

Influenza A(H5N1) Vaccines: Are We Better Prepared for the Next Pandemic?

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(See the major article by van der Velden et al on pages 12–23.)

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The ongoing epizootic of influenza A(H5N1) infections has resulted in 641 reported human cases since 2003, 380 (59%) of which resulted in death [1]. These cases have been reported to the World Health Organization (WHO) from 15 countries in Asia, Africa, the Pacific, Europe, and the Near East, and influenza A(H5N1) viruses continue circulate and evolve in poultry in Asia and northeast Africa. Most infections have been the result of exposure to sick or dead poultry; however, limited human-to-human spread has occurred. Although these viruses are capable of producing infection and illness in humans and most individuals lack of immunity, to date their pandemic potential has been limited by their inability to transmit readily from an infected person to others. International efforts are ongoing to prepare for a possible influenza A(H5N1) pandemic.

Four influenza pandemics have occurred since 1918, and the impact of

these pandemics varied according to age group. For example, death rates in the 1918 pandemic were highest among persons aged <45 years, whereas death rates during the 1957 and 1986 pandemics were highest among persons aged >65 years. Infection rates during the 2009 influenza A(H1N1) pandemic were highest among children. The epidemiology of human influenza A(H5N1) cases varies from country to country, but the median age of patients infected with influenza A(H5N1) viruses is approximately 18 years [2]. Hence, a substantial burden of illness occurs in the pediatric population. Should an influenza A(H5N1) pandemic occur and the epidemiological pattern of past influenza A(H5N1) infections persist, efforts must be focused on protecting this vulnerable population [3]. This is particularly important because children play an important role in the community-wide spread of influenza [4].

Immunization is the cornerstone to the control of seasonal and pandemic influenza. The results of numerous clinical trials of candidate influenza A(H5N1) vaccines in adult populations have yielded several common themes. The avian H5 hemagglutinin (HA) is poorly immunogenic relative to seasonal HAs, 2 doses of vaccine are necessary to elicit serum antibodies in most subjects, and inclusion of an adjuvant (particularly oil-in-water emulsions) or use of whole-virus (WV)

preparations can increase the frequency and magnitude of antibody responses and reduce the amount of vaccine antigen required to achieve antibody levels that have been associated with protection (ie, antigen-sparing approaches). In most cases in which mineral-containing adjuvants such as aluminum hydroxide were evaluated, little additional benefit was observed [5]. Limited studies of live attenuated (LAIV) influenza A(H5N1) vaccines have shown restricted replication and lower immunogenicity than that seen after immunization with seasonal LAIV [6, 7].

The process of influenza A(H5N1) vaccine development is complicated by the ongoing evolution of influenza A(H5N1) viruses [8]. Numerous clades now circulate among birds, and which one, if any, will acquire the ability to transmit easily from human to human is unknown. Several studies have explored the effect of priming with one clade (1 or 2 doses) and boosting with another clade. These studies have shown that prior priming results in more broadly cross-reactive antibodies and higher levels of antibody than those observed after priming.

The results of clinical trials of influenza A(H5N1) vaccines among children are consistent with those seen in adult populations. In this issue of the *Journal*, van der Velden et al report that a Vero cell culture-derived WV influenza A(H5N1)

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vaccine derived from wild-type virus was well tolerated in infants and children aged 6 months to 8 years [9]. Two doses containing 7.5 μ g of A/Vietnam(H5N1) HA elicited neutralization antibody titers associated with protection in animal models in 68.8%, 72.9%, and 85.4% in children aged 6–35 months, 3–8 years, and 9–17 years, respectively. Booster immunization at 1 year with A/Indonesia(H5N1) vaccine elicited the same neutralization antibody levels against both strains in \geq 93%, \geq 95%, and 100%, respectively. Single radial hemolysis antibody assays indicated that 2 priming doses containing 7.5 μ g of HA elicited responses that satisfied licensure thresholds established by European authorities (European Medicines Agency). High rates of seropositivity to the neuraminidase (NA) also were observed following immunization. Similar to studies conducted in adults with WV and adjuvanted or nonadjuvanted subvirion or purified recombinant HA influenza A(H5N1) vaccines, boosting with vaccine derived from another influenza A(H5N1) clade elicited higher and more broadly cross-reactive antibodies. Immunization was reported to be well tolerated. Fever was reported among 17%–19% of children in the youngest age stratum and was less frequent after the second and boosting doses.

The results of this and other studies conducted among all age groups raise important questions regarding issues related to assessing the immunogenicity of both seasonal and pandemic vaccines. Serum hemagglutination inhibiting (HAI) antibodies have been regarded as a benchmark for assessing the immunogenicity of seasonal influenza vaccines by the Food and Drug Administration [10]. Serum HAI antibody responses following immunization with the WV vaccines described in the article were low and not reported, making comparisons between results from this trial to results from other trials difficult. Furthermore, neutralization antibody responses were lower than those observed following immunization of children with vaccines containing

oil-in-water adjuvants (MF59 and AS03). Lack of standardization of HAI and neutralization antibody assays is well recognized, and repeated calls for international cooperation to develop more reproducible assays have been made [11]. However, these assays will need to be clade specific, which poses a major hurdle.

Even if assays could be standardized, our understanding of the correlates and determinants of protection against both seasonal and pandemic influenza is far from complete. An HAI titer of \geq 40 has been associated with a 50% reduction in the risk of infection in adults and is used as a major immunization target. However, the level of antibody may vary with age such that HAI levels of \geq 110 appear necessary for children [12]. Even less is known about the level of neutralization antibody required for protection. NA antibody, CD4⁺ T-cell responses, and mucosal antibody responses all may contribute to protection against influenza A(H5N1) and/or other influenza virus infections [13–15]. Identification of epitopes that stimulate broadly cross-reactive immune responses is a high priority, and vaccines prepared using these epitopes are in development [16].

Another important consideration is vaccine safety. The use of an AS03-adjuvanted 2009 influenza A(H1N1) vaccine was associated with an increased risk of narcolepsy, an autoimmune disease, particularly among adolescents [17]. Other rare adverse events may only be observed when millions of people are exposed, as in a pandemic setting. In 1976, large-scale immunization of the US population with another influenza A(H1N1) vaccine was associated with an increased risk of an autoimmune disease known as Guillain-Barré syndrome [18]. WV vaccines have been associated with an increased risk of fever in young children, but the outcomes have not been serious. Depending on the severity of a future pandemic, risk/benefit assessments will need to be made with regard to which vaccines can be used in various age and risk groups. We will need all available manufacturing

capacity and accelerated manufacturing approaches to produce and distribute vaccine to the entire population if a pandemic occurs. On the basis of the 2009 influenza A(H1N1) pandemic experience, it took about 6 months from the recognition of a pandemic virus to the start of delivery of pandemic vaccines (live and inactivated) to the population. This was truly a Herculean feat by all the partners involved, although not fast enough to have an impact on the major fall wave of the pandemic.

Finally, several prepandemic influenza A(H5N1) vaccines have been licensed and are being stockpiled. It is time to tackle the difficult issue regarding the use of these vaccines before a pandemic occurs. The benefits include priming for robust responses to the actual pandemic strain, obviation of the need for 2 doses under difficult if not extreme circumstances, and expansion of the safety database. Risks include adverse events associated with vaccination and diversion of limited resources in the absence of a pandemic. The Strategic Advisory Groups of Experts on Immunization, which provides guidance on the work of the WHO Immunization, Vaccines, and Biologicals Department, has developed risk-based recommendations for the use of prepandemic vaccines [19], as follows. Vaccination is strongly recommended for laboratory workers who are at high risk of infection and for first responders to avian outbreaks and healthcare professionals in enzootic areas, and it may be made available to other laboratory workers and other healthcare professionals. Notably, vaccination with influenza A(H5N1) vaccine is not recommended for the general population or other essential workers in enzootic or nonenzootic areas.

As we learned in 2009, it is not possible to predict with any certainty what virus will cause the next pandemic. Influenza A(H7N9) viruses recently caused infections in China [20], and influenza A(H3N2) variant (swine), influenza A(H7N7), and influenza A(H9N2) viruses have caused human infections in

recent years. Influenza A(H2N2) was responsible for a pandemic in 1957; thus, some experts consider this subtype to be of major concern [21]. Vaccines containing both seasonal and candidate pandemic vaccine antigens are being developed, but which viruses to include, in whom, and when is a matter for serious consideration. Although vaccine development is a critical component of a program designed to prepare for the next pandemic, stockpiling of antivirals and antibiotics, development of plans for distribution of vaccines and antimicrobials, and ensuring the availability of adequate supplies of effective countermeasures are but a few of the critical approaches that will be necessary [22], but are they sufficient to prepare the global community for the next pandemic? Let the discussion continue!

Note

Potential conflicts of interest. P. A. P. is on the speakers bureau for MedImmune. W. A. K. certifies no potential conflicts of interest.

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