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Commentary

A research and development (R&D) roadmap for broadly protective coronavirus vaccines: Setting a path to address coronavirus threats

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1. The persistent threat of coronaviruses

The emergence and spread of three pathogenic coronaviruses over the last 20 years serves as a dire warning for the future and must galvanize the global scientific and public health communities to act now to prepare for the next coronavirus threat. We need to acknowledge that the COVID-19 pandemic is not a "black swan" event and that future spillovers of coronaviruses from animal reservoirs to humans are very likely to occur; the question is not "if" but "when." The first novel coronavirus (severe acute respiratory syndrome coronavirus [SARS-CoV-1]) emerged in 2003 and was followed by Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012. The current COVID-19 pandemic and the rapid, ongoing evolution and emergence of new SARS-CoV-2 variants of concern (VOCs) that are capable of evading immune protection present a crucial opportunity for action and highlight the need to improve global pandemic preparedness, particularly through the development of new and improved vaccines before the next coronavirus threat appears.

When SARS-CoV-1 emerged in 2003, the scientific community was taken off guard. Cases were first recognized in November 2002, when an outbreak of atypical pneumonia occurred in Guangdong Province, China [1]. Additional outbreaks occurred in early 2003 in Hong Kong, Singapore, and Toronto. Over the next 3 to 4 months, SARS-CoV-1 spread to 26 different countries on five continents, with just over 8,000 cases and 774 deaths identified, yielding a case-fatality rate (CFR) of about 10% among reported cases [1]. Because transmission occurred primarily when people were severely ill, most cases were associated with outbreaks in healthcare settings, although some were associated with public "superspreader events." Fortunately, widespread person-to-person transmission did not occur and cases subsided during the summer of that year. In 2004, a second independent spillover event occurred in China, but only four cases were identified [2]. Since then, the virus has essentially disappeared; no further outbreaks have been recognized nor has the virus been found in natural settings.

MERS-CoV was first identified as a cause of atypical pneumonia in the Kingdom of Saudi Arabia in 2012 [3]. Since then, cases have continued to occur at low levels, primarily in the Middle East and particularly in Saudi Arabia. Most cases have had contact with dromedary camels, which serve as the primary host reservoir. Person-to-person transmission has been limited, although a relatively large outbreak of person-to-person transmission, involving 186 cases and 38 deaths, occurred in the Republic of Korea in 2015 following the importation of the virus from a traveler who had been in the Middle East [4]. To date, cases have been reported from 27 countries across the Middle East, North Africa, Europe, North America, and Asia (primarily related to travel). As of July 2022, 2,603 cases had been identified globally, with a CFR of 36% among reported cases [5].

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) [6]. 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 [7]. Over 500 coronaviruses have been identified in various bat species [8] and bats are considered to be the major evolutionary reservoir and ecological driver of coronavirus diversity globally [9]. Given that coronavirus genomes have a fair amount of genetic plasticity, can evolve extremely rapidly, and are capable of jumping to different animal species, we can expect that pathogenic coronaviruses will continue to emerge from the bat reservoir or some intermediate animal host in the future [6].

Although SARS-CoV-1 and MERS-CoV are highly pathogenic, neither virus has been shown to be highly transmissible between humans. Conversely, SARS-CoV-2 is much less virulent (with a case fatality rate of 1% or less) but much more transmissible, including the potential for transmission from those who are asymptomatic, which has made it difficult to control and has led to more than 500 million reported cases and 6 million deaths globally since the pandemic began in early 2020 [10]. A major concern is that a new coronavirus that is both highly pathogenic *and* highly transmissible could emerge from an animal reservoir at any point in

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the future. The consequences of the COVID-19 pandemic would pale in comparison to such a scenario. Thus, broadly protective and durable coronavirus vaccines that can prevent severe disease, and ideally prevent infection and reduce transmission, are urgently needed to mitigate the ongoing emergence SARS-CoV-2 VOCs and to protect against the future emergence of additional novel coronaviruses with pandemic potential.

2. Limitations of existing coronavirus vaccines

The global scientific community responded with remarkable speed and efficiency to create vaccines against SARS-CoV-2 in an unprecedented cooperative effort, which prevented an estimated 20 million deaths during the first year of the pandemic [11]. We now realize that these vaccines, while a remarkable achievement, are falling short for several reasons. First, mRNA vaccines do not provide durable protection. This may, in part, be attributable to the lack of mucosal immunity generated by these injection-based vaccines. Second, SARS-CoV-2 is continuing to evolve, with rapid emergence of new VOCs that are capable of evading immune protection; existing vaccines do not offer broad enough protective immunity to counter all of these new variants. Vaccines that require boosting several times—because of waning immunity or the need to respond to a new target—do not offer a sustainable option from either the vaccine manufacturing or public-health vaccination program perspectives. Third, the current vaccines are not effective at preventing transmission. Ongoing widespread transmission has contributed to the emergence of new VOCs and until chains of transmission are substantially diminished, new variants will likely continue to emerge. Finally, mRNA vaccines require complex manufacturing capabilities and cold chains and are not specifically designed for use in low- and middle-income countries (LMICs), which is an important barrier against global immunization efforts. While existing vaccines have reduced the impact of the COVID-19 pandemic, next-generation broadly protective coronavirus vaccines are urgently needed to address these ongoing limitations.

3. Challenges with developing broadly protective coronavirus vaccines

Although the need for next-generation coronavirus vaccines is clear, a number of important challenges exist to move such vaccines forward. One early and critical need is for researchers, regulators, and policy makers to clearly articulate and agree upon a set of preferred product characteristics (PPCs) or a target product profile (TPP) for broadly protective coronavirus vaccines. This should not only include the vaccine's performance characteristics (efficacy, safety, and durability), but also should include the importance of designing vaccines with the end users in mind and ensuring that future coronavirus vaccines are practical and suitable for use in all areas of the world, including in LMICs. Additionally, an adequately resourced, sustainable financial model for vaccine R&D is needed that expands current public–private partnerships toward the goal of developing these vaccines.

Examples of a few of the many focused research questions that need to be addressed for developing broadly protective coronavirus vaccines include the following: (1) **better characterization** of the universe of coronaviruses that exist in natural reservoirs (particularly in bats and for the sarbecovirus subgenus of betacoronaviruses) to understand the breadth of coverage required for broadly protective vaccines; (2) **improved understanding** of which coronaviruses may be most likely to spill-over from animals into humans (such as by conducting serosurveys for antibodies to different coronaviruses among people who work at the human-animal interface in high-risk areas); (3) **identification of** highly conserved B and T cell epitopes across a broad range of coronaviruses, which can inform vaccine design; (4) **clarification** regarding the role of mucosal immunity in creating durable vaccines and strategies for how best to stimulate mucosal immunity in non-naïve populations; and (5) **development** of validated and standardized correlates of protection (potentially including correlates for T cell responses) to allow meaningful comparisons of vaccine-induced immunity across different vaccines.

4. An R&D roadmap for broadly protective coronavirus vaccines

Thus, the acute need is for coronavirus vaccines that produce broadly protective immunity and induce durable mucosal immunity at the portal of viral entry. These needs were affirmed at the White House Summit on the Future of COVID-19 Vaccines on July 26, 2022. Furthermore, a number vaccine developers, non-profit organizations, and government agencies are working toward this goal, with the Coalition for Epidemic Preparedness and Innovations (CEPI) and the US National Institute of Allergy and Infectious Diseases (NIAID) at the forefront [12]. Because the research, regulatory, and policy issues involved in generating broadly protective coronavirus vaccines are complex and diverse, a research and development (R&D) roadmap can serve as a comprehensive framework for guiding R&D efforts over time. R&D roadmaps have been developed for a number of other pathogens, including roadmaps specifically focused on vaccines, such as for influenza, tuberculosis, and malaria [13–15]. The World Health Organization's Blueprint to Prevent Epidemics has also supported the development of R&D roadmaps aimed at diagnostics, therapeutics, and vaccines for a number of high-priority pathogens, including Ebola/Marburg, Lassa, Nipah, and Zika viruses; MERS-CoV; COVID-19; Crimean Congo Hemorrhagic Fever; Rift Valley Fever; and Pathogen X (a novel previously unknown pathogen) [16].

The Center for Infectious Disease Policy and Research (CIDRAP) at the University of Minnesota, with support from The Rockefeller Foundation and the Bill & Melinda Gates Foundation, has embarked on a process to create an R&D roadmap for broadly protective coronavirus vaccines. This process harnesses the engagement of approximately 50 world-renowned subject matter experts with diverse backgrounds in virology, immunology, vaccinology, use of animal and human infection models, and policy, financing, and regulation. The resulting draft roadmap will be shared for broad public comment in October 2022 and will be finalized by early 2023. By involving key experts, funders, and stakeholders in the development process, the roadmap will identify the highest priority activities needed to achieve the goal of broadly protective vaccines that can mitigate future coronavirus pandemic threats and can serve to galvanize the global community to advance a coordinated investment for such vaccines. Additionally, the roadmap will provide a framework to guide and stimulate research by academia, biotechnology companies, and large pharmaceutical companies needed to respond to the complex issues surrounding SARS-CoV-2 transmission, broad protection against VOCs and pre-emergent novel coronaviruses, immune memory and durability, acceptability for all ages, and global equity with affordable vaccine pricing. Without such vaccine advances, we will continue to chase viruses already in circulation, with the hope of limiting the morbidity, mortality, and the global economic and social disruption that such viruses cause. With a proactive strategy, however, we will be better prepared to mitigate future pandemic threats and control the recurrent cycle of new SARS-CoV-2 variants. If now isn't the time to launch such an aggressive approach, what are we waiting for?

Data availability

No data was used for the research described in the article.

Declaration of Competing Interest

Drs. Moore, Osterholm, and Lackritz report no competing interests. Dr. Poland declares the following interests: Dr. Poland offers consultative advice on COVID-19 vaccine development to AstraZeneca, Pfizer, Medicago, Johnson&Johnson/Janssen, Novavax, and Moderna. Dr. Poland has received grant funding from ICW Ventures for preclinical studies on a peptide-based COVID-19 vaccine for which he holds a patent. These activities have been reviewed by the Mayo Clinic Conflict of Interest Review Board and are conducted in compliance with Mayo Clinic Conflict of Interest policies.

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