccines are needed to protect against the emergence of additional SARS-CoV-2 variants and future novel coronaviruses with pandemic potential.

Strategies for development and use of broadly protective coronavirus vaccines

Protection of infection versus protection against severe disease

An important consideration for R&D of broadly protective coronavirus vaccines is defining what is meant by “protection.” Ideally, future coronavirus vaccines would protect against infection and, in doing so, would not only prevent disease, but would also be transmission-blocking. This approach would decrease the level of circulating viruses in the population. Existing vaccines for SARS-CoV-2 do not appear to protect against infection, but rather primarily protect against severe disease and death. This allows SARS-CoV-2 viruses to continue to circulate, which in turn, can lead to viral mutagenesis and the potential for new VOCs to emerge. Creating

transmission-blocking vaccines is challenging, however, and may require a strong mucosal immune response. As preferred product characteristics for next-generation coronavirus vaccines are defined, it is likely that transmission-blocking will be considered aspirational or optimal, while preventing severe disease and death will continue to be the more realistic goal.

Breadth of protection

Researchers have several options to consider when developing broadly protective coronavirus vaccines, including the following:

- "Variant-proof" SARS-CoV-2 vaccines: These vaccines would protect against all SARS-CoV-2 variants—those that have emerged and those that could emerge in the future.
- Vaccines that protect against a wide range of sarbecoviruses: These vaccines would include protection against SARS-CoV-1 and SARS-CoV-2 variants and, potentially, against other novel viruses in the sarbecovirus subgenus.
- Vaccines that protect against a wide range of betacoronaviruses vaccines: These vaccines would protect viruses in the betacoronavirus genus, including known human pathogens and potentially "pre-emergent" betacoronaviruses in zoonotic reservoirs that could spill over into humans.
- Vaccines that protect against a wide range of all coronaviruses: Such vaccines would protect against representative viruses from all of the coronavirus genera (including alphacoronaviruses, betacoronaviruses, gammacoronaviruses, and deltacoronaviruses), including the milder "common cold" species and any novel coronaviruses with pandemic potential.

Although betacoronaviruses are currently of greatest concern, the potential for alphacoronaviruses or other coronaviruses to cause serious human disease is also of importance and should not be minimized. Therefore, this roadmap is geared toward development of broadly protective coronavirus vaccines, ultimately aimed at protecting against all existing and emergent coronaviruses. A stepwise approach for vaccine development, however, starting with the highest priority viruses and then gradually expanding coverage over time may be the most practical strategy. For example, vaccines against SARS-CoV-2 variants may be the highest priority, followed by vaccines against sarbecoviruses, then merbecoviruses, then all betacoronaviruses, then alphacoronaviruses, and finally, vaccines that additionally protect against a wide range of coronaviruses from the remaining two genera.

When designing broadly protective coronavirus vaccines applicable to one or more of the categories outlined above, different approaches are possible. For next-generation SARS-CoV-2 vaccines, a primary strategy is to identify immunogens that generate broadly neutralizing antibodies against conserved regions of SARS-CoV-2 variants. Such vaccines can potentially capitalize on the fact that SARS-CoV-2 viruses bind primarily to the hACE2 receptor on human epithelial cells. Host cell binding is mediated through the receptor binding domain (RBD) on the virus spike (S) glycoprotein, which appears to be relatively immunodominant, and neutralizing antibodies to this area appear to inhibit receptor attachment in the host (although there is a large mutational space in the RBD that can escape antibodies but still retain ACE2 binding activity).

The search for broadly protective sarbecovirus vaccines is complicated by the fact that not all sarbecoviruses use hACE2 as the host receptor (Wells 2021). However, there may be other immunogenic epitopes on the S protein (e.g., within the RBD, the N-terminal domain [NTD], or subdomains of the S1 subunit or the S2 subunit) that are shared across sarbecoviruses; therefore, additional efforts to identify such epitopes are warranted (Yuan 2020). Several recent studies, for example, found that a SARS-CoV-2 RBD and spike nanoparticle with an adjuvant elicited cross-neutralizing antibody responses against SARS-CoV-1, several SARS-CoV-2 variants, and several bat coronaviruses (Joyce 2022, Saunders 2021). An alternative approach for developing broadly protective sarbecovirus vaccines is to generate vaccines that contain multiple representative immunogens from different clades within the sarbecovirus subgenus, such as through development of chimeric spike vaccines or mosaic/multiplexed nanoparticle vaccines (Cohen 2021, Cohen 2022, Martinez 2021, Walls 2021, Wuertz 2021). Prime-boost strategies using different immunogens may offer a third option toward creating broadly protective sarbecovirus vaccines (Tan 2021). Finally, use of T cell epitopes and non-structural proteins as immunogens is another option.

Similar approaches can be used for developing broadly protective betacoronavirus vaccines. One recent study, for example, identified a monoclonal antibody that cross-reacts with the S glycoproteins from eight different betacoronaviruses, including all five betacoronaviruses known to be pathogenic in humans (Sauer 2021). Studies such as this suggest that it may be possible to identify epitopes that are broadly protective and immunogenic across different genera of coronaviruses. Alternatively, multivalent approaches that combine immunogens from different virus groups may enable the development of vaccines that protect across the different genera.

Use of broadly protective coronavirus vaccines

There are several strategies for using broadly protective coronavirus vaccines.

- The most expansive approach is to use broadly protective coronavirus vaccines as part of routine childhood or adult vaccination programs (prophylactic use). This strategy would be an option if vaccines that are more durable can be developed (i.e., durability of a year or more), and may be important if new SARS-CoV-2 variants continue to circulate over time in the global population.
- Another approach is to use these vaccines to enhance pandemic preparedness by having vaccines available that will protect against novel coronaviruses with pandemic potential if such viruses emerge from an animal reservoir (reactive use). Such vaccines could be stockpiled in sufficient quantities for early use at the onset of an outbreak to rapidly interrupt transmission and prevent escalation into a pandemic, with production to be scaled-up quickly as needed. This approach limits the lag time necessary to generate a new vaccine.

While several organizations have developed draft preliminary target product profiles (TPPs) for broadly protective coronavirus vaccines, an initial important step is to arrive at broad consensus among key stakeholders on a set of preferred product characteristics (PPCs) that clearly articulate the minimal and optimal vaccine characteristics and outline how such vaccines will be

used. Examples of properties for broadly protective coronavirus vaccines include the following: ability to prevent clinical disease (particularly severe disease); ability to protect against all sarbecoviruses and merbecoviruses; ability to elicit rapid and robust immune responses; immunogenic in persons with preexisting immunity; safety and acceptability to the public; and suitability in all age groups, immunocompromised individuals, those who are pregnant, and other special populations (Morens 2022b). Other desirable properties include durability (for at least 1 year), effectiveness with one dose (or only a few doses), ability to prevent transmission, and affordability and suitability in LMICs (Morens 2022b).

TOPIC 1: VIROLOGY APPLICABLE TO VACCINE R&D

Issue: Coronaviruses are globally distributed and the coronavirus universe has not been well characterized.

Barriers

- Coronaviruses have the capacity to readily transmit within and between a wide, yet not fully defined, range of hosts (Millet 2021, Morens 2022, Singh 2021). Owing to their expansive presence in various geographic settings and diverse host species, efforts to better characterize this virus family through sampling and sequencing are inherently complicated by issues such as accessibility and scale (Ghai 2021, Morens 2022, Terrier 2021).
- Bats (and possibly rodents to a lesser degree) are considered the primary zoonotic reservoir for coronaviruses, with other species likely serving as intermediate hosts (Sánchez 2022). Bats are found on six of the seven continents and are the second most diverse order of mammals, with more than 1,400 species identified. Moreover, more than 500 coronavirus species have been found in bats (Chen 2014) and researchers suggest that the actual number may be more than 3,000 (Anthony 2017). This remarkable diversity and wide geographic range create major challenges for efforts to globally characterize coronaviruses within the bat reservoir (Lattine 2020, Ruiz-Aravena 2021).
- While bats may be the primary reservoir, other animal hosts may play an important intermediate role between bats and humans (Ghai 2021, Terrier 2021); therefore, an improved understanding is needed of intermediate animal reservoirs to better define the risk of spillover events to humans (Morens 2022, Ruiz-Aravena 2021, Terrier 2021).
- SARS-CoV-2 has been transmitted from humans to a number of animal species such as mink, white-tailed deer, and large cats (referred to as reverse zoonotic transmission or zooanthroponosis) (Goraichuk 2021, Telenti 2022), which adds another layer of complexity to the coronavirus ecosystem.
- Efforts to further define the coronavirus universe elicit potential questions and concerns about biosafety and biosecurity, particularly regarding viruses with undefined characteristics and virulence or where gain-of-function research may be conducted.

Gaps

- While recent efforts have been undertaken to expand sampling of wild and captive animals for coronaviruses, further work is needed to improve understanding of the geographic distribution, viral diversity, host range, and prevalence of this family of viruses and to link such information to vaccine R&D (Baric 2022, Morens 2022, Terrier 2021).
- Further identification and characterization of diverse coronaviruses is needed to guide a coordinated, well-informed process of virus strain selection for research aimed at broadly protective coronavirus vaccine development (Baric 2022).
    - To achieve this, a key consideration is to determine the degree of phylogenetic diversity of strains necessary to ensure adequate breadth of coverage for vaccine R&D. Therefore, obtaining viruses from the different genera will be

necessary to obtain representative sampling of coronaviruses that have potential for spillover into human populations.

- Betacoronaviruses are considered to be at high risk for spillover; therefore, research campaigns are particularly needed to better characterize these viruses. Group 2d betacoronaviruses (hibcoviruses and nobicoviruses) are not available for study and virus stocks of group 2c betacoronaviruses (merbecoviruses) are limited.
- Availability of a wide range of coronaviruses for study can promote the discovery and characterization of conserved B and T cell epitopes that exist within different coronavirus species, which is a critical issue for R&D of broadly protective vaccines (Baric 2022, Morens 2022, Starr 2021).
- Serologic studies are important to improve understanding of the frequency and scale at which exposure to coronaviruses occurs in various species and geographic settings. Serosurveys of wild and captive animals could uncover potential reservoirs, which would inform subsequent research efforts and risk assessments. Serosurveys in human populations, particularly those living or working in close contact with known and potential animal reservoirs, would help enhance understanding of exposure frequency and associated risk factors (Morens 2022, Ruiz-Aravena 2021, Sánchez 2022).
- Procurement of accessible and sufficiently diverse cell lines that are readily susceptible to an array of bat-derived coronaviruses would support virus isolation and propagation efforts, and facilitate genotypic and phenotypic characterization of bat-derived coronaviruses (Letko 2020a).
- A limitation in culturing and studying bat-derived coronaviruses in the laboratory is an overall lack of accessible reagents; therefore, efforts are needed to ensure availability and accessibility of the necessary reagents (Letko 2020a, Ruiz-Aravena 2021).

Issue: Coronaviruses frequently undergo mutation and recombination, which complicates understanding and tracking host range and viral spread.

Barriers

- The wide geographic distribution of coronaviruses, the broad range of hosts, and the large genome size offer ample opportunity for coronaviruses to undergo mutation and recombination (Morens 2022, Terrier 2021, Zhu 2020, Forni 2017, Kistler 2021, Millet 2021). This overall propensity to tolerate change applies to the spike protein (particularly the S1 subunit), ultimately enabling the possibility of distinct modifications to occur within or near antigenic sites without sacrificing viral fitness (Cotten 2021, Telenti 2022).
- The co-circulation of distinct coronaviruses among host species in the same geographic area can result in co-infections and subsequent recombination events (Lattine 2020, Ruiz-Aravena 2021, Wells 2021). Evidence suggests that certain bat populations—which can live in large colonies and share densely populated roosts with other species—frequently experience co-infections involving one or more coronaviruses (Ruiz-Aravena 2021). Co-infections can facilitate rapid viral adaptation to new hosts and ecologic environments (Forni 2017, Telenti 2022, Woo 2009).

- Significant gaps in the phylogeny of coronaviruses limit assessment of their genetic and antigenic diversity and complicates interpretation of historic evolutionary pathways (Baric 2022, Singh 2021, Terrier 2021).
- Selective pressures on at least several human coronaviruses—including OC43, 229E, and SARS-CoV-2—are dynamic and capable of altering antigenic sites (Cameroni 2022, Eguia 2021, Kistler 2021).
- Current capacity for phenotypic characterization of coronaviruses is limited by the lack of available tools, the high-level technical expertise required to perform such work, its time-consuming nature, and the associated costs (Letko 2020a, Letko 2020b). In turn, the overall lack of functional characterization restricts the interpretation of genomic sequencing data and delays understanding of the viral factors associated with traits such as zoonotic potential and virulence (Letko 2020a, Telenti 2022).

Gaps

- Bridging gaps in the phylogeny of coronaviruses is needed to:
  - Develop a more comprehensive understanding of the genetic and antigenic diversity of human and animal coronaviruses, which can ultimately inform vaccine R&D (Baric 2022).
  - Identify patterns that provide further insight on the frequency, timing, and role of viral recombination.
- Implementation of a collaborative, long-term effort to conduct genomic sequencing of coronaviruses from various animal species across multiple, diverse regions of the globe is needed to inform coronavirus surveillance and risk assessment to identify coronaviruses with pandemic potential. Generated viral sequencing data that are open, accessible, standardized (including metadata), and thorough would permit high-throughput analyses that could ultimately help bridge phylogenetic gaps present in the coronavirus virome and illustrate the diversity that exists across different populations and geographic settings (Baric 2022, Chen 2022, Morens 2022).
- Additional analysis of endemic seasonal human coronaviruses—comprised of betacoronaviruses OC43 and HKU1 and alphacoronaviruses 229E and NL63—is needed to gain additional insight on their evolutionary pathways and the mechanisms by which they evolved (Morens 2022).
- Investment in resources and global initiatives that expedite the functional characterization of coronaviruses is important for deciphering the relationship between genotype and phenotype and identifying genetic markers that can alter—and potentially enhance—characteristics such as transmissibility, immune evasion, and virulence (Forni 2017, Letko 2020a, Obermeyer 2022, Terrier 2021).

Issue: SARS-CoV-2 variants of interest, concern, and high consequence will likely continue to emerge, and expanded efforts are needed to track viral phylogenetic evolution over time.

Barriers

- The continued circulation and adaptability of SARS-CoV-2 over time has manifested in the emergence of multiple VOCs and descendent subvariants, raising the risk of immune evasion to existing vaccines or previous infection. The role of selective pressure from therapeutics and vaccines on VOC emergence over time remains unclear.
- The VOCs that have emerged to date have done so independently, with each leveraging the characteristics conferred by its distinct constellation of mutations to outcompete previously circulating variants (Obermeyer 2022, Telenti 2022). Although initial variants displayed heightened infectivity, growing immunity in the population achieved through vaccination or previous infection has potentially placed selective pressure on antigenic evolution (Harvey 2021, Markov 2022, Yewdell 2021). The tolerance that SARS-CoV-2 has for significant changes in antigenic sites is apparent, with multiple VOCs and descendent subvariants having noticeable impacts on the effectiveness of available vaccines and treatments, particularly in relation to occurrence of less severe disease (Hachmann 2022, Mannar 2022).
- Existing disparities among countries and global regions in systems infrastructure, expertise, human and financial resources, and overall sequencing and surveillance capacity constrain the implementation of coordinated and uniform efforts to improve SARS-CoV-2 global genomic surveillance (Chen 2022, Houtman 2022). Even if infrastructure, funding, and expertise are available, wide variations in technology used for such ventures can slow data turn-around times and the associated costs can limit capacity.
- Research involving SARS-CoV-2 is classified as Biosafety Level (BSL)-3, which creates challenges for working with virus strains in the laboratory; efforts are needed to reclassify SARS-Cov-2 from BSL-3 to BSL-2.
- Genomic surveillance data for SARS-CoV-2 are available through the Global Initiative on Sharing All Influenza Data (GISAID) and other platforms; however, the data are not necessarily accurate or standardized and similar information for other coronaviruses is not easily accessible.
- Countries may not be willing to share coronavirus genomic or prevalence data quickly with the global scientific community because of concerns about public image, the potential for border closings, and economic implications (Mendelson 2021).
- Widespread and persistent circulation of SARS-CoV-2 in both human and animal populations elicits the theoretical possibility of recombination with other coronaviruses (Telenti 2022), which could propagate viruses with unanticipated characteristics. Furthermore, sustained circulation of SARS-CoV-2 among a range of wild and domestic animals presents the risk of long-term reservoirs that could result in divergent or recombinant strains and spillback into humans (Peacock 2021, Pickering 2022, Rabalski 2021, Silva 2022).
- The lack of a standardized nomenclature for variants, coupled with the fact that sequences are being made available on several databases and platforms without consistency across systems, obfuscates the interpretation and representativeness of available sequencing data for SARS-CoV-2 (Chen 2022, Lancet 2021).

Gaps

- Expanding global capacity to conduct genomic sequencing for SARS-CoV-2 (particularly in LMICs and other low-resourced settings) is critical for generating meaningful genomic surveillance and obtaining a more comprehensive and representative understanding of coronavirus distribution and evolution. In areas where this capacity already exists (including expansion since the emergence of COVID-19), systems should be maintained and a greater understanding of the specific barriers and bottlenecks that limit sequencing and data sharing is needed. Furthermore, strategies are needed to build laboratory capacity in a manner that is best integrated with existing programs to improve systems while also preserving limited resources.
- Establishing the upload of raw, standardized genomic sequencing data and metadata to public databases as a norm, whenever possible, would enhance the ability to accurately interpret sequencing data, critically evaluate data sets, and provide opportunities for quality assurance.
- The effect, if any, of the Nagoya Protocol on virus sharing and the advancement of novel coronavirus vaccines should be assessed over time, including the impact of national Access and Benefit Sharing (ABS) legislation (CIDRAP 2021, Mueni Katee 2021).
- Building and sustaining collaborative international programs that are capable of quickly identifying, characterizing, and sharing data on coronaviruses in human and animal populations through standardized methods is vital for monitoring human coronavirus evolution and understanding the impacts of antigenic changes (DeGrace 2022). More specifically, data generated from such initiatives are important for both evaluating the effectiveness of available vaccines and ensuring that broadly protective vaccine candidates will protect against antigenically drifted variants. The WHO's Global Influenza Surveillance and Response System is a model for developing a coordinated network (Harvey 2021, Subbarao 2021) and perhaps could be expanded to incorporate coronaviruses; additionally, the WHO has launched the WHO BioHub System, which may hold the potential to contribute to these issues.
- Efforts to expand the use of computational and machine learning tools for genome sequence data sets can improve capabilities for predicting SARS-CoV-2 virus evolution, which could assist in vaccine R&D aimed at broadly protective coronavirus vaccines (Telenti 2022).

Issue: Coronaviruses are capable of binding to different cell receptors and the breadth and specificity of host-cell receptors for coronaviruses has not been fully elucidated.

Barriers

- Coronavirus spike proteins are capable of binding to a diverse array of cell receptors in both animals and humans, which helps facilitate their broad host ranges (Forni 2017, Kistler 2021, Millet 2021). For example, SARS-CoV-1 and SARS-CoV-2 utilize the angiotensin converting enzyme-2 (ACE2) receptor and MERS-CoV uses the dipeptidyl peptidase 4 (DPP4) receptor. For a number of coronaviruses, the host-cell receptor has yet to be characterized.

- In addition to the receptor, an undefined array of host-cell factors, such as proteases, often play a significant role in viral entry (Millet 2021). Receptor binding appears to be an evolvable trait, with analyses suggesting that SARS-CoV-2 obtained its ability to use hACE2 through recombination (Wells 2021). Notably, evidence exists of non-ACE2-using coronaviruses circulating in the same geographic areas with ACE2-using coronaviruses, which poses the risk of shifting receptor usage and altering host ranges. In addition, many sarbecovirus RBDs can acquire the ability to bind to select ACE2 receptors from a single amino-acid change (Starr 2022).
- Studying coronaviruses may involve gain-of-function research. Definitions regarding what constitutes gain-of-function research are not clear and are open to interpretation. Furthermore, gain-of-function research is controversial and some policy makers believe that such research should be restricted, which could hinder important research applicable to coronavirus vaccine R&D.

Gaps

- Further research is needed to:
  - Identify the main host-cell receptors to which different coronaviruses bind (Ghai 2021). In particular, defining the range of ACE2-using coronaviruses could improve capacity to assess zoonotic risk (Wells 2021). For example, coronaviruses identified in bats and pangolins have RBDs closely resembling that of SARS-CoV-2, which can readily bind to hACE2 (Holmes 2021, Telenti 2022, Temmam 2022). Further understanding of the full range of host receptor binding is important for development of broadly protective coronavirus vaccines.
  - Understand, through deep mutational scanning, what residue changes confer loss or gain of binding to key human receptors such as ACE2 or DPP4.
  - Determine the presence or absence of host-cell receptors and additional factors (such as proteases) important for viral entry and map their distribution across different species and in different tissue types to determine tissue tropism (Hu 2020, Millet 2021, Ruiz-Aravena 2021).

Strategic Goals and Aligned Milestones

Strategic Goal 1.1: Enhance and sustain the capacity to identify, characterize, and share SARS-CoV-2 variants of interest, concern, and high consequence among researchers globally.

Milestones:

a. By 2023, initiate the risk assessment and decision-making processes necessary to reclassify Biosafety Level (BSL) requirements for SARS-CoV-2 from BSL-3 to BSL-2.
b. By 2023, develop a strategy to ensure that the global capacity developed during the COVID-19 pandemic to conduct genomic sequencing of SARS-CoV-2 viruses sampled from humans can be maintained over time, particularly in low-resource settings.
c. By 2023, improve standardization of SARS-CoV-2 genomic sequencing data and metadata (including nomenclature) to enhance accurate interpretation and use.

d. By 2024, generate a sustainable collaborative international program for quickly identifying, characterizing, and sharing antigenic information on SARS-CoV-2 viruses identified in humans, potentially building on what currently exists for influenza, such as the WHO's Global Influenza Surveillance and Response System (GISRS) (Harvey 2021, Subbarao 2021).

Strategic Goal 1.2: Improve characterization of the coronavirus universe to determine the diversity of strains necessary to ensure adequate breadth of coverage for vaccine R&D.

Milestones:

a. By 2023, establish best practices and standard operating procedures for research (in the field and in the laboratory) involving coronaviruses of unknown pathogenicity to ensure that biosafety and biosecurity risks are minimized.
b. By 2023, initiate research campaigns aimed at: (1) identifying additional bat-derived coronaviruses (particularly group 2d betacoronaviruses) and (2) generating critical reagents needed to study such viruses.
c. By 2024, develop a coordinated international framework to enhance sampling of both wild and captive animal populations (particularly bats) in geographically diverse regions for improving understanding of the distribution, viral diversity, host range, and prevalence of coronaviruses globally (Baric 2022, Morens 2022, Terrier 2021).
d. By 2024, ensure availability of reagents (such as reference monoclonal antibodies for antigen characterization) necessary for evaluating priority coronaviruses (Letko 2020a, Ruiz-Aravena 2021).
e. By 2024, devise an approach to prioritize and select coronavirus strains that would comprise an optimally diverse panel to be used in vaccine R&D for assessing breadth of protection (Baric 2022). Selection should initially focus on coronaviruses that: (1) use the hACE2 receptor, (2) grow in primary human cells, (3) are genetically diverse, (4) have been antigenically characterized, and (5) have strains available for study.
f. By 2025, ensure that one or more panels of virus stocks featuring different coronaviruses and diverse cell lines that are readily susceptible to a wide range of coronaviruses are accessible to researchers working on coronavirus vaccine R&D (Letko 2020a, Ruiz-Aravena 2021).
g. By 2025, develop the serologic platforms needed for conducting serosurveillance studies in high-risk populations (based on a diverse panel of coronaviruses that may pose a risk to human health) to identify signals suggesting the potential for spillover from animals to humans.
h. By 2025, establish a global framework for serosurvey methodologies (including populations to study) to help synchronize study designs.

Strategic Goal 1.3: Improve understanding of the phylogenetic evolution over time of animal-derived coronaviruses.

Milestones:

a. By 2023, initiate and implement a collaborative, coordinated and sustainable effort to conduct genomic sequencing of coronaviruses from relevant animal species sampled across multiple regions of the globe and ensure that the generated viral sequencing data are openly accessible with standardized metadata (Baric 2022, Chen 2022, Morens 2022).

Strategic Goal 1.4: Improve understanding of the breadth of host-cell receptors for coronaviruses.

Milestones:

a. By 2027, identify the host-cell receptors to which a range of different coronaviruses bind, with an initial focus on priority viruses, such as betacoronaviruses, to determine the species distribution for different receptors (Ghai 2021).
b. By 2028, once host-cell receptors are identified for different coronaviruses, determine which are present in humans (Hu 2020, Millet 2021, Ruiz-Aravena 2021). For those host-cell receptors that are present in humans, assess the distribution across various tissue types in both humans and commonly used animal models to determine tissue tropism.

Additional Research Priorities

- **Continue to obtain** additional SARS-CoV-2 isolates over time and ensure that these isolates are made equally accessible to suitable researchers, which could broaden phenotypic characterization.
- **Perform** additional analyses of endemic seasonal human coronaviruses to further understand the pathways and mechanisms of coronavirus evolution.
- **Conduct** ongoing high-throughput analyses of genomic sequence data for diverse coronaviruses to bridge phylogenetic gaps present in the coronavirus universe and improve understanding of the antigenic diversity of these viruses.
- **Update** the supply of necessary reagents routinely as additional viruses are identified.
- **Expand** the use of computational and machine learning tools for genomic sequence data sets to improve capabilities for predicting SARS-CoV-2 virus evolution.
- **Ensure** that raw genomic sequencing data on SARS-CoV-2 sequences are readily and widely accessible whenever possible.
- **Expand** the functional characterization of coronaviruses to improve understanding of the relationship between genotype and phenotype of coronaviruses (Forni 2017, Letko 2020a, Obermeyer 2022, Terrier 2021).
- **Continue to build** global infrastructure and capacity for conducting virologic surveillance, particularly in LMICs.
- **Assess on an ongoing basis** the risks and benefits of gain-of-function research related to coronaviruses to ensure that such research meets acceptable bioethical and safety standards.

TOPIC 2: IMMUNOLOGY AND IMMUNE CORRELATES OF PROTECTION

Issue: An improved understanding is needed regarding the mechanisms of mucosal and systemic immunity relevant to SARS-CoV-2 infection and the development of broadly protective coronavirus vaccines.

Barriers

- Innate and adaptive immune responses to SARS-CoV-2 and other coronaviruses involve complex, interrelated physiologic mechanisms and biomarkers that are inadequately understood. Fundamental questions remain concerning the nature of protective and cross-protective immunity to coronavirus infection and vaccination (Diamond 2022, Siggins 2021).
- Various host and environmental factors, such as age, sex, comorbidities, and geographic location, influence protective immune responses to viral antigens, which can complicate research on broadly protective coronavirus vaccines (Tomalka 2022).
- Mucosal immunity is likely to be important for protection against coronavirus infection and transmission, since coronaviruses are respiratory pathogens that do not have obligate viremic spread (Yewdell 2021). This creates a number of important challenges, since the role of mucosal immune protection is not well elucidated, nor are the strategies to stimulate and measure mucosal immunity (Iwasaki 2016, Lavelle 2021).
- Obtaining appropriate and adequate clinical samples for studying mucosal and systemic immunity related to coronavirus virus infection can be challenging for researchers (Logue 2022).

Gaps

- A greater understanding is needed of innate and adaptive immunity, which is critical for developing vaccines to control respiratory infections such as COVID-19 (Sette 2021), particularly with regard to preventing severe disease, but also potentially preventing infection and transmission. Specifically, information is needed to clarify the following:
    - How innate immunity influences adaptive (B cell and T cell) immune responses to SARS-CoV-2 infection, such as determining the signaling pathways underlying establishment of long-lived plasma cells and memory T cells (Tomalka 2022, Sette 2021).
    - The potential for improving breadth of protection against coronaviruses by stimulating innate “trained” immunity (Mettelman 2022, Tayar 2022, Ziogas 2022).
    - The role of the three main components (B cells, CD4 T cells, and CD8 T cells) of adaptive immunity to SARS-CoV-2 virus infection and vaccination (and to other coronaviruses), with a focus on their specific functions and kinetics (Moss 2022, Sette 2021, Sette 2022, Wherry 2022); this includes a specific focus on the role of key subpopulations, such as T follicular helper cells, regulatory T cells, and memory T cells (Kent 2022, Moss 2022, Tarke 2022, Zheng 2021).

735 - The role and mechanisms of adjuvants in mediating interactions between innate
736 and adaptive immune responses (Carmen 2021, Lee 2022) (e.g., driving breadth
737 of response via CD4 T cell activation) (Joyce 2022).
738 - The relative roles of mucosal versus systemic immunity in protecting against
739 coronavirus infection and limiting the potential for virus transmission (Mettelman
740 2022, Poland 2021).
741 - The role of T cells for: viral clearance, preventing infection in the absence of
742 seroconversion, limiting the extent of disease following infection, generating
743 robust immune memory, and responding to different viral variants (Wherry 2022).
744 - Defining the features of an optimal coordinated cellular immune response to
745 primary SARS-CoV-2 infection and determining the optimal vaccine-elicited
746 cellular immune responses needed to prevent infection and transmission, which
747 could in turn prevent the emergence of new viral variants (Moss 2022).
748 - The immune responses to different vaccine constructs and strategies for
749 administering them (including different routes such as intranasal, transdermal
750 and intramuscular administration), particularly regarding tissue resident memory
751 (T_{RM}) cells in B and T cell populations in the upper and lower respiratory tracts
752 (Mettelman 2022, Nelson 2021).
753 - The processes by which immune dysregulation may contribute to severe COVID-
754 19 disease following infection and the implications for development of next-
755 generation vaccines, particularly with regard to determining the role that CD8 T
756 cell responses or the innate immune response may play in stimulating pro-
757 inflammatory reactions or enhanced immunopathology (Ahmed-Hassan 2020,
758 Zheng 2021).
759 • Immunologic assays, including high-throughput neutralization assays and T cell assays,
760 that at a minimum are qualified and ideally are validated, are needed to evaluate broadly
761 protective coronavirus vaccines (e.g., to determine the effect of pre-immune status on
762 vaccine performance; evaluate vaccine performance in naïve or vulnerable populations;
763 measure immune kinetics, immune memory, and breadth and durability of protection;
764 and develop correlates of protection) (Baric 2022, Goldblatt 2022a, Vardhana 2022).
765 • Biomarkers for innate immunity are needed to evaluate and predict mechanisms of the
766 adaptive immune response to coronavirus infection (Espinoza 2022).
767
768 ***Issue: The mechanisms for stimulating broadly protective immune responses that are***
769 ***cross-reactive against different coronaviruses are not well defined.***

770 **Barriers**

771 • SARS-CoV-2 evolves rapidly, leading to the emergence of new viral variants capable of
772 escaping antibody-induced immune protection from vaccination or prior infection.
773 • To date, many of the available SARS-CoV-2 vaccines focus on generating neutralizing
774 antibodies to the RBD of the S protein, an immunodominant region prone to mutation.
775 The immunodominance of the S protein could complicate the incorporation of other
776 conserved epitopes, which may be immunosubdominant, in future vaccine development.

- Memory B cell responses mature relatively slowly, which may be an important limitation for immune protection against infection and disease (particularly non-severe disease) caused by new viral variants with shorter incubation periods (such as Omicron) compared with the ancestral SARS-CoV-2 strain.

Gaps

- Immunologic research in the following areas is needed for generating broadly protective coronavirus vaccines:
  - Develop a detailed understanding of the human antibody response to SARS-CoV-2 and other coronaviruses (Pecetta 2022).
  - Identify epitopes (other than the RBD of the S protein) that generate neutralizing humoral immunity and are conserved across different viruses (J Cohen 2021, Crowe 2022, Martinez 2021, Saunders 2021, Walls 2021).
  - Identify T cell epitopes that may provide broader cross protection against different coronaviruses by stimulating CD4 and CD8 T cell responses.
  - Evaluate the potential for conserved epitopes to drift or remain stable under immune pressure (e.g., when used as an antigenic target for broadly protective vaccines).
  - Evaluate whether prior infections to previously or currently circulating coronaviruses, such as SARS-CoV-1 and the common cold coronaviruses, provide cross-protection against heterologous human coronaviruses (Dangi 2021, Moss 2022).
  - Identify broadly neutralizing antibodies against the conserved S2 region of the spike protein, which may be important for developing broadly protective coronavirus vaccines (Zhou 2022).
  - Promote understanding of the role of binding but non-neutralizing antibodies vs. neutralizing antibodies produced by SARS-CoV-2 vaccines (Poland 2021).
  - Identify mechanisms underlying the induction of broadly protective memory B cells.
  - Determine the kinetics and magnitude of B cell response to conserved antigens sufficient to provide broad protection from coronavirus infection, independently or in combination with T cell responses, for different vaccine platforms (Sette 2022).
  - Determine whether increased levels of broadly reactive antibodies exacerbate autoimmune disease by increasing autoreactive antibodies (Labombarde 2022).
  - Determine the relative contribution of multiple arms of the immune system (including T cells, non-neutralizing antibodies, neutralizing antibodies to conserved epitopes, innate immune responses, and mucosal immunity) in eliciting broadly protective immunity (Hauser 2022).

Issue: The mechanisms underlying long-term immune responses to coronaviruses require further clarification.

Barriers

- Because initial SARS-CoV-2 infection occurs primarily in epithelial cells on mucosal surfaces, there is limited involvement of systemic immunity and protective immunity following infection or injected vaccines is short-lived (Morens 2022b). This is also potentially true for other coronaviruses that cause infection in humans (Belyakov 2009, Karczmarzyk 2022).
- More information is needed on the length of time that protective immunity (either against infection or against development of severe disease) can possibly be sustained for coronaviruses through vaccination is unknown.
- Immune memory responses elicited by vaccines, involving primarily long-lived plasma cells and memory B cells, are critical for inducing long-term protection, but the mechanisms and determinants of the process are incompletely understood (Gaebler 2021, Inoue 2022, Laidlaw 2022, Siggins 2021).

Gaps

- Further research is needed to:
  - Understand how prime vaccination, boosting, and immune memory processes interact, leading to broadly protective immunity.
  - Determine the factors that influence duration of antibody and memory B and T cell responses following SARS-CoV-2 infection or vaccination (Bhattacharya 2022, Moss 2022, Siggins 2021, Tarke 2022), particularly regarding protection against heterologous strains.
  - Identify the determinants of longevity for antigen-specific plasma cells in bone marrow and in mucosa-associated lymphoid tissue (Siggins 2021).
  - Identify mechanisms that promote persistence of the germinal center following infection and/or vaccination, which is needed to establish immune memory (Laidlaw 2022).
  - Define the role of T_{RM} cells in the upper and lower respiratory tract in promoting durability of immune protection (Nelson 2021, Sette 2022).

Issue: The impact of preexisting partial immunity to SARS-CoV-2 (infection-acquired and vaccine-mediated) on future vaccinations is unknown.

Barriers

- Much of the world's population has either been infected with SARS-CoV-2 or has been vaccinated against the virus, which complicates research aimed at understanding protective immunologic responses to new vaccines.
- Regional differences likely exist with regard to past exposures to other coronaviruses, which further complicates research efforts.

Gaps

- Further research is needed to:
  - Determine levels of baseline immunity to coronaviruses in different populations and assess the impact of preexisting heterosubtypic immunity (e.g., from prior infection with SARS-CoV-1, MERS-CoV, common cold coronaviruses, and

SARS-CoV-2 variants) on susceptibility to infection and disease from future coronavirus exposures (Bean 2021, Tan 2021, Yu 2022).
    - Identify mechanisms of imprinting by population characteristics and immune responses to previous exposure to coronavirus vaccines or infection (Mettelman 2022, Pecetta 2022).
    - Improve understanding of antigenic imprinting to the S protein, which is important for developing vaccines designed to stimulate immune responses to future SARS-CoV-2 variants and to a broad range of other coronaviruses.
    - Better understand glycan masking of antigenic epitopes by preexisting antibodies (from vaccination or infection), the role of glycoprotein chemistry in immune imprinting, and its implications for designing broadly protective coronavirus vaccines (Zarnitsyna 2015).
    - Clarify the interaction between preexisting immunity and subsequent response to vaccination, including immune kinetics, breadth of protection, and the role of immune memory (Sette 2022).
    - Determine how a primed immune system can be reprogrammed or whether preexisting immunity will dominate recall responses (Pecetta 2022).

Issue: Additional correlates of protection are needed for assessing broadly protective coronavirus vaccines.

- A correlate of protection (CoP) is a measureable biomarker used to reliably predict the level of vaccine efficacy against a clinical outcome (e.g., vaccine-induced protection against infection, severe disease, or post-acute sequelae of SARS CoV-2 infection [PASC])" (Sherman 2022). The use of CoPs can facilitate down-selecting and vetting promising broadly protective vaccine candidates for clinical trials and can streamline various aspects of late-stage evaluation, potentially bypassing large-scale field trials by providing a primary endpoint for provisional or traditional approval of vaccines for specified contexts of use (Karim 2021, Openshaw 2022, Plotkin 2010).

Barriers

- Neutralizing antibodies have been identified as a potential CoP for protection against symptomatic SARS-CoV-2 infection; however, CoPs for broadly protective coronavirus vaccine outcomes have yet to be clearly defined and will likely include additional measures of adaptive and innate immune responses (Britto 2022, Gilbert 2022, Khoury 2021, Morens 2022b). This may reduce the expediency of advancing new vaccines through evaluation, regulatory approval, and post-licensure updating.
- CoPs against coronavirus infection may be distinct from those against severe disease and CoPs for mucosal immunity may be distinct from those for systemic immunity (Goldblatt 2022a).
- CoPs for broadly protective vaccines will need to take into account widespread exposures to SARS-CoV-2 antigens via prior vaccination and/or infection.
- CoPs can vary depending on the viral load at exposure, the role of immune memory, individual characteristics such as overall immunostatus, and the method used to detect

the CoP (Misra 2022). This creates obstacles for defining the necessary biomarkers to predict coronavirus vaccine efficacy.

- Determining CoPs is complicated by the absence of standardized or harmonized clinical trial endpoints for broadly protective and durable coronavirus vaccines (Misra 2022, Pecetta 2022).
- T cell assays may be important for identifying CoPs for broadly protective coronavirus vaccines; however, they are technically more difficult and costly than serologic assays, and techniques for measuring T cells are currently impractical for clinical trials (Goldblatt 2022a).
- Different vaccine platforms may have different protective immune mechanisms leading to different CoPs, which can complicate efforts to evaluate vaccine efficacy (Sui 2021).
- Studying the persistence of antibodies following infection is complicated by the lack of standardization of antibody assays, differences in sensitivity and specificity of commercially available assays, and the characteristics of participants studied (Goldblatt 2022a).

Gaps

- To identify CoPs for broadly protective and durable coronavirus vaccines, research is needed to determine the following:
  - The underlying immune mechanisms of adaptive (humoral and cellular) and innate immune responses that mediate protection against coronavirus infection and disease in different tissues and physiologic compartments, including sites of virus entry and propagation (in the mucosa and dissemination in the blood), and in different populations by age, sex, preexisting immunity, exposure histories, and other relevant characteristics (e.g., ethnicity) (Britto 2022, Rodda 2022, Sherman 2022, Sui 2021, Tan 2022).
  - The kinetics of each relevant type of immune response in the various compartments at different phases of infection, which has implications for the timing of sampling for CoP measurement. Different biomarkers have different durability profiles (e.g., anti-spike neutralizing antibody titers that correlate with short-term protection from symptomatic COVID-19) (Huang 2020).
  - Protective thresholds (i.e., a biomarker above a CoP threshold implies a high level of vaccine protection) for different key immune responses in appropriate animal models after infection, vaccination, or both (“hybrid immunity”) (Misra 2022, Suryawanshi 2022, Vardhana 2022), which are important for evaluating vaccine candidates, consistency of production, and updates over time (Goldblatt 2022b, Krammer 2021). Protective thresholds also are needed for different clinical endpoints (Sherman 2022).
  - While protective thresholds provide the most practically useful CoPs, the goal to reliably predict vaccine efficacy in some clinical context of use can be potentially satisfied with a CoP that uses the whole distribution of the immunologic biomarker or uses other features besides a threshold cut-off such as geometric mean. The requirement is to validate a statistical algorithm for predicting vaccine

efficacy based on measuring the immunological biomarker from a sample of vaccine recipients (and possibly also from another group of comparator vaccine recipients for comparison), where this algorithm may or may not make use of a threshold cut-off for the CoP.
    - There is a potential need for multiple biomarkers to increase the reliability of measurements for different intended outcomes (Jang 2020, Misra 2022, Plotkin 2020). Key components relevant to durable and broadly protective immune responses include neutralizing antibodies, memory B cells, Fc effector antibodies, and CD4 and CD8 T cell functions (Goldblatt 2022a, Kaplonek 2022, McGrath 2022).
- Reliable CoPs will be needed for different coronavirus vaccine constructs, based on different antigens (potentially strain-specific and broadly protective antigens), different vaccine platforms, and different modes of administration, in conjunction with the development of appropriate animal models and the establishment of regulatory pathways for their review (Krammer 2022).
- Even though neutralizing antibodies to the S protein appear to be a reasonable CoP for SARS-CoV-2, the titers that correlate with protection in populations with different histories of exposure to SARS-CoV-2 viruses need to be determined (Simon 2022).
- Research into CoPs for additional coronaviruses will require the availability of the necessary reagents and virus stocks.
- Defining and harmonizing clinical or efficacy endpoints is necessary for determining and comparing CoPs for different vaccines (Sherman 2022).
- Standardized, validated high-throughput assays for T cell responses are needed to advance CoP development and facilitate their use in clinical trials (Goldblatt 2022a, Huang 2020, McGrath 2022, Misra 2022, Pecetta 2022, Vardhana 2022).
- Innovation is needed to scale up T cell assays by simplifying sample collection and storage, and standardizing data collection and laboratory methods.
- A central database that includes potential CoPs for current vaccines could potentially be useful to assess multiple variables as CoPs and to test if a CoP identified in one trial is valid in other trials (Karim 2021). Depending on the use/immunobridging application of a CoP, the CoP may differ and the means to validate the CoP may differ; accordingly, the central database needs to include adequate meta-data to support the ability of data analyses to meet objectives.
- Once one or more CoPs are identified, standardized assays are needed for that CoP to ensure comparability between different vaccine platforms, modes of administration, and conditions of use (Sherman 2022, Krammer 2022). Given rapid emergence of new coronavirus genotypes, a particular challenge is achieving a common or otherwise comparable scale of CoPs to different genotypes.

Strategic Goals and Aligned Milestones

Strategic Goal 2.1: Ensure that clinical samples and immunoassays are available to the research community for improving understanding of the mechanisms of mucosal and systemic immunity related to SARS-CoV-2 infection.

Milestones:

a. By 2023, develop a centralized or virtual biorepository of historical (pre-COVID-19 pandemic) clinical samples to include mucosal (e.g., nasal lavage and saliva) and serological samples that are currently available from a range of research laboratories, potentially by tapping into existing biobanks.
b. By 2024, establish a centralized or virtual biorepository involving a new cohort of subjects from multiple regions of the world, to include those with breakthrough SARS-CoV-2 infections, for obtaining high-impact (e.g., mucosal, bronchoalveolar lavage, serologic, bone marrow), appropriately collected and timed clinical samples.
c. By 2024, establish a governance structure for collection and use of specimens from the biorepositories, to include strategies for promoting specimen sharing.
d. By 2024, create a plan for assay development aimed at generating assays to answer the key immunologic mechanistic questions related to SARS-CoV-2 that the biorepository samples can address.
e. By 2025, develop new immunologic assays as outlined in the plan and ensure that such assays are appropriately harmonized, standardized, and reproducible.
f. By 2027, develop immunologic assays for a broader range of coronaviruses that are harmonized, standardized, and reproducible.

Strategic Goal 2.2: Define mechanisms of mucosal and systemic immunity relevant to SARS-CoV-2 infection and the development of broadly protective coronavirus vaccines.

Milestones:

a. By 2024, determine how SARS-CoV-2 variants (and potentially other coronaviruses) evade antibody responses.
b. By 2025, define the initial humoral mechanisms of protection at the mucosal barrier for SARS-CoV-2 infection.
c. By 2026, determine how SARS-CoV-2 variants (and potentially other coronaviruses) evade T cell responses.
d. By 2027, define the initial cellular mechanisms of protection at the mucosal barrier for SARS-CoV-2 infection.
e. By 2027, determine mucosal biomarkers that are predictive of mucosal immune protection against SARS-CoV-2 infection.
f. By 2027, develop a “mucosal immunity atlas” to collect and organize information on innate and adaptive coronavirus mucosal immunity that maps responses across different age groups and geographies.
g. By 2027, determine the relative roles of mucosal (in the upper and lower airways) versus systemic humoral immunity in protecting against coronavirus infection and limiting the potential for virus transmission (Mettelman 2022, Poland 2021).

Strategic Goal 2.3: Clarify mechanisms for stimulating broadly protective mucosal and systemic immune responses that are cross-reactive for different coronaviruses.

Milestones:

a. By 2024, identify epitopes (other than the RBD area of the S protein) that generate protective humoral immunity and are conserved across different virus types (Cohen 2021, Crowe 2022, Martinez 2021, Saunders 2021, Walls 2021).
b. By 2025, identify broadly protective antibodies against the conserved S2 region of the SARS-CoV-2 spike protein, which may be critical for developing broadly protective coronavirus vaccines (Zhou 2022).
c. By 2025, identify mechanisms underlying the induction of broadly protective antibodies, such as via production and recall of long-lived memory B cells that recognize conserved epitopes in SARS-CoV-2 viruses (Qi 2022).
d. By 2026, identify T cell epitopes for non-spike proteins that may provide broad cross protection against different coronaviruses by stimulating CD4 and CD8 T cell responses.

Strategic Goal 2.4: Understand the mechanisms of durability of immune protection from SARS-CoV-2 and other coronaviruses.

Milestones:

a. By 2024, determine initial factors that influence duration of antibody and memory B and T cell responses following SARS-CoV-2 infection or vaccination (such as persistence of the germinal center) (Bhattacharya 2022, Moss 2022, Siggins 2021, Tarke 2022).
b. By 2029, identify the determinants of longevity for antigen-specific plasma cells in bone marrow and in mucosa-associated lymphoid tissue (Siggins 2021).

Strategic Goal 2.5: Improve understanding of the impact of preexisting immunity (infection-acquired and vaccine-mediated) on immune responses to future circulating coronaviruses.

Milestones

a. By 2025, clarify the interaction between preexisting immunity to coronaviruses and subsequent response to vaccination (such as looking at immune kinetics, breadth of protection, the role of epitope masking, and the role of immune memory) (Sette 2022).
b. By 2026, ensure that longitudinal cohort studies are implemented to determine levels of baseline immunity to coronaviruses in geographically diverse populations and assess the impact of preexisting heterotypic immunity (e.g., from prior infection with SARS-CoV-1, MERS-CoV, common cold coronaviruses, and SARS-CoV-2 variants) on susceptibility to infection and disease from future coronavirus exposures (Bean 2021, Tan 2021, Yu 2022).
c. By 2027, identify mechanisms of imprinting by population characteristics and immune responses to previous exposure to coronavirus vaccines or infection (Mettelman 2022, Pecetta 2022).
d. By 2028, determine how preexisting immunity affects recall responses and how a primed immune system can be induced to generate broadly protective immune responses to divergent coronaviruses (Pecetta 2022).

Strategic Goal 2.6: Identify mechanistic correlates of protection for vaccine-induced immunity against SARS-CoV-2 and potentially other coronaviruses.

Milestones:

a. By 2023, create a central database (primarily from observational studies) that includes potential CoPs for current SARS-CoV-2 vaccines to allow different investigators to assess multiple or alternative CoPs (Karim 2021), with new information being added as it becomes available.
b. By 2025, define and harmonize the clinical or efficacy endpoints (e.g., mild vs. severe disease) for determining and comparing CoPs for different vaccines (Sherman 2022). (Also see the Vaccinology section.)
c. By 2026, identify statistically validated CoPs for predicting efficacy of SARS-CoV-2 vaccines based on different key immune responses for different clinical endpoints and for different viral variants that have different intrinsic infectivity and transmissibility.
d. By 2027, determine whether assays for T cell responses or surrogate markers for T cell responses could serve as CoPs.
e. By 2027, conduct studies in animal models to identify CoPs for at least several coronaviruses other than SARS-CoV-2.
f. By 2027, determine one or more CoPs for mucosal vaccines.
g. By 2028, determine whether multiple biomarkers are needed to increase the performance of a CoP for predicting vaccine efficacy (Jang 2020, Misra 2022, Plotkin 2020) (such as neutralizing antibodies, memory B cells, Fc effector antibodies, and CD4 and CD8 T cell functions [Goldblatt 2022a, Kaplonek 2022, McGrath 2022]).
h. By 2028, ensure that one or more CoPs are validated.
i. By 2028, standardize and develop mechanisms to harmonize CoP assays to facilitate comparability among different vaccine platforms and modes of administration (Sherman 2022, Krammer 2022).

Additional Research Priorities

- **Continue** to study how innate immunity influences adaptive (B cell and T cell) immune responses to SARS-CoV-2 infection (Sette 2021, Tomalka 2022), particularly among different age groups.
- **Develop** a detailed understanding of the human antibody response to SARS-CoV-2 and other coronaviruses (Pecetta 2022).
- **Determine** the potential for improving breadth of protection against coronaviruses by stimulating innate "trained" immunity (Mettelman 2022, Tayar 2022, Ziogas 2022).
- **Determine** the role and mechanisms of adjuvants in mediating interactions between innate and adaptive immune responses (Carmen 2021, Lee 2022) (e.g., driving breadth of response via CD4 T cell activation) (Joyce 2022).
- **Clarify** the role of memory T cells in reducing disease severity (Kent 2022, Moss 2022, Zheng 2021).
- **Continue** to study the role of innate immunity, including development of biomarkers for innate immunity.
- **Continue to assess** the role of different immune compartments and components of adaptive immunity to SARS-CoV-2 virus infection and vaccination (or to other

coronaviruses), with a focus on the specific functions and kinetics of the three key components of the adaptive immune response (Moss 2022, Sette 2021, Sette 2022):
    - B cells, the source of neutralizing antibodies
    - CD4 T cells, which produce helper T cells, Th1 cells, and T follicular helper cells
    - CD8 T cells, which kill infected cells
- **Clarify** the role in immune protection of binding but not neutralizing antibodies produced by coronavirus vaccines (Poland 2021).
- **Determine** the kinetics and magnitude of B cell responses to conserved antigens sufficient to provide broad protection from coronavirus infection, independently or in combination with T cell responses, for different vaccine platforms.
- **Continue to assess** the immune responses to different vaccine constructs and strategies for administering them.
- **Determine** whether increased levels of broadly reactive antibodies exacerbate autoimmune disease by increasing autoreactive antibodies (Labombarde 2022).
- **Determine** the role for activating multiple arms of the immunity system (including T cells, non-neutralizing antibodies, neutralizing antibodies to conserved epitopes, innate immune responses, and mucosal immunity) in eliciting broadly protective immunity (Hauser 2022).
- **Continue to employ** innovative techniques to scale up T cell assays by simplifying sample collection and handling, and standardizing data collection and laboratory methods.
- **Consider** studies with experimental manipulation of immune markers that enable more direct assessment of mechanistic CoPs, including vaccine challenge studies, monoclonal antibody challenge studies, and field trials of monoclonal antibodies for prevention.
- **Determine** the processes by which immune dysregulation may contribute to severe COVID-19 disease following infection and the implications for development of next-generation coronavirus vaccines.
- **Continue to assess** evolution of the human B cell repertoire and antibody responses after SARS-CoV-2 infection and immunization to determine the underlying parameters that contribute to broadening of immune responses (Pecetta 2022).

TOPIC 3: VACCINOLOGY

Issue: A set of preferred product characteristics (PPCs) for broadly protective coronavirus vaccines that has been widely vetted and agreed upon by key stakeholders is needed to inform vaccine R&D.

Barriers

- Since the next coronavirus threat is unknown in terms of timing and source of emergence, transmissibility, morbidity, mortality, and clinical presentation, typical risk-benefit calculations for broadly protective coronavirus vaccines are not possible.
- Development of PCCs is complicated by the potential need for different product characteristics for vaccines that target different viruses or have different indications (e.g., transmission blocking vs. reducing morbidity and mortality).

Gaps

- Important efforts have gone into the development of target product profiles (TPPs) for broadly protective coronavirus vaccines. A set of PPCs is also necessary to provide overall guidance to the research community and to industry regarding key characteristics for such vaccines. Issues include the following:
    - Guidance on the short-term versus long-term goals will help bring the needed vaccines to market most efficiently (e.g., SARS-CoV-2 variant-proof vaccines versus vaccines that protect against multiple coronavirus species).
    - Consensus on vaccine efficacy endpoints, such as blocking infection, interrupting transmission, and/or mitigating morbidity and mortality, will help prioritize efforts in bringing next-generation broadly protective vaccines to market.
    - Clarity is needed on how durability can be measured and against which outcomes, factors affecting durability, whether or not vaccines can be made more durable and for how long, and defining realistic expectations for vaccine durability.
    - Consensus is needed on how broadly protective coronavirus vaccines will be used (i.e., proactively as part of routine vaccination programs vs. reactively as part of a pandemic or epidemic response strategy), as this will inform what is envisioned as the end products and will determine the markets for different approaches.
    - Up-front discussions are needed on how to simplify manufacturing, distribution, administration schedules (i.e., spacing, number of doses, mode), and stability (i.e., cold chain and storage requirements) without sacrificing vaccine safety or effectiveness, to facilitate equity in vaccine access (Rees 2022).
    - Emphasis should be placed on the importance of developing vaccines for global use that are not only suitable for high-income countries (HICs), but that can also be easily used in remote or low-resource settings.
- Since developing a broadly protective vaccine will be a difficult task, especially considering the many issues outlined above, it is important to define a minimally acceptable TPP or set of PPCs that focus on broad protection as a starting point.

Issue: Broadly protective coronavirus vaccine candidates will need to provide protection against a range of existing and novel coronaviruses.

Barriers

- Many novel vaccine technologies and approaches for eliciting broad protection against coronaviruses are under investigation, but additional ongoing resources and investments will likely be needed to move new vaccine candidates through the development pipeline, particularly into clinical trials.
- Selection of antigen(s) to optimize broad immunogenicity and cross-reactivity is challenging owing to the phylogenetic diversity of coronaviruses, antigenic breadth within coronaviruses, and limited understanding of conserved B and T cell epitopes across different coronavirus subgroups (Baric 2022, Pack 2022).
- Multiple scientific, methodologic, and regulatory challenges exist for development of vaccines against pathogens that have not yet emerged.

Gaps

- Researchers are studying a variety of antigen presentation platforms for eliciting broad protection such as focusing on highly conserved viral regions, and using multiplexed chimera or nanoparticle vaccine technologies (Chiu 2021, Martinez 2021, Saunders 2021, Walls 2021, Joyce 2022). At this time, it remains unclear as to which of these approaches are the most efficacious for broadly protective coronavirus vaccines.
- Further research into immunogenic antigens other than the S protein may identify novel vaccine targets that could be more broadly protective, such as the nucleocapsid, membrane or envelope proteins (Soraci 2021).
- It is unclear which vaccine platform(s) will induce the broadest and most durable protection. A number of different platforms are currently under investigation, such as live-attenuated virus vaccines, whole inactivated virus vaccines, viral-vectored vaccines, recombinant protein subunit vaccines, virus-like particle and nanoparticle vaccines, and nucleic acid (DNA or RNA) vaccines (Begum 2021, Li 2020, WHO 2022a, Sung 2021).
- Further research is needed into antigenic imprinting and heterologous prime-boost vaccination strategies for generating broad protection against multiple different coronavirus strains (Shepherd 2022, Tan 2021). For example, different vaccination approaches (e.g., immunization schedules with multiple boosters, differing schedules, the use of different vaccine platforms in a prime-boost heterologous strategy, etc.) may produce a more effective response than modifications to antigens or adjuvants alone (Shepherd 2022).
- Understanding of SARS-CoV-2 mutations and evolution, which are necessary for vaccine development, can be enhanced by an expansion of whole genomic sequencing and genomic databases, bioinformatics approaches, structure-based rational immunogen design, antigenic mapping, and computational analyses assisted by machine learning (Soraci 2021, Pack 2022).
- A set of principles could be useful for funders and developers to down select vaccine candidates for further evaluation, based on the PPCs (or a specific TPP) and use cases

for particular vaccines. Considerations should include not just vaccine efficacy, but also vaccine safety, manufacturing considerations, cold-chain issues, and ease of distribution and use, particularly in low-resource settings.

- The impact of immune imprinting and preexisting partial immunity to SARS-CoV-2 (infection-acquired and vaccine-mediated) on future vaccinations is unknown. (*Note*: This issue is further addressed in Immunology and Immune Correlates of Protection).

Issue: Candidate vaccines need to elicit durable protection.

Barriers

- Durability of protection is not easily assessed in humans or in animal models, given the lack of immune correlates of protection against infection and particularly against severe disease (Altmann 2022), and the lack of early signatures for durable immunity. (See Animal and Human Infection Models.)
- Determining how best to assess vaccine durability in preclinical development remains a major scientific challenge.
- Sustained protection against infection and disease relies on both neutralizing and non-neutralizing (T cells, memory B cells, and Fc dependent humoral responses) systemic and mucosal protective responses against a broad range of coronaviruses (Krause 2022, Hsieh 2021). The roles of these different responses in promoting durability is still under investigation (see Immunology and Immune Correlates of Protection). Additionally, immune markers for all of these responses are not readily available.
- Clinical trials may require 1 to 2 years or multiple seasons of follow-up to determine vaccine durability, which adds cost and complexity to research efforts (Hodgson 2021).
- Repeated boosting with additional doses of existing vaccines or with slightly modified vaccines may limit the ability to study novel vaccines that elicit a more broadly protective response (Pack 2022).
- Vaccines are often licensed and used before a detailed understanding of durability is available, to support a rapid response with an immediate impact on disease incidence.

Gaps

- The length and type of protection (e.g., from hospitalization, death, reinfection, and/or transmission) expected from a durable vaccine are not well-defined (Pack 2022).
- More information is needed regarding the durability afforded by different vaccine platforms.
- Adjuvants and carefully designed immunization schedules that involve periodic boosting may or may not be needed to stimulate effective and long-term protection in a primed population (Altmann 2022, Pack 2022).
- Vaccines that induce mucosal immunity may elicit greater durability (Bhattacharya 2022). Additional information is needed to determine whether or not such vaccines actually can elicit greater immunity and/or durability and how those can be achieved.

Issue: Further optimization of coronavirus vaccines is needed to improve access to future vaccines within and across different populations.

Barriers

- Stimulating mucosal immunity may be important for promoting breadth and durability of protection and may also be necessary to prevent viral entry into mucosal cells, which will prevent infection and decrease the potential for asymptomatic transmission of coronaviruses (Soraci 2021). Current injectable coronavirus vaccines do not appear to significantly stimulate adequate mucosal immunity (Azzi 2022, Collier 2022, Mudgal 2020).
- Some technologies under investigation, such as live-attenuated virus vaccines, may not be appropriate for those who are pregnant, the elderly, or others with compromised immune systems (Ansariniya 2021, Soraci 2021).
- Route of administration for future coronavirus vaccines could include existing or novel approaches to vaccine administration (intramuscular, transdermal, or nasal); experience with alternative routes of administration is limited.

Gaps

- Additional efforts are needed in the following areas to optimize future coronavirus vaccines:
    - Research into vaccines that stimulate mucosal immunity (including IgA antibodies, local mucosal IgG production, and cytotoxic T lymphocyte activation) and will likely be administered intranasally or orally. An important issue for mucosal vaccines is the need to establish a correlate of protection for mucosal immunity. (See Immunology and Immune Correlates of Protection.)
    - Improvements in vaccine thermal stability to address cold-chain issues that may limit access to certain vaccine platforms in remote or low-resource settings (Soraci 2021).
    - Strategies to increase vaccine immunogenicity among people who are immunocompromised, frail, or elderly (Sung 2021).
    - Research to determine the role of different adjuvants for improving immunogenicity of next-generation coronavirus vaccines, including the design, development, and selection of the most potent adjuvants for different vaccine platforms (Pack 2022).

Issue: Clinical trial design or other alternative approaches for demonstrating efficacy, non-inferiority, or superiority is complicated for broadly protective coronavirus vaccines.

Barriers

- The target virus (or viruses) must be circulating in humans to perform the gold standard randomized controlled clinical trial (RCT) for vaccine efficacy (Hodgson 2021). RCTs that assess the efficacy of a vaccine across the full breadth of its protection may not be possible for viruses or variants that are not yet circulating in the human population, although it may be possible to conduct RCTs to determine if a broadly protective vaccine is superior or non-inferior against whatever SARS-CoV-2 strains are circulating compared to one or more approved vaccines.

- Broad protection and cross-reactive immunity will need to be assessed in naïve, previously vaccinated, and previously infected individuals, which adds complexity to future research (Pecetta 2022).
- For SARS-CoV-2 variants, vaccine efficacy assessed during clinical trials is difficult to extrapolate because results will be dependent on currently circulating strains in a given area (Pecetta 2022).
- Differences in vaccine efficacy are likely to be observed in different geographic locations, not just because of differences in the circulating strains or prevalence of infection, but also because of health factors such as demographics, poverty, malnutrition, access to high-level medical care, and prevalence of comorbidities (Hodgson 2021).

Gaps

- The absence of standardized or harmonized clinical trial endpoints, outcomes of interest, and assays for the evaluation of the human immune response makes interpretation and comparison of clinical trial data difficult (Pecetta 2022).
- The research and regulatory communities will need to establish how to best assess efficacy of broadly protective coronavirus vaccines in light of preexisting immunity, either from natural infection or vaccination (Rees 2022). Additionally, it is unclear what regulators will require for demonstrating breadth of protection.
- Researchers may need to use one or more CoPs or well-characterized immune markers as surrogate endpoints for assessing vaccine efficacy in the absence of circulating virus (Krause 2022); however, more efforts are needed to define them.
- Owing to challenges with conducting clinical trials for broadly protective coronavirus vaccines, alternative approaches for assessing vaccine efficacy may be necessary and feasible. For example, some have proposed an alternative framework that involves comparing a new vaccine to a vaccine that is already approved for use. Examples of issues regarding using this framework include (Krause 2022):
    - The selection of comparator vaccines will rely on availability and a solid knowledge base for existing vaccines; therefore, researchers need to ensure that adequate information for the comparator vaccine is available.
    - The framework requires the ability to make direct or indirect comparisons of immune responses induced by the new and the comparator vaccine; therefore, a thorough understanding of the immune responses for each vaccine will be necessary.
    - If neutralizing immune responses are used for immunobridging, they will need to be predictive of other overall protective responses. Data validating this concept will be needed.
    - More research is needed regarding whether or not vaccines involving different platforms can be compared to each other.
- Other approaches for assessing efficacy exclusive of clinical trials include animal studies (with further immunobridging to human populations) or human infection studies. Additional efforts are needed to clarify how these alternative strategies can be used to assess vaccine efficacy, particularly for determining breadth of protection. (See Animal and Human Infections Models.)

Issue: The regulatory pathway demonstrating efficacy or non-inferiority or superiority is particularly complicated for coronavirus vaccines designed to be broadly protective.

Barriers

- It will be challenging to do more than lay out the regulatory strategies for approval of any broadly protective coronavirus vaccine until the characteristics of the viruses, the characteristics of the vaccine, and the potential indications for the vaccine's use are known.
- Accelerated pathways or Emergency Use Listing (EUL) may also be options for authorization in the case of a marked increase in the sense of urgency. Use of these pathways, however, depends on the public health risk and available data (Beasley 2016, WHO 2020).
- Opportunities for emergency use authorization and expedited licensing procedures for coronavirus vaccines may be more limited in the future (Branswell 2022), unless new pathogenic viruses emerge.
- Good clinical practice (GCP), good manufacturing practice (GMP), and good laboratory practice (GLP) form the foundation for regulatory compliance and are assessed by the country in which the activity takes place. Yet, not all national regulatory authorities (NRAs) are stringent with their GMPs and not all countries have the capacity within their NRAs to ensure GMP (Brüssow 2021).
- Regulatory issues focused on specific products cannot be readily discussed in a multilateral manner among NRAs and instead are limited to bilateral discussions among NRAs with non-disclosure agreements in place (Farley 2022 2:35:00, Cavaleri 2022 2:38:00).
- Broadly protective coronavirus vaccines will likely need to show protection not only against coronaviruses that are circulating in the human population but also potentially against viruses that are not circulating, which creates challenges for regulatory approval.

Gaps

- In some scenarios, regulatory approval may be granted by immunobridging to a comparator vaccine with known effectiveness. However, this option requires an authorized comparator vaccine that utilizes similar technology and has a similar breadth of antigenic composition. If these conditions are not met, candidate vaccines would likely need to perform additional clinical trials to demonstrate effectiveness. Measurement and understanding immune response for a comparator vaccine and a candidate vaccine are key to making direct comparisons for regulatory purposes (Krause 2022).
- Regulatory approval may be granted based on alternative pathways if the requirements of traditional regulatory pathways cannot be met for broadly protective vaccines. However, it is not yet clear what pathways will be acceptable for regulatory approval.

Strategic Goals and Aligned Milestones

Strategic Goal 3.1: Define goals for broadly protective coronavirus vaccines by establishing a widely agreed upon and vetted set of PPCs and determine use cases for such vaccines.

Milestones:

a. By 2023, building on existing TPPs, develop a broadly agreed upon and internationally vetted set of PPCs to identify key product characteristics, including optimal and critical minimal criteria. (These could follow a tiered approach, with an initial focus on variant-proof SARS-CoV-2 vaccines, then moving to other, more broadly protective tiers.)
b. By 2024, develop initial use cases for broadly protective coronavirus vaccines, defining how, where, and under what circumstances such vaccines would be used (e.g., target populations, cold-chain and vaccine stability considerations, equitable access in resource-constrained settings). (*Note*: Following initial development, the use cases and PPCs may need to be modified over time through an iterative process.)

Strategic Goal 3.2. Leverage new technologies or new approaches to create effective, durable vaccines that offer broad protection across different coronaviruses.

Milestones:

a. By 2023, determine, in coordination with regulators, which coronaviruses should be included in a panel to be made available to researchers for assessing breadth of protection for coronavirus vaccine candidates—in alignment with the characteristics outlined in the set of PPCs (Milestone 3.1.a). (Also see Virology Applicable to Vaccine R&D.)
b. By 2023, define a set of principles that can be used by funders and developers to down select vaccine candidates for further evaluation, based on the set of PPCs (or a specific TPP) and use cases for particular vaccines [Strategic Goal 3.1]), and taking into consideration the end goals for different vaccines.
c. By 2024, advance a strategy or mechanism to promote collaboration among researchers and developers aimed at combining technologies to expand breadth of coronavirus vaccine coverage, such as assessing combinations of vaccines in animal models or early clinical trials, or assessing prime-boost combinations of different approved vaccines.
d. By 2023, conduct a workshop on SARS-CoV2 transmission-blocking vaccines to identify gaps in mucosal approaches for vaccine development.
e. By 2024, develop and make available to researchers, an initial repository of coronaviruses (as available), pseudoviruses (if they can be made), and antigens, as identified in the panel in Milestone 3.2.a. The repository could be developed in a tiered fashion, with an initial focus on the highest risk viruses and then adding additional viruses over time.
f. By 2024, conduct an analysis of existing adjuvants and create a repository of available adjuvants to ensure that they are accessible and available to vaccine R&D researchers.
g. By 2025, determine, primarily through preclinical studies, if any adjuvants can substantially improve vaccine efficacy, breadth, or durability for SARS-CoV-2 variants and other coronaviruses.

h. By 2027, determine, through clinical studies, if intranasal, transdermal, and oral vaccines can enhance mucosal immunity and protect against both disease and transmission.

Strategic Goal 3.3. Establish principles for conducting clinical trials that allow for comparisons between vaccines.

Milestones:

a. By 2024, develop a set of harmonized clinical (e.g., infection, severe disease, death) and immunologic endpoints that can be used in vaccine efficacy studies for broadly protective coronavirus vaccines.
b. By 2025, develop a structure for rapidly identifying and agreeing on standardized clinical and/or immunologic endpoints that can be used to capture vaccine efficacy quickly after the emergence of a novel coronavirus.
c. By 2025, develop a scientifically rigorous framework that addresses the requirements for clinical evaluation of broadly protective coronavirus vaccines and provides guidance on streamlining the clinical trial research process.
d. By 2025, based on outcomes of the previous milestones, status of scientific knowledge, and circulating viruses at the time, develop and disseminate an international concept protocol that includes principles for clinical trials to allow for comparisons between vaccine candidates and comparator vaccines.

Strategic Goal 3.4. Build a foundation for regulatory evaluation of future coronavirus vaccines.

Milestones:

a. By 2023, initiate annual meetings between the scientific community, regulatory authorities, and vaccine developers to share the latest immunology, virology, vaccinology, and regulatory science advances and challenges to assist in building a foundation for regulatory evaluation of new coronavirus vaccines that would allow NRAs to have multilateral specific discussions on the regulatory evaluation of such vaccines.
b. By 2025, develop a set of principles for regulatory evaluation of new coronavirus vaccines that: (1) outlines what information is needed to provide confidence in the efficacy or added value of variant-proof SARS-CoV-2 vaccines, particularly in comparison to existing vaccines; (2) follows a tiered or stepwise approach (such as starting with demonstrating efficacy against circulating SARS-CoV-2 variants and then expands on that over time to assess or predict efficacy against other SARS-CoV-2 variants, then to other sarbecoviruses, merbecoviruses, or additional coronaviruses of concern as necessary); (3) takes into consideration the various mechanisms of protection that different vaccines may employ, which may help predict the potential breadth of protection for a given vaccine construct; (4) clarifies what is meant by a "broadly protective coronavirus vaccine"; (5) identifies approaches for predicting protection (i.e., predicting potential clinical benefit) against coronaviruses that are not circulating in the human population; (6) defines the potential roles and limitation of tools such as animal studies, human infection studies, and immunobridging for predicting

breadth of infection for new vaccines; and clarifies regulatory pathways for new coronavirus vaccines.

Strategic Goal 3.5. Facilitate the development of vaccine candidates with characteristics that meet global needs.

Milestones:

a. By 2023, advance the involvement of LMICs in clinical development programs, so that clinical trials of broadly protective coronavirus vaccines include LMIC settings.
b. By 2026, support the development of broadly protective coronavirus vaccines that can be made with less-complex manufacturing systems, to ensure the potential to manufacture such vaccines in more regions, which will lead potentially lead to more equitable distribution of such vaccines.
c. By 2027, support the development of coronavirus vaccine technologies that are suitable for broad access and global distribution (such as cold-chain independent technologies) and that are scalable and can be produced affordably.

Additional Research Priorities

- **Continue to expand** the use of whole genomic sequencing and genomic databases, bioinformatics approaches, structural vaccinology, and computational analyses to improve vaccine design (Soraci 2021, Pack 2022).
- **Conduct** further research into immunogenic antigens other than the S protein to identify novel vaccine targets that could be more broadly protective, such as the N or S2 antigens (Soraci 2021).
- **Evaluate**, on an ongoing basis, the potential for antigenic drift among conserved epitopes under immune pressure (e.g., when used as an antigenic target for broadly protective vaccines).
- **Encourage** innovation to improve coronavirus vaccines, building on the success of existing vaccines.
- **Continue to assess** the durability afforded by different vaccine platforms.
- **Promote** coordination between immunologists, laboratory scientists, statisticians, clinicians, and computational biologists in efforts to conduct clinical trials for broadly protective coronavirus vaccines.
- **Strategize** as to how new technologies can be deployed on a global scale with greater equitable access.
- **Continue to develop** mechanisms to improve public communications regarding safety of coronavirus vaccines, such as tracking safety concerns from the public and developing consensus communication strategies to address them.
- **Focus** additional research on the effectiveness, side-effects, and durability of vaccines in special populations, such as children, pregnant and immunocompromised people, and people with advanced age.

TOPIC 4: ANIMAL AND HUMAN INFECTION MODELS FOR CORONAVIRUS VACCINE RESEARCH

ANIMAL MODELS

Issue: Multiple animal models may be needed to assess vaccines that protect against multiple coronaviruses.

Barriers

- SARS-CoV-1 and SARS-CoV-2 bind to the hACE2 receptor; however, not all human coronaviruses bind to this site. MERS-CoV binds to DPP4, and the receptor site remains unknown for some of the viruses that cause more mild disease in humans (Gralinski 2015). Therefore, several different animal models will likely be needed to study vaccines that protect against multiple coronaviruses of different genera or subgenera.
- Animal models for studying MERS-CoV are limited by differences in critical amino acids in the S-binding domain of the DPP4 receptor (Baseler 2016).
- Appropriate animal models for SARS-CoV-1 and SARS-CoV-2 include Syrian hamsters; mice (e.g., transgenic mice, knock-in mice, mice transduced with adenovirus or adeno-associated virus expressing hACE2 or mice infected with mouse-adapted virus strains); and NHPs (Muñoz-Fontela 2020, Qin 2022, Singh 2020, Casel 2021, Shou 2021, McCray 2007, Sun 2020, Wong 2022). While these various animal models can provide useful information, they all have important limitations (Qin 2022); key examples include the following:
    - Small animal models offer several advantages because they are readily available, can be handled with less effort and cost, and may be used in large numbers for stronger statistical power during data analysis. The primary limitation is the intrinsic biological differences between humans and rodents or small mammals.
    - For NHPs, several issues limit their use. First, coronavirus illness in NHPs is generally mild and does not recapitulate the pathology seen in humans. Second, a high cost is associated with using NHPs (Gralinski 2015), which limits the number of animals that may be included in a study and thus adversely affects the statistical power. Third, most NHPs are outbred animals and have a wide variability in genetic backgrounds, which sometimes makes it difficult to interpret the outcome of a study because of variability in results among individual animals (Trichell 2021). Fourth, ethical considerations for research constrain their use (Carvalho 2018). Finally, the COVID-19 pandemic has significantly increased the demand for NHPs, which has created issues with supplies of these animals (Contreras 2021).
- Currently, virus stocks for different coronaviruses are limited. For example, 2d betacoronaviruses are not available for animal model research and stocks for 2c betacoronaviruses viruses other than MERS-CoV are very limited.
- Different animal models will be needed for studies with different aims (Wang 2021). For instance, when trying to determine whether SARS-CoV-2 still exists in the upper

respiratory tract after vaccination or to study transmission, the Syrian hamster is a potential choice, although these animals develop limited clinical disease. For SARS-CoV-2-induced pulmonary disease, as well as a preliminary exploration of mucosal COVID-19 vaccines, hACE2 transgenic mice or use of mouse-adapted viruses are potential options.

- The US Food and Drug Administration's (FDA's) Animal Rule could potentially be an appropriate regulatory pathway for facilitating approval of a broadly protective coronavirus vaccine through the use of animal studies; however, achieving approval through the Animal Rule requires demonstrating efficacy in either multiple animal species or in a single well-characterized animal model (Brockhurst 2021).
- There is lack of standardization for experimentation and reporting for research involving NHPs (Witt 2021).

Gaps

- Research needs include the following:
  - Standardized, validated, and well-characterized animal models (including NHPs) to evaluate and compare broadly protective coronavirus vaccines. Examples of parameters to consider include the challenge virus strain, dose, route, volume, and timing of challenge. Also, the appropriate clinical or virologic endpoints for each animal species need to be determined.
  - Animal models for SARS-CoV-2 VOCs are needed to assess whether the available vaccines offer protection against clinical disease (Fan 2022).
  - Further elucidation of receptor sites for non-ACE2-binding coronaviruses (Dai 2020).
  - Additional information is needed (such as data from fatal human MERS-CoV infections) to determine which animal model best represents MERS-CoV in humans (Singh 2020).
  - Animal models are needed for studying bat-derived coronaviruses, such as group 2d betacoronaviruses.

Issue: Animal models are needed that: (1) recapitulate the range of clinical features of coronavirus infection found in humans, including severe and lethal disease, and (2) can address the impact of host factors on vaccine efficacy.

Barriers

- Most animal models exhibit limited lethality in response to SARS-CoV-2 infection (Fan 2022, Kim 2022).
- With the exception of mice, comorbidities related to coronavirus disease (e.g., diabetes, obesity, cardiovascular disease) are difficult to mimic in animal models (Kim 2022).
- Animal models are needed that are suitable for both antigenically naïve populations (i.e., infants and very young children) and antigenically experienced populations (i.e., adults and children who have been exposed to SARS-CoV-2 or vaccinated and those with exposures to coronaviruses causing mild illness).

Gaps

- Research needs related to animal models include:
  - Identification of animal models that recapitulate the severe and lethal forms of human SARS Co-V-2 infection (Muñoz-Fontela 2022).
  - Identification of animal models that can assess disease for viruses that have not yet jumped the zoonotic barrier.
  - Further refinement of animal models to mimic different human conditions such as route of infection, underlying morbidities, sex, advanced age, pregnancy, and immunocompromised status that impact immune response to broadly protective coronavirus vaccines (Braxton 2021).
  - Experimentation in different animal models and using different emerging SARS-CoV-2 variants to ensure validity of research conclusions (Muñoz-Fontela 2022).
  - Animal models (particularly mouse models) for assessing human T cell responses (e.g., T helper cells [Th1 and Th2]) (Fan 2022, Jarnagin 2021).
  - Animal models for assessing "long COVID" (Frere 2022), although numerous challenges exist for this, since "long COVID" has not been clearly defined and multiple pathologic pathways may result in chronic illness following acute SARS-CoV-2 infection.

Issue: Additional challenges exist to accurately assess broadly protective coronavirus vaccines in animal models.

Barriers

- Studying broadly protective coronavirus vaccines will require availability of representative virus stocks for research in animal models, which may be challenging to obtain, particularly across different genera and subgenera of coronaviruses (Cohen 2021).
- SARS-CoV-1, SARS-CoV-2, and MERS-CoV animal experimentation must be done in at least an ABSL-3 laboratory, making work cumbersome. Furthermore, ABSL-3 laboratory space for NHP studies is limited (Hild 2021).
- A new SARS-CoV-2 variant might change the host range or affect the pathophysiology and response in certain animal models (such as Syrian hamsters). This in turn may render study in that animal difficult or lacking validity (Muñoz-Fontela 2022).
- Durable protection will be an important consideration for broadly protective coronavirus vaccines; however, duration of protection is difficult to study in animal models.
- As the COVID-19 pandemic continues and more of the human population is infected or vaccinated, the majority of humans are likely to have preexisting immunity to SARS-CoV-2, which will be difficult to mimic in animal models.
- Gain-of-function research may be necessary to optimize animal models for studying coronaviruses and coronavirus vaccine responses in animals. For example, viruses may need to be made more pathogenic to cause illness in certain animals so that vaccine effectiveness can be studied in those animals (such as through serial passage of viruses to enhance their virulence to a given animal species).

    - One challenge is that definitions regarding what constitutes gain-of-function research are not clear and are open to interpretation, which creates lack of clarity in addressing this issue.
    - Gain-of-function research is controversial and some policy makers believe that such research should be restricted. If gain-of-function research is restricted too rigorously, however, this could limit the types of vaccine R&D that can be performed in animal studies, which in turn, could hinder vaccine development. While ethical and scientific oversight of gain-of-function research is critical, efforts to overly restrict such research may be ultimately detrimental to R&D of broadly protective coronavirus vaccines.
- As SARS-CoV-2 strains evolve and become more adapted to humans, they may become less able to infect animals or cause disease in animal models (McMahan 2022).

Gaps

- Head-to-head studies in animal models with multiple vaccine candidates could enhance understanding of vaccine-induced immunity.
- Ongoing efforts are needed to ensure that validated, reliable reagents, updated virus strains and stocks, and harmonized assays are available to the research community to improve understanding of the innate and adaptive immune responses against coronavirus infection in various animal models.
- Efforts are needed to adapt animal models to reflect preexisting immunity to SARS-CoV-2 in the human population (DeGrace 2022, Fan 2022).
- SARS-CoV-2 animal models are needed in which the virus replicates for extended periods of time to allow assessment for emergence of resistant variants against vaccines (Muñoz-Fontela 2022).
- Efforts are needed to ensure adequate, sustained supplies of animals and resources (including laboratory space) for research involving NHPs, particularly specific pathogen-free NHPs (Contreras 2021). Additionally, efforts are needed to conserve animal resources and develop strategies for good stewardship of such resources (Fan 2022).

CONTROLLED HUMAN INFECTION MODEL (CHIM)

Issue: The role of a CHIM in coronavirus vaccine research needs to be further clarified and defined.

Barriers

- The potential for severe disease or long-term sequelae (e.g., “long COVID” or PASC) following infection, although uncommon, may limit the utility of a CHIM studies to investigate SARS-CoV-1, SARS-CoV-2, and MERS-CoV because of ethical considerations (Williams 2022).
- The United Kingdom is the first, and remains the only, country to perform SARS-CoV-2 CHIM studies (Killingley 2022); therefore, recent experience with a CHIM for coronavirus research is limited. Efforts are underway to expand use of the CHIM to other countries.

- Similar to influenza and other pathogens, CHIM studies are limited to healthy adults without comorbidities and thus do not reflect potential outcomes in special populations (Sherman 2019).
- CHIM studies are currently limited to small sample sizes (Killingley 2022). Capacity to run larger studies is needed so that efficacy trials can deliver results in a timely fashion. This capacity gap includes quarantine facilities and expertise.
- Obtaining challenge viruses can be a barrier to conducting CHIM research. GMP Delta and Omicron SARS-CoV-2 challenge viruses funded by the Wellcome Trust and the Bill & Melinda Gates Foundation are being made available to researchers with the capacity for CHIM studies and their rigorous safety requirements. An independent international Access Management Group as specified by the Wellcome Trust will provide oversight of these programs.

Gaps

- Additional research needs include the following:
  - Clarification of the role of CHIM studies for evaluating broadly protective coronavirus vaccines (Sekhar 2020).
  - Standardization of parameters for CHIM research in assessing broadly protective coronavirus vaccines.
  - Development of best practices for using a CHIM in coronavirus vaccine research, including risk mitigation strategies that reflect a changing landscape of disease and therapies.
  - Determining the potential impact of prior infection or vaccination against SARS-CoV-2 on CHIM studies of more broadly protective coronavirus vaccines and strategies to address this issue. It may be difficult or very resource intensive to find volunteers who are naïve to SARS-CoV-2 infection or vaccination.
  - Regulatory harmonization for conducting CHIM studies.
- Coronaviruses that cause mild disease in humans (human betacoronaviruses HKU1 and OC43 and human alphacoronaviruses 229E and NL63) or possibly attenuated wild type SARS-CoV-2 viruses may be suitable for use in a CHIM. Further clarification is needed regarding how such studies could contribute to coronavirus vaccine R&D (Morens 2022b).
- Delta and Omicron programs are funded and underway to establish models in pre-immune volunteers, so data on the effect of prior immunity on infection by variants will be generated.
- Studies in naïve participants are effectively no longer possible as almost all adults have immunity from vaccination and/or infection.
- There is a need to improve international collaboration so that products can be tested against different strains/viruses that may be available in different institutions around the world. Alignment of protocols and processes will allow meaningful comparison of results with different products and virus strains.

Strategic Goals and Aligned Milestones

Strategic Goal 4.1: Ensure that appropriate animal models are developed and available for conducting R&D for broadly protective coronavirus vaccines.

Milestones:

a. By 2023, convene an international workshop on animal models for studying broadly protective coronavirus vaccines. Examples of topics for the workshop include: (1) review existing animal models for coronaviruses (to include but not limited to SARS-CoV-1, SARS-CoV-2, and MERS-CoV); (2) determine which animal models are best suited for R&D of broadly protective coronavirus vaccines; (3) identify strategies to optimize the use of mouse models (and other small mammals including hamsters and ferrets) for coronavirus vaccine research; (4) determine how best to optimize the use of NHPs for R&D efforts, particularly given their limited supply; (5) determine how to mimic preexisting immunity in animal models; (6) determine how animal models can be used to assess the impact of host genomics or the microbiome on vaccine performance (e.g., the use of "dirty mice"); (7) determine the role of animal models in measuring mucosal immunity, breadth, and durability of vaccines; (8) determine the role of animal models in defining immune CoPs; (9) determine the role of animal models in studying long COVID; (10) address issues around gain-of-function research applicable to animal models; (11) identify gaps in the current animal model landscape; and (12) develop strategies and plans for meeting animal-model research needs going forward.

b. By 2023, develop a strategy to ensure that validated, reliable reagents, virus strains and stocks, and harmonized serological assays are available for studying a broader range of coronaviruses (with initial focus on additional sarbecoviruses [group 2b betacoronaviruses] and a wider variety of MERS-related merbecoviruses [group 2c betacoronaviruses]).

c. By 2025, ensure that standardized, validated, and well-characterized animal models are available to evaluate and compare broadly protective coronavirus vaccines. Examples of parameters to consider include the challenge virus strain, dose, route, volume, and timing of challenge, and animal responses to human-adapted variants. Immune history and prior exposure to ancestral coronaviruses should also be considered. The appropriate surrogate markers of clinical disease severity (such as weight loss or markers for lung pathology) are needed for each animal species.

d. By 2025, conduct side-by-side comparisons of various animal models to determine transmission dynamics in different animals and which animals are most appropriate for studying different SARS-CoV-2 variants or other coronaviruses.

e. By 2026, conduct head-to-head comparison studies of multiple vaccine candidates in different animal models (including small mammals and NHPs).

f. By 2026, conduct parallel studies of vaccine candidates in humans and NHPs that are aligned as closely as possible (e.g., by using similar dosing and schedules) to obtain information for immunobridging from animals to humans.

g. By 2027, ensure that standardized, validated, and well-characterized animal models are available that recapitulate the range of severe acute disease associated with human COVID-19 (such as severe lung disease, coagulopathies, and neurological manifestations) (Muñoz-Fontela 2022).

h. By 2027, determine the role of animal models in studying long COVID/PASC.

Strategic Goal 4.2: Establish the role of a CHIM in R&D for broadly protective coronavirus vaccines and optimize the model for vaccine research.

Milestones:

a. By 2023, conduct a workshop to clarify the role of CHIM studies for evaluating broadly protective coronavirus vaccines (Sekhar 2020). Examples of key issues include: (1) developing consensus on how CHIM models can be used for coronavirus vaccine research; (2) identifying strategies for studying the role of prior immunity from infection or vaccination on vaccine performance; (3) determining how CHIM studies can be used to assess mucosal immunity and mucosal inflammatory markers; (4) determining the role of the CHIM in establishing CoPs; (5) identifying strategies for assessing vaccine durability; and (6) clarifying how CHIM studies involving coronaviruses that cause mild disease in humans could inform additional coronavirus vaccine R&D (Morens 2022b).
b. By 2024, determine the potential impact of prior infection or vaccination for SARS-CoV-2 on CHIM studies involving SARS-CoV-2 vaccines.
c. By 2024, develop a set of best practices for using a CHIM in coronavirus vaccine research to include risk mitigation strategies that reflect a changing landscape of disease and therapies.
d. By 2025, work with global regulators to establish parameters for use of CHIM studies and immunobridging for licensure of candidate vaccines.
e. By 2025 (assuming candidate vaccines are available) standardize parameters for a CHIM model in assessing broadly protective coronavirus vaccines, such as defining appropriate strain selection, standardizing panels of immunologic assays and assay harmonization, identifying mucosal inflammatory markers, and harmonizing protocols to the degree possible.
f. By 2026, establish international capacity and collaborative networks for conducting CHIM studies of broadly protective coronavirus vaccines.
g. By 2028, (assuming candidate vaccines are available) determine the potential impact of prior infection or vaccination for SARS-CoV-2 on CHIM studies involving broadly protective coronavirus vaccines.

Additional Research Priorities

- **Further elucidate** receptor sites for non-ACE2 binding coronaviruses to inform animal model development for coronavirus vaccine research (Dai 2020).
- **Continue to identify** the most suitable animal models for studying MERS-CoV infections (Singh 2020).
- **Conduct research** to determine suitable animal models for bat-derived coronaviruses, such as group 2d betacoronaviruses.
- **Further refine** animal models over time to mimic different human conditions such as route of infection, underlying morbidities, sex, advanced age, and immunocompromised

status that impact immune response to broadly protective coronavirus vaccines (Braxton 2021).

- **Determine** on an ongoing basis the best strategies for using animal model studies in assessing the emergence of SARS-CoV-2 viral variants that can evade immune protection from vaccination or infection (Muñoz-Fontela 2022).
- **Continue to explore** how data from animal models or human infection models can be used to support vaccine licensure and what the parameters are for defining the role of such data.
- **Ensure**, on an ongoing basis, adequate and sustained supplies of animals and resources (including laboratory space) for research involving NHPs, particularly specific pathogen-free NHPs (Contreras 2021).
- **Employ** single-cell transcriptomics in the CHIM to dissect cell-specific responses.
- **Assess** on an ongoing basis the risks and benefits of gain-of-function research related in animal and human infection models to ensure that such research meets acceptable bioethical and safety standards.

TOPIC 5: POLICY AND FINANCING

Issue: Multiple market forces work against bringing broadly protective coronavirus vaccines to the global community in high, middle, and low-income countries

Barriers

- The current coronavirus vaccine R&D field is filled with an array of existing patents, contracts and agreements, social and economic inequities, geographic maldistribution of manufacturing capacity, and unstable funding.
- R&D of new vaccines is exceedingly expensive. Recently, governments and foundations provided billions of dollars to bring SARS-CoV-2 vaccines to market; however, the political will and public interest for continued funding are challenging to maintain in a landscape where there is always the next variant, virus, or pandemic threat (Lancet Commission 2021), and public support for such large-scale investments is diminishing (Branswell 2022). Also, once a crisis has passed, government funding will be more difficult to obtain, since governments face pressures to address urgent crises rather than long-term strategies.
- Vaccines can be a winner-takes-all (or most) market with a significant advantage to being first to market. This is especially true in pandemic or epidemic situations, where the first vaccine to demonstrate efficacy is fully purchased by governments before other candidate vaccines have had a chance to complete their clinical development. One way to address this is for the governments to divide the market share once other vaccines enter the market. The rapidly waning immunity of early SARS-CoV-2 vaccines and decreased vaccine efficacy against variants, however, may reduce some of the first-to-market advantage for current coronavirus vaccines.
- Unless problems are noted with a vaccine, there is little incentive to invest in better or next-generation vaccines (Agarwal 2022). With SARS-CoV-2 vaccines, the financial risks and benefits of the current situation tend to favor minor changes to existing technologies rather than investment in novel technologies. For example, one current commercial model is to create boosters specific to new variants as they arise, using existing platforms. This model may play into the status quo of creating strain-specific vaccines, rather than expanding vaccine R&D to generate broadly protective vaccines.
- Unless opportunity costs are absorbed by governments or other funding bodies, companies face a high opportunity cost when it comes to focusing on vaccines rather than other pharmaceuticals with a likely higher per-unit profit, on-going use, and stable demand.
- Coronavirus vaccines face a large global market that is dominated by a few large purchasers. A large market size can be seen as both an opportunity and a hindrance for private investment into new vaccines. For example, a large market size in HICs can lead to higher pricing; however, larger market size can also negatively impact vaccine per-unit pricing, as governments or large global purchasers, such as Gavi, the Vaccine Alliance, negotiate for extensive contracts, which can be market shaping and lead to less flexibility in pricing (Haugen 2020, Agarwal 2022, Monrad 2021).

- Ensuring global equity in vaccine access will need to address the current geographic concentration of vaccine R&D, manufacturing, and purchasing power of HICs, which can lead to gross inequities in the vaccine market. Organizations such as Gavi played a critical role in securing COVID vaccines for the world's poorest countries through the newly established COVAX Facility; it remains unclear what the role of Gavi and the COVAX Facility would be for procurement of future broadly protective coronavirus vaccines for LMICs.
- Maximizing the potential benefit of vaccination relies on global demand and vaccine uptake. There is a collective memory among vaccine developers of times when the vaccine markets lacked demand and therefore recouping development costs was seen as less reliable.

Gaps

- There are a multitude of ongoing efforts in basic and applied research, laboratory systems, research infrastructure, and global capacity-building to bring broadly protective coronavirus vaccines to a global market. However, efforts are not coordinated, broadly shared, or designed for efficiency and avoidance of duplication.
- Unlike at the beginning of the COVID-19 pandemic, when there was considerable urgency to invest in novel products, at this stage, a focused set of incentives may be needed to encourage novel vaccine technologies that may be superior to first-generation vaccines. However, until novel technologies are shown to be superior to first-generation vaccines, vaccines that have a proven track-record cannot be abandoned or ignored.
- Alongside the push incentives of government funding and non-monetary drivers, pull incentives, such as advanced market commitments that signal a predictable and sufficient market, are needed in high, middle, and low income countries to drive products toward approval, manufacturing, and availability. Strategies to support these incentives are needed.

Issue: Intellectual property rights are a critical aspect of vaccine innovation, yet come at a cost.

Barriers

- New vaccine candidates will likely be based on a series of patented technologies, many of which already exist. Many different patents apply to vaccines from development to components to manufacturing to delivery (WIPO 2022).
- Although governments heavily fund academic and corporate R&D, the resulting intellectual property rights of these public funds end up in private sector, non-governmental domains. The public sector is reluctant to increase public investment when it is unclear if there will be a commensurate public access to intellectual property established through the use of public monies (Rees 2022a).
- Only a partial picture is available as to the patents that exist surrounding next-generation coronavirus vaccines.
    - Four hundred seventeen patents related to COVID-19 vaccine development were filed from 2020 through September 30, 2021 (WIPO 2022). However, patent

publications can take 18 months to be published (Alshrari 2022, Kitsara 2022, WIPO 2022). The time to patent publication varies by country, from 7.7 months in China to 18.8 in the US and 18.9 in Japan (WIPO 2022). Because of the lag in entering the public domain, these 417 are just an early indication of the patent activity surrounding COVID-19 vaccines, not to mention technology related to vaccine research, development, testing, and production.

- Negotiating licensing agreements and understanding the intellectual property landscape can be quite costly and require expertise, which may cause vaccine developers to hesitate in pursuing a new approach.

Gaps

- The future application of World Trade Organization (WTO) agreements, including but not limited to Trade Related Aspects of Intellectual Property Rights (TRIPS) flexibilities for public health emergencies, is uncertain and needs clarification.
- Awards of public monies for research and development do not always include clauses to improve intellectual property access for smaller developers, those in LMICs, and more broadly during in times of public health need. Similarly, with few exceptions (e.g., CEPI), public investment does not compel developers to commit to ensuring access in LMICs in the event that their product is successfully developed.
- The long-term outcomes of voluntary licensing and sharing being undertaken during the COVID-19 pandemic are unknown. It is unclear what will happen to intellectual property rights not currently being enforced when the pandemic is truly "over."
- Efforts are needed to clarify the role of patent pools, such as WHO's COVID-19 Technology Access Pool (C-TAP), and vaccines capitalizing on established technologies that are not patent protected (Hotez 2021, WHO 2020).

Issue: Timely access to broadly protective coronavirus vaccines will require a greater degree of manufacturing capacity.

Barriers

- If a new coronavirus emerges to cause another pandemic, rapid access globally to either a strain-specific vaccine or to broadly protective coronavirus vaccines will be critical for mitigating pandemic impact. A global concentration of manufacturing and regulatory capacity exists in HICs and in some countries with very large populations, guaranteeing them a large national market. Furthermore, the current vaccine industry can, in a time of a public health emergency and vaccine shortages, become protectionist either because of government constraints on vaccine exports or because of tiered pricing structures that favor HICs. In the case of COVID-19, both considerations likely contributed to the inequity in vaccine access between those countries with and without these capacities.
- Successful technology transfer is complex and requires trusted partners with the expertise and capacity, long-term human and financial investment, and political will.
- Countries have highly variable levels of regulatory capacity to monitor GCP, GMP, and GLP, and very few regulatory authorities in LMICs have received a WHO maturity level 3

for vaccines, which is required if locally manufactured vaccines are to be considered for the global market.

- Intellectual property waivers alone may not be as successful as good and complete technology transfers based on manufacturing capacity and expertise (Prasad 2022).
- Patent holders are looking for trusted partners for technology transfer to ensure there is the expertise and experience to produce high-quality, safe vaccines that can pass regulatory approval (Kahla 2022, Nohynek 2022, Rizvi 2022).
- Manufacturing capacity is not merely an issue of building the facilities and expertise, but also the ability to maintain this capacity in a way that is financially sustainable over time, particularly during non-pandemic times.

Gaps

- It is unknown how voluntary technology transfers, pledges to not enforce patents, WTO actions, TRIPS flexibilities, and licensing agreements will play out in the next phases of the COVID-19 pandemic or as the pandemic wanes.
- Funding at-risk manufacturing, or scaling up dose production ahead of clinical trial completion or vaccine regulatory approval, may be a way to speed up the availability of new vaccines in the event of a public health emergency (Sampat 2021). However, there is little appetite for these mechanisms at the current time and how this could be used to promote broadly protective coronavirus vaccines is unknown; thus, further exploration of mechanisms to address these issues is warranted.
- WHO and partners have established the mRNA Technology Transfer Hub, the global biomanufacturing training hub in the Republic of Korea, and the Global Benchmarking Tool for regulatory authorities to address global manufacturing capacity. However, efforts are still needed to operationalize these programs, expand engagement of companies with the most advanced capacities, and expand efforts to other vaccine platforms beyond mRNA technologies (WHO 2022b, WHO 2022).

Strategic Goals and Aligned Milestones

Strategic Goal 5.1. Establish and convey the value of sustained financial support and demand for development of broadly protective coronavirus vaccines.

Milestones:

a. By 2024, develop and disseminate a detailed economic case for broadly protective coronavirus vaccines through a full value of vaccine assessment (FVVA) or a series of detailed cost-benefit analyses for vaccines from SARS-CoV-2 variant-proof vaccines to more broadly protective coronavirus vaccines. These assessments will need to include a multitude of perspectives (e.g., health payers, economic, and societal) at a number of levels (e.g., global, national, and regional) and take into account varying contexts (e.g., demographics, healthcare capacity, competing health priorities) (Giersing 2021).
b. By 2024, develop targeted communications and advocacy strategies and necessary communication tools that build on the FVVA or cost effectiveness analyses and provide information on the economic costs, risks of future coronavirus threats, and the need for continuing investment in coronavirus vaccine R&D.

c. By 2024, convene a meeting of vaccine investors, purchasers (including governments and large global institutions), producers, and governmental representatives aimed at exploring strategies for providing a reliable marketplace and financial model for broadly protective coronavirus vaccines. Meeting participants will assess the current push (e.g., grants, subsidies) and pull incentives (e.g., advance market commitments) and appropriate thresholds to move from push to pull, as well as establish a pricing model in line with the PPCs that can be anticipated for vaccines of various characteristics (e.g., number of doses required, stability, duration of protection, protection offered).
d. By 2025, explore strategies for ensuring a 10-year international funding stream, involving public and private partners, aimed at supporting R&D for broadly protective coronavirus vaccines.

Strategic Goal 5.2. Reassess the current landscape of intellectual property rights to improve information sharing involving new technologies.

Milestones:

a. By 2023, develop a consensus vision for how licensing of intellectual property rights derived from academic or publicly funded research can address inequity and adopt global equitable access clauses from the earliest stage of research.
b. By 2024, initiate a resource center to support licensing negotiations and intellectual property capacity building by scientists that may not have the resources or background knowledge to effectively achieve access to patented technologies.

Strategic Goal 5.3. Build a sustainable and more balanced geographic distribution of manufacturing capacity with expertise to manufacture high-quality vaccines for local use.

Milestones:

a. By 2024, establish a consensus as to what is acceptable geographic distribution for vaccine manufacturing and potential pathways for transitioning from variant-specific SARS-CoV-2 vaccines to broadly protective vaccines.
b. By 2027, provide the necessary resources to ensure 100% of countries with vaccine manufacturing capacity are able to at least partially implement the WHO inspection indicators, as defined by the WHO Global Benchmarking Tool (WHO 2021).
c. By 2028, through the WHO mRNA Technology Transfer Hub and additional global initiatives supporting the manufacture of other vaccine platform technologies: (1) design and build manufacturing sites meeting the GMP criteria for vaccines, (2) transfer expertise for mRNA platforms and other relevant technologies, and (3) begin producing vaccines in at least several new locations with consideration as to how to maintain capacity over time and through inter-pandemic years (Medicines Patent Pool 2022).

Additional Research Priorities

- **Coordinate** efforts to address the various challenges facing financing of R&D for broadly protective coronavirus vaccines.

- **Maintain** increased global sharing and communication across scientists, vaccine developers, manufacturers, funders, and government bodies.
- **Review** the experience with the TRIPS agreements and voluntary non-enforcement of intellectual property rights during the early years of the COVID-19 pandemic.
- **Continue to build** capacity and collaboration among NRAs worldwide, including joint reviews of clinical trials and licensure applications, and agreement on global standards for licensure of protective coronavirus vaccines.
- **Continue to gather data** on the role and impact of coronavirus vaccines (including vaccine effectiveness) to build vaccine demand, which will in turn impact policy development.

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