Vaccination Strategies for an Influenza Pandemic

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(See the articles by Stephenson et al. and Lipatov et al., on pages 1210–5 and 1216–20, respectively.)

An influenza pandemic represents one of the greatest acute infectious threats to health. The 1918–1919 influenza pandemic caused an estimated 500,000 deaths in the United States, making it the most fatal event in all of US history. The spread of highly pathogenic avian H5N1 influenza across much of Asia creates a substantial risk of igniting the next pandemic. In 2004, 44 human cases caused by this strain were documented and resulted in 32 deaths. The evolution of a strain that is effectively transmitted between people may be a single reassortment event away or could occur through continuing mutation.

Vaccination offers the best opportunity to prevent disease and death in a pandemic, but there will be limitations on the timeliness and availability of vaccine [1]. Optimistic projections are that it could take at least 6 months for the first pandemic vaccine doses to be produced after the identification of a pandemic strain. Global influenza-vaccine production capacity has nearly doubled over the preceding decade, and increased demand for annual influenza vaccine will continue to encourage an expansion of production capacity. However, current industrial capacity for a monovalent pandemic influenza vaccine formulated with 15 µg of hemagglutinin antigen would be far lower than the amount needed worldwide [1]. Under the assumption that a 2-dose schedule would be recommended for vaccination to a novel influenza strain and that the entire population would be susceptible, US-based production for 1 year would be sufficient for full vaccination of only about one-half the American population. Efforts to expand the global industrial base and to optimize the amount of vaccine antigen that can be produced are urgently needed.

Extraordinary threats call for consideration of innovative strategies that, in less-threatening circumstances, might be dismissed. Although it has been assumed that pandemic vaccine cannot be stockpiled or that vaccination cannot occur before the start of a pandemic, might these approaches actually be possible? Major barriers to stockpiling or preemptive vaccination are uncertainty over when the next pandemic might occur, whether it will be caused by H5 or some other influenza subtype, and whether the stockpiled vaccine would be a match for the pandemic strain. Production of an H5N1 or other potential pandemic vaccine would need to occur without an interruption in the production of the annual influenza vaccine, which is a substantial challenge given the delays or shortages in influenza vaccine that have occurred in recent years. In addition, the administration of a vaccine against a viral strain that currently causes no or very limited human disease raises ethical issues, because recipients would be exposed to potential adverse reactions for no definite benefit. Most important, would receipt of a vaccine prepared before the pandemic be effective in providing some protection or in priming recipients so that a single subsequent dose of vaccine would be protective?

Because influenza strains undergo antigenic drift, the hemagglutinin antigen in a vaccine that is stockpiled or administered before a pandemic would be different from that of the pandemic strain. The articles in this issue of the Journal of Infectious Diseases by Lipatov et al. [2] and Stephenson et al. [3] address the issue by assessing seroconversion in people and protection in mice to homologous and heterologous strains after immunization with candidate H5 vaccines. Lipatov et al. show high rates of protection in mice against lethal challenge with homologous and heterologous H5 strains after immunization with candidate H5 vaccines administered with Freund’s adjuvant. These data provide proof of concept that H5 vaccines produced by use of reverse genetics can be immunogenic and effective in an animal model. However, no conclusions can be reached regarding levels of protection in humans, the number of doses needed, the amount of antigen required per dose, the need for an adjuvant, or the degree of protection against all heterologous H5 strains.

Stephenson et al. assessed seroconvert-
sion among healthy adult volunteers after 2 or 3 doses of MF59-adjuvanted or nonadjuvanted H5N3 vaccine developed from a 1997 apathogenic avian isolate. They show seroconversion to the vaccine strain in 100% of subjects who received 3 doses of the adjuvanted vaccine and 43%–100% seroconversion to heterologous H5N1 strains. Nevertheless, the need for 3 vaccine doses, the use of an adjuvant not licensed in the United States, and uncertain levels of protection even in a young and healthy population limit the viability of such a vaccination strategy. Nonadjuvanted vaccine was poorly immunogenic for the vaccine strain as well as for the heterologous strains; it is unclear whether this is a function of the specific hemagglutinin antigen or of some other factor, and this issue deserves additional investigation. The studies by Stephenson et al. and Lipatov et al. do provide a good foundation for further work to develop and test candidate pandemic vaccines and assess pandemic vaccination strategies [4, 5]. The evaluation of seroconversion to heterologous H5 antigens and the assessment of whether priming with a different H5 vaccine improves immunogenicity would be important investigations to undertake, because they could contribute to development of novel vaccination strategies.

Stockpiling or administering vaccine before a pandemic is not the only approach that would increase vaccine availability in a pandemic. For example, developing vaccine reference strains and reagents to novel influenza viruses that could cause a pandemic might shorten the time required to produce the first doses of a pandemic vaccine. To increase production capacity, the US Congress has appropriated funding to stimulate licensure and US production of influenza vaccine made by use of cell-culture technology [6]. Because it will take several years to achieve this objective, other approaches to increase vaccine availability also are being investigated.

A more-rapid solution may come through the investigation and licensure of an “antigen-sparing” strategy that would increase the number of vaccine doses made at existing production capacity by decreasing the amount of antigen needed in each dose. Seroconversion has been documented in immunologically naive adults for H2 and H9 vaccines that contained 3.9 μg of antigen and a licensed aluminum adjuvant, compared with the 15 μg included in current nonadjuvanted vaccine formulations [7, 8]. Changing the route of injection from intramuscular to intradermal also might stimulate good immunogenicity with less antigen by recruiting potent antigen-presenting dendritic cells within the dermis [8–11]. Studies of these approaches with pilot lots of H5N1 vaccine are urgently needed.

On 26 August 2004, the US Department of Health and Human Services (DHHS) posted a draft US pandemic influenza preparedness and response plan [12]. Critical preparedness activities that have been implemented include planning by state and local health departments, coordination and surge-capacity planning in the health care system, supporting industry to strengthen production, and stockpiling of antiviral drugs. The plan’s research annex identifies a range of research priorities that include improving the understanding of the genetic diversity among novel influenza strains, uncovering the mechanisms by which highly pathogenic influenza viruses emerge and can be efficiently transmitted, identifying the genetic mutations that correlate with antiviral resistance, and developing new vaccine formulations and production technologies that would allow for a timely and effective response to an emerging pandemic.

DHHS efforts to specifically address the H5N1 threat include sponsorship of clinical trials of investigational lots of H5N1 vaccine (A/Vietnam/1203/2004 [H5N1]) produced by use of reverse-genetics methods [13] and a contract with Aventis-Pasteur to produce 2 million doses of H5N1 vaccine to test commercial-scale production of this candidate pandemic vaccine [14]. In addition, surveillance, particularly in Asia, has been enhanced, and mathematical modelers are evaluating potential strategies to contain an initial outbreak or decrease the spread of a potential pandemic strain.

The optimal long-term solution to pandemic vaccination is the development of a new influenza vaccine against an antigen that is present in all influenza subtypes and does not change [15]. This will be challenging, because natural influenza infection in 1 year does not provide optimal protection against infection with another strain the following year. However, the availability of various strategies to enhance immune responses beyond what occurs in nature and the global importance of an influenza vaccine that can be administered or stockpiled before a pandemic argue for a well-funded and aggressive research effort to achieve this outcome.

References