not technical but ethical: the paramount fiduciary responsibility is to all humans and to the persistence of medicine as a moral and human profession.

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Anticipating the Next Pandemic

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Reflecting on a pandemic that killed nearly twice as many people in the United States as the 1918 influenza pandemic — which had been the worst infectious disease outbreak in the country's recorded history before Covid-19 — offers several lessons for pandemic preparedness and response. First, the Covid-19 pandemic led to extraordinary advances in vaccinology, resulting in the availability of safe and effective vaccines and demonstrating the ability of the medical community to rapidly address a major challenge in the face of an urgent public health need. Paradoxically, a second lesson is about the fragile state of the national and global vaccine enterprise, including issues associated with vaccine distribution and acceptance. A third lesson is that partnerships involving private, government, and academic resources were critical for facilitating the rapid development of the first generation of Covid-19 vaccines. Building on these lessons in the current interpandemic period, the Biomedical Advanced Research and Development Authority (BARDA) is seeking to support the development of a new generation of improved vaccines.

Project NextGen is a $5 billion initiative sponsored by the Department of Health and Human Services aimed at developing next-generation medical countermeasures against Covid-19.[1] This initiative will support double-blind, active-comparator, controlled phase 2b trials assessing the safety, efficacy, and immunogenicity of experimental vaccines relative to approved vaccines in ethnically and racially diverse populations. We anticipate that the vaccine platforms could be adapted to vaccines for other infectious diseases, thereby enabling a rapid response to future health security threats. These trials will address several considerations (see table).

The primary end point of the proposed phase 2b clinical trials will be a greater than 30% improvement in vaccine efficacy over a 12-month period relative to currently approved vaccines. Efficacy will be based on protection against symptomatic Covid-19; in addition, participants will conduct weekly self-testing using nasal swabs to capture data on asymptomatic infections as a secondary end point. Whereas vaccines that are currently available in the United States are based on the spike antigen and are delivered intramuscularly, next-generation candidates will rely on more diverse platforms that contain spike genes as well as more conserved regions of the viral genome, such as the genes encoding nucleocapsid, membrane, or other nonstructural proteins. New platforms may include recombinant viral vector vaccines that use replication-incompetent or -competent vectors and contain genes encoding SARS-CoV-2 structural and nonstructural proteins. Second-generation, self-amplifying mRNA (samRNA) vaccines are a rapidly emerging form of technology that will be evaluated as another option. SamRNA

Objectives for Next-Generation Covid-19 Vaccines.

Objective	Justification
Establishment of a correlate of protection	Reduce the need for large, expensive clinical trials to assess vaccine efficacy
Broader protection	Prevent pan-sarbecovirus transmission and infection, including for SARS-CoV-2 variants and seasonal coronaviruses
Greater duration of immunity	More effectively induce innate and adaptive immunity, with less need for booster dosing
Prevention of infection (sterilizing immunity)	Reduce the risk of transmission and asymptomatic infection
Alternative routes of administration	Permit needle-free administration, such as mucosal or transcutaneous administration
Sustainable manufacturing approaches	Promote simplicity in production; reduce costs and the need for ultrarefrigeration
Improved safety profile	Reduce the risk of local and systemic reactions
Platform plasticity	Permit scalability and rapid production; facilitate targeting of new antigens for new variants and pathogens
Increased trust and acceptance	Enhance vaccine uptake

vaccines encode a replicase with the sequence of the selected immunogen that can be delivered in lipid nanoparticles to stimulate a precise adaptive immune response. Potential advantages of this platform include RNA dose sparing (which could lead to less reactogenicity), a more durable immune response, and increased vaccine stability at refrigerator temperatures.

A correlate of protection (CoP) is defined by a specific adaptive humoral and cellular immune response that confers protection against infection or reinfection by a specific agent. Phase 2b studies will evaluate potential CoPs for Covid-19 vaccines. For many viruses, including coronaviruses, identifying a CoP has been difficult because multiple components of the immune response work synergistically to inactivate the virus, including neutralizing and nonneutralizing antibodies (such as agglutinating, precipitating, or complement-fixing antibodies), antibody isotypes, CD4+ and CD8+ T cells, antibody Fc effector functions, and memory cells.[2] Adding further complexity, the role of these components in protecting against SARS-CoV-2 probably varies depending on the anatomical location (e.g., circulation, tissue, or respiratory mucosal surface) and the end point under consideration (e.g., asymptomatic infection, symptomatic infection, or severe illness).

Although establishing a CoP remains challenging, results from prelicensure vaccine trials have helped quantify the relationship between the level of circulating neutralizing antibodies and vaccine efficacy.[3] Identifying a CoP would have several benefits. A well-established CoP might enable immunobridging studies for new vaccine platforms that are quicker and less expensive to conduct than large, placebo-controlled efficacy trials and could facilitate assessment of vaccine protection in populations that weren't included in efficacy trials, such as children. Identifying a CoP would also permit assessment of the duration of immunity after infection with or vaccination against emerging strains and assist in determining when vaccine boosters are needed.

The first omicron variant emerged in November 2021 and was designated a variant of concern on the basis of its roughly 30 amino-acid substitutions (including 15 in the spike protein) relative to the original strain. Antibodies generated by infection during the preceding alpha, beta, gamma, and delta waves or by vaccination demonstrated reduced neutralizing activity against the omicron variant, which enabled omicron to outcompete delta globally within weeks. Despite a reduced capacity for replication in the cells of the lower respiratory tract relative to earlier strains, omicron initially caused a dramatic increase in infection rates. Subsequent omicron variants evolved with progressively increasing ability to evade existing neutralizing antibodies and with enhanced binding avidity to angiotensin-converting enzyme 2 (ACE2) receptors, which resulted in increased transmission. These lineages (including JN.1, a descendent of BA.2.86) were associated with a lower burden of severe disease, however. Nonhumoral immunity probably contributed to lesser disease severity than was reported during previous waves. The survival of people with Covid-19 who didn't develop neutralizing antibodies (such as patients with treatment-induced B-cell deficiencies) further implies the importance of cellular immunity.

These observations suggest that antigen-specific memory T cells are less affected than antibodies by escape mutations in a variant strain's spike protein. Memory T cells appear to retain the ability to recognize more highly conserved peptide epitopes within and outside the receptor-binding domain of the spike protein as well as on other viral encoded structural and nonstructural proteins. This finding may explain why mutant strains with less sensitivity to preexisting neutralizing antibodies may be associated with less severe disease and emphasizes the need for improved assays for measuring T-cell–mediated immune responses.

The upper respiratory tract is the first site of contact and the portal of entry for inhaled respiratory viruses, such as coronaviruses (the nasal cavity epithelium is rich with ACE2 receptors), where both innate and adaptive immune responses are elicited. Currently available intramuscular vaccines have a limited capacity to elicit strong mucosal immune responses. In highly vaccinated populations, infection with variants that continue to circulate can generate selective pressure for mutated strains with an increased potential for immune escape. The ability to limit community transmission with a mucosal vaccine that stimulates both a localized respiratory mucosal immune response and a systemic immune response is highly desirable. Alternative routes of administration include intradermal (microarray patch), oral (tablet), intranasal (spray or drops), or inhaled (aerosol). Availability of a needle-free vaccine might reduce vaccine hesitancy and increase vaccine acceptance. Regardless of the route, simplified vaccine administration would reduce burdens on health care professionals, thereby increasing vaccine access and benefiting future pandemic responses, especially if mass vaccination programs become necessary. Single-dose boosting with enterically coated, temperature-stable vaccine tablets and intranasal vaccines will be evaluated by assessing antigen-specific IgA responses in the gastrointestinal and respiratory tracts.

. . . simplified vaccine administration would reduce burdens on health care professionals, thereby increasing vaccine access and benefiting future pandemic responses, especially if mass vaccination programs become necessary.

Equally important as the demonstration of improved efficacy in phase 2b clinical trials is the careful monitoring of participant safety. Safety data will be systematically collected and analyzed. Despite the well-established safety profile of current Covid-19 vaccines, adverse reactions may occur after any vaccination, and systems are in place to capture these reactions for licensed products.[4] In the NextGen trials, the risk of adverse reactions will be assessed among approximately 10,000 participants randomly assigned 1:1 to an experimental vaccine or a licensed vaccine. Detailed assessment of local and systemic adverse reactions will provide important information, including on the incidence of complications such as myocarditis or pericarditis.

A daunting challenge for vaccine manufacturers is the need to maintain surge capacity; manufacturers must be able to produce hundreds of millions of vaccine doses within the proposed federal target of 100 days after the onset of a pandemic. As a pandemic wanes and during interpandemic periods, vaccine demand will decrease dramatically and manufacturers will face challenges related to preserving supply chains, essential materials (enzymes, lipids, buffers, and nucleotides), and fill-finish capacity. The current demand for Covid-19 vaccines is lower than it was in

2021, but manufacturing processes operating at smaller than "full pandemic" scale still require validation by the Food and Drug Administration. Regulatory validation will also be required for further clinical development, which may include lot-to-lot consistency studies and follow-on phase 3 efficacy programs. Results from the planned phase 2b studies, if promising, should substantially reduce the risks associated with conducting phase 3 studies and spur private investment in such trials, which could potentially lead to commercial development.

The length of the current interpandemic period cannot be known, but recent experience suggests that this time shouldn't be wasted.[5] This period offers an opportunity to expand understanding of vaccine immunology and to reestablish trust and confidence in vaccines among as many people as possible.

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Department of Health and Human Services or its components.

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My First Patient

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It was a small nodule. He had noticed it on the lateral aspect of his left wrist, just where his watch strap lay. No pain nor discoloration, 1 cm in diameter, subcutaneous, firm and mobile. Being a 20-year-old medical student in his clinical years, he knew exactly what the diagnosis was: occasionally, the links of his metal watch strap would pull at the hairs on his wrist, so this bump was no more than a granuloma secondary to watch-strap–induced trauma. No treatment necessary. Case closed.

"Not so," said his mother when she came to visit from out of town. And after some cajoling and persuading, he dutifully went off to see his family doctor, who promptly referred him to a general surgeon. One cursory examination and not much of a medical history later, a date was set for excision. The procedure was uncomplicated, and the pathology report read, "Nodular fasciitis, clear margins." No treatment necessary. Case closed.

Not so. Six months later, my patient noticed that the lump had recurred in the linear 3-cm surgical scar on his forearm. He was now in his fifth year of medical school and had completed a surgical rotation, so he took himself directly off to "his" surgeon. A cursory examination, some tut-tutting, a date for excision, a simple procedure. The pathology report was forthcoming: "Nodular fasciitis, clear margins." No treatment necessary. Case closed.

Not so. Six months later, my patient was now in his final year of studies. The lump returned. Now that he was married, his young wife had replaced his mother as his objective other and suggested that perhaps for round number three he should try out another surgeon. He self-referred to one of the senior general surgeons on staff at his medical school. A more thorough history, a careful local and general physical examination, some tut-tutting ("nodular fasciitis shouldn't recur, you know"), a date for excision, a simple procedure . . . no pathology report. Some weeks later, a call from his surgeon. "I think you