VIEWPOINT

Novel Vaccine Technologies
Essential Components of an Adequate Response to Emerging Viral Diseases

Barney S. Graham, MD, PhD
Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland.

John R. Mascola, MD
Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland.

Anthony S. Fauci, MD
Office of the Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland.

Corresponding Author: Anthony S. Fauci, MD, Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, 31 Center Dr, MSC 2520, Bldg 31, Room 7A-03, Bethesda, MD 20892-2520 (afauci@niaid.nih.gov).

The availability of vaccines in response to newly emerging infections is impeded by the length of time it takes to design, manufacture, and evaluate vaccines for clinical use. Historically, the process of vaccine development through to licensure requires decades; however, clinicians and public health officials are often faced with outbreaks of viral diseases, sometimes of a pandemic nature that would require vaccines for adequate control. New viral diseases emerge from zoonotic and vector-borne sources, such as Middle East Respiratory Syndrome coronavirus and Chikungunya, and while these diseases are often detected in resource-rich countries, they usually begin in low- and mid-income countries.[1] Therefore, part of the timeline for a vaccine involves surveillance and detection of new pathogens in remote areas and transfer of specimens to laboratories capable of vaccine development.

Development of vaccines for viral infections has historically been an empirical and iterative process based on the use of attenuated or inactivated whole virus. This requires unique methods of cultivation for each virus, development of animal models for vaccine testing, and a prolonged process of fine-tuning product formulation and immunogenicity, and for live-attenuated vaccines, pathogenicity. Thus, preclinical vaccine development can take years, followed by several more years of early-phase clinical testing and defining of dose and schedule. Moreover, efficacy testing and registration with regulatory agencies often takes another 5 to 10 years. In total, 15 to 20 years would be a typical timeframe from virus discovery to vaccine availability if the process proceeds smoothly and there are no major biological or logistical challenges.

Fortunately, during the last decade, there have been substantial technological advances for conceiving, developing, manufacturing, and delivering vaccines. Rapid genetic sequencing allows both early identification of new pathogens and the identity of the genes encoding structural proteins that can form the basis for vaccine immunogen development. Also, rapid isolation of human monoclonal antibodies has proven to be extremely helpful in defining epitopes that are the targets of protective immunity.

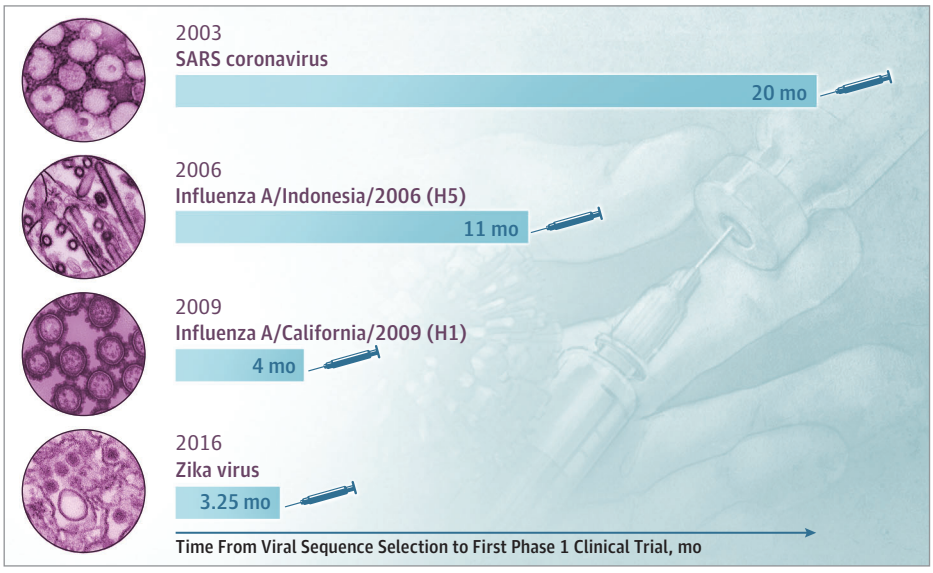
Additional tools of modern vaccinology include (1) delineation of atomic-level structures of viral proteins that facilitates structure-enabled immunogen design and protein engineering; (2) cell sorting and sequencing technologies that allow single-cell analysis of immune responses; and (3) genetic knock-in technologies that allow construction of animal models with human antibody genes for vaccine testing. These tools have already provided the potential not only for solving long-standing problems in vaccinology, such as the development of a new candidate vaccine for respiratory syncytial virus, but they have facilitated rapid development of new candidate vaccines for emerging pathogens such as the Zika virus and pandemic strains of influenza virus. Synthetic vaccinology and platform manufacturing are important innovations that can speed the initial vaccine immunogen design and vaccine development process, and shorten the time needed for manufacturing and initial regulatory approval to begin phase 1 testing.

Synthetic vaccinology is the process of using viral gene sequence information to accelerate vaccine development.[2] For example, if a new influenza virus emerges anywhere in the world and is identified through genomic sequencing, the digitally transferred information can be used to synthesize nucleic acids encoding the viral surface proteins (hemagglutinin and neuraminidase). The process of gene synthesis is now extremely rapid and relatively inexpensive. Thus, within a few weeks, DNA plasmids encoding viral proteins can be available for preclinical testing. These genetic vectors (DNA and mRNA) can be used directly for immunization whereby intramuscular immunization leads to muscle cells producing the viral proteins. Alternatively, the genetic vectors can be used to express recombinant protein antigens, in vitro, that can be used for immunization.

Similarly, if an outbreak of a new flavivirus becomes an epidemic or even a pandemic threat, as with Zika in 2015, the gene sequences that encode the viral surface proteins premembrane and envelope can be rapidly identified and form the basis for vaccine immunogen design strategies, based on prior knowledge of flavivirus structure and mechanisms of neutralization.[3] Once a structurally authentic immunogen is available, the protein or genetic vectors encoding the protein can be used to immunize animals. In addition, the vaccine proteins can be used as probes to identify monoclonal antibodies secreted by B cells of convalescent humans. Such antibodies are valuable not only for refining vaccine immunogen designs, but also for development of diagnostic assays and potentially for use in passive transfer as therapeutic agents. Thus, development of reagents, diagnostics, candidate vaccines, and immune assessment assays can be done without having the actual virus in hand. This has particular value for viruses with extreme pathogenicity because it avoids the need for high-level containment in laboratory and manufacturing facilities.

Platform manufacturing technologies allow more rapid production and clinical implementation once the vaccine immunogen design is established. The term *platform* is used in many ways; however, in vaccine production,

Figure. Decreasing Timelines for Platform Manufacturing of DNA Plasmid Vaccines



Timeline from viral sequence selection to first-in-human studies with DNA plasmid vaccine platform. Image credits (from top to bottom): Charles D. Humphrey and T. G. Ksiazek, Cynthia Goldsmith, National Institute of Allergy and Infectious Diseases, and Cynthia Goldsmith; Centers for Disease Control and Prevention.

it implies that the method for generating and presenting a vaccine immunogen can be applied across multiple pathogens. In essence, the cell substrates, production approach, purification processes, and analytical assays used as release criteria for products made under current Good Manufacturing Procedures are the same even though the immunogen may change. DNA or mRNA nucleic acid vaccines are good examples of how platform manufacturing can shorten timelines from pathogen identification to phase 1 clinical trials.[4] DNA vaccine delivery and immunogenicity have evolved and improved over the last 2 decades, making it a viable platform for vaccination.

For DNA plasmid vaccines, the manufacturing process is well established, and their toxicity profile is well understood. The National Institute of Allergy and Infectious Diseases Vaccine Research Center has developed candidate DNA vaccines for several viral disease threats during outbreaks, including SARS coronavirus in 2003, H5N1 avian influenza in 2005, H1N1 pandemic influenza in 2009, and most recently for Zika virus in 2016. Once these pathogens were identified, the time from viral sequence selection to initiation of the phase 1 clinical trial was shortened from 20 months to slightly longer than 3 months (**Figure**).

Other examples of vaccine platform technologies include viral vector–based approaches where genes encoding viral proteins are incorporated into viral vectors (eg, adenovirus, poxvirus, vesicular stomatitis virus, or paramyxovirus vectors) for gene-based immunogen expression and delivery, or chimeric replication-competent viruses in which the vaccine antigens of one virus are expressed in a common replication-competent virus allowing uniform manufacturing processes (eg, yellow fever or other flavivirus antigens expressed in dengue virus, or human parainfluenza or pneumovirus antigens expressed in bovine parainfluenza or Sendai virus vectors).

Traditional approaches, such as live-attenuated virus vaccines (eg, Sabin polio) or whole-inactivated virus vaccines (eg, Salk polio) would not qualify as platform approaches because the requirements for growth in cell culture and purification are usually different among virus families. Protein-based approaches are also likely to have different requirements for purification and formulation, and they may not be amenable to platform approaches unless the display of proteins on nanoparticles or other carrier systems brings more uniformity to downstream manufacturing approaches. Having a standard manufacturing approach reduces the time needed for current Good Manufacturing Procedures process development and simplifies regulatory approval because the safety database that has accumulated for a given platform can be applied to multiple vaccine products.

In summary, emerging viral diseases with pandemic potential are a perpetual challenge to global health. The time-honored approach to vaccinology, which depends predominantly on isolating and growing the pathogen, has not adequately met this challenge. To effectively prepare for and respond to these continually emerging threats, it will be critical to exploit modern-day technological advances, preemptively establish detailed information on each family of viral pathogens, and invest in more infrastructure for surveillance in developing countries to expedite pathogen identification and jump-start the process of vaccine development using these new technologies.[2] Failure to do so will result in the untenable situation of not optimally using vaccinology in the response to newly emerging infectious disease threats.

ARTICLE INFORMATION

Published Online: March 22, 2018. doi:10.1001/jama.2018.0345

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Drs Graham and Mascola reported they are inventors on a pending patent application for a Zika DNA vaccine for which a licensing agreement is being negotiated. No other disclosures were reported.

REFERENCES

1. Jones KE, Patel NG, Levy MA, et al. Global trends in emerging infectious diseases. *Nature*. 2008;451(7181):990-993.

2. Graham BS, Sullivan NJ. Emerging viral diseases from a vaccinology perspective: preparing for the next pandemic. *Nat Immunol*. 2018;19(1):20-28.

3. Dowd KA, Ko SY, Morabito KM, et al. Rapid development of a DNA vaccine for Zika virus. *Science*. 2016;354(6309):237-240.

4. Ulmer JB, Geall AJ. Recent innovations in mRNA vaccines. *Curr Opin Immunol*. 2016;41:18-22.