Vaccines against Influenza A (H5N1): Evidence of Progress

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(See the article by Goji et al., on pages 635–41, and the article by Levie et al., on pages 642–9.)

Although media attention has decreased, the influenza A (H5N1) virus nonetheless continues to pose a major health threat to birds and humans. As of May 2008, an estimated 500 million birds have died in >60 countries, and 382 humans are known to have been infected in 15 countries, with a mortality rate of >60% [1]. Should this virus mutate such that upper airway infection of humans occurs, allowing human-to-human transmission, an influenza pandemic would result. The consequences of such a pandemic cannot be predicted with clarity; nonetheless, it will result in excess morbidity and mortality and, if severe enough, widespread global social and economic disruption [2]. Of note is that Japan recently announced plans to immunize health care workers and other essential personnel against H5N1 virus beginning in 2009 and that the US Department of Defense offered a Food and Drug Administration–approved H5N1 vaccine to those in high-risk specialties (such as laboratory workers and first-response teams). Most recently, on 14 May 2008, the European Commission approved an adjuvanted split-virion H5N1 vaccine (A/Vietnam/1194/2004 NIBRG-14 strain; Prepandix, GlaxoSmithKline) for stockpiling for use in humans.

Of concern to those developing vaccines is that the influenza A (H5N1) virus continues to mutate into genetically discernable clades and subclades, and uncertainty as to whether vaccination with one H5N1 clade will lead to cross-protection against other H5N1 clades exists. Only 2 areas have remained unchanged in the dynamic arena of avian influenza—we remain in phase 3 of the World Health Organization pandemic schema, and the public and global health need for safe and efficacious vaccines continues to be clear and compelling.

In this issue of the Journal, 2 groups report the results of separate influenza A (H5N1) human clinical trials. We have previously noted that key to mitigating the effects of an influenza pandemic “is the development, testing, licensing, manufacturing, and stockpiling of vaccines. Safe and effective vaccines are likely to be the singularly most important public health tool in decreasing the morbidity, mortality, and economic effects of pandemic influenza” [3, p. 1411]. The data reported in this issue of the Journal further advance the science of H5N1 vaccinology and contain some novel and interesting results.

In the study by Goji et al. [4], immunization with 2 doses of a clade 0 vaccine (inactivated, baculovirus–expressed, recombinant hemagglutinin subvirion A/Hong Kong/156/1997) at doses of either 25, 45, or 90 μg with boosting 8 years later with a single 90-μg dose of a clade 1 vaccine (inactivated subvirion A/Vietnam/1203/2004) among 37 subjects is reported. Serum samples from these subjects were tested by hemagglutination-inhibition (HI) assays against wild-type A/Vietnam/1203/2004 (clade 1), A/Indonesia/05/2005 (clade 2), and A/Hong Kong/156/1997 (clade 0) viruses. While 70%–76% of the subjects who had been primed earlier with A/Hong Kong/156/1997 hemagglutinin showed an HI or neutralization titer of ≥1:40 against the antigenically distant A/Vietnam/1203/2004 virus, only 44% of the H5-naive subjects developed titers of ≥1:40. It is also important to point out that 63%–67% of nonresponders to the A/Hong Kong/156/1997 hemagglutinin vaccine in 1998 subsequently generated HI and neutralization titers of ≥1:40 after a booster dose with A/Vietnam/1203/2004 split vaccine. The results demonstrate evidence for a prime-boost phenomenon, with higher antibody titers among those being primed even as long as 8 years ago (clade 3 followed by clade 1), compared with H5-naive subjects re-
ceiving 2 doses of the same vaccine, as well as evidence for cross-reactivity to an antigenically variant clade 2 strain of influenza A (H5N1) virus.

In the report of a phase 1 trial of healthy 18–40-year-old subjects by Levie et al. [5], the results suggest that an oil-in-water adjuvanted vaccine induced enhanced antibody titers compared with vaccine alone. In this study, subjects received 2 doses of split-virion A/Vietnam/1194/2004 vaccine (clade 1) at 1.9, 3.8, 7.5, or 15 μg with an oil-in-water adjuvant or 7.5 μg without adjuvant. Even at doses of 1.9 μg with adjuvant, >90% of subjects developed a ≥4-fold rise in antibody titers. Significant but low levels of cross-reactivity against A/Indonesia/05/2005 (clade 2) were determined by neutralization assay among 12% of the recipients of adjuvanted vaccine at doses of 7.5 and 15 μg of hemagglutinin. A dose-response trend was observed for doses of 1.9 to 7.5 μg but not for the 15-μg dose. It is not clear whether there are differences among the oil-in-water adjuvant systems, given that results from an earlier study of a different oil-in-water adjuvanted vaccine published by the same group indicated significant seroconversion (≥4-fold increase in >80% of vaccinees) or seroprotection (titers of ≥1:40 in >85%–90% of vaccinees) [6]. Systemic reaction rates were comparable, whether adjuvanted or nonadjuvanted vaccines were received. Solicited local reaction rates were higher with adjuvanted vaccine, with 94% of subjects receiving adjuvanted vaccine reporting pain versus 48% of recipients of nonadjuvanted vaccine.

These data support the following general conclusions:

- Evidence now exists for a prime-boost phenomenon across H5 clades—even years after the priming dose(s).
- Evidence now exists for cross-clade immunoreactivity after vaccination (i.e., cross-protection).
- Evidence now exists, in light of additional data from other studies [6–8], for the superior immunogenicity of oil-in-water–based adjuvanted versus nonadjuvanted split-virion vaccines against novel influenza subtypes.
- Evidence now exists for the feasibility of prepandemic administration of H5N1 vaccine, with later boosting with antigenically different but clade-specific vaccines if needed.

Important provisos in interpreting human influenza A (H5N1) clinical trials remain. First, immunoassays, including HI and microneutralization assays, have sufficient intercenter variability and uneven standardization to suggest that comparisons between studies are difficult. Second, a serologic correlate of protection has not yet been defined. The standard antibody titer threshold of ≥1:40 is not based on evidence and has been investigated only in the context of circulating strains of seasonal influenza viruses. In addition, vaccines that result in immune responses that protect against death, even if not against infection and illness, may be useful. Each of these issues deserves further study. Other research needs include clinical trials of intradermal and other routes of vaccine administration, the testing of additional vaccine adjuvants, approaches that increase the stability and maintenance of vaccine potency, approaches that shorten the vaccine production timelines in the event of a pandemic, better defined and predictable regulatory pathways for licensure of adjuvants and adjuvanted H5N1 vaccines, more broadly cross-protective vaccines against heterologous novel influenza strains (or better, a so-called universal vaccine against all influenza types), head-to-head clinical trial comparisons of vaccine candidates, and data that better enable us to understand how antigenically different substrains can be and still allow cross-priming and, therefore, prime-boost strategies. Furthermore, no data exist regarding the immunogenicity, safety, or efficacy of H5N1 vaccine candidates among major portions of the population, including infants, children, adolescents, the elderly, and the immunocompromised, as well as among different races and ethnicities. For populations unlikely to respond well to vaccines, passive transfer of polyclonal human or humanized antibodies (for example, convalescent plasma or polyclonal purified immunoglobulin from animals that carry human immunoglobulin loci) against influenza A (H5N1) needs to be considered. The recent observation that all clusters of influenza A (H5N1) in Indonesia have occurred only among genetically related family members [9] raises the issue of genetic susceptibility to infection and, by extension, the possibility of immunogenetically mediated vaccine success or failure, as has been demonstrated for other viral vaccines [10–13]. Finally, additional thought needs to be given to the development of vaccines with targeted goals—that is, vaccines that prevent infection versus transmission versus disease and/or complications.

Much in the way of resources, as well as scientific and public health attention, have been applied toward developing safe and efficacious influenza A (H5N1) vaccines. New knowledge and unexpected findings have resulted. One H5N1 vaccine is already licensed for use in the United States and another in the European Union, and yet others are pending licensure. While much remains to be done with regard to developing an optimal set of vaccines, determining who should receive these vaccines, when, in what order, and under what circumstances deserves widespread debate. Our own opinion is that it is worth seriously considering the potential use of prepandemic H5 vaccine either as a stand-alone vaccine or in combination with seasonal influenza immunization to begin to “prime” for these novel influenza strains at a population level. Should evidence of human-to-human transmission occur, “boosting” with the same or other H5 vaccines now appears feasible. Questions such as the theoretical risk of immunopotentiating disease after immunization and the consequences of original antigenic sin need to be answered in order to proceed. However, preliminary data, such as those provided by Goji et al., suggest that such a
prime-boost strategy using vaccines derived from different H5 clades, separated by years, may be worthwhile, immunologically feasible, and safe. If so, we may well be on the path toward a different strategy for the use of influenza vaccines for pandemic preparedness—that of either priming the population with pre-pandemic vaccine or of including H5 antigens in seasonal influenza vaccine.

References