

## EDITORIALS



## Vaccines against Avian Influenza — A Race against Time

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Avian influenza A (H5N1) virus poses an important pandemic threat. A study by the Congressional Budget Office estimates that the consequences of a severe pandemic could, in the United States, include 200 million people infected, 90 million clinically ill, and 2 million dead.<sup>1</sup> The study estimates that 30 percent of all workers would become ill and 2.5 percent would die, with 30 percent of workers missing a mean of three weeks of work — resulting in a decrease in the gross domestic product of 5 percent. Furthermore, 18 million to 45 million people would require outpatient care, and economic costs would total approximately \$675 billion. As of March 10, 2006, the World Health Organization (WHO) had reported 176 confirmed human cases of influenza A (H5N1) across seven countries, with 97 deaths (a 55 percent mortality rate for identified cases).<sup>2</sup>

A major worry is that influenza A (H5N1) continues to evolve into antigenically distinct clades — infecting mammalian hosts other than humans, expanding its ecologic niche of domestic fowl to include wild migratory birds, and causing outbreaks among birds in more than 30 countries. The virus is close to meeting the criteria for a pandemic virus — one that is new, can cause human illness, and can be transmitted from human to human<sup>3-5</sup> — and the world is currently in phase three of the six WHO phases of alert for pandemic influenza (higher numbers represent greater seriousness). Influenza A (H5N1) is not yet pandemic because of a single factor: the inefficiency of human-to-human transmission. Once such transmission is efficient and sustained, even assuming that the current mortality rate of approximately 50 percent decreases, we will be in the midst of a serious pandemic.

For this reason, maintaining the public health requires attempts to mitigate, avert, and treat infection with influenza A (H5N1) virus, and the key to meeting these goals is the development, testing, licensing, manufacturing, and stockpiling of vaccines. Safe and effective vaccines are likely to be the single most important public health tool for decreasing the morbidity, mortality, and economic effects of pandemic influenza — particularly in view of the reported resistance of influenza A (H5N1) to antiviral agents.<sup>6</sup>

Thus, the data reported in this issue of the *Journal* by Treanor et al.<sup>7</sup> from their multicenter randomized, double-blind, placebo-controlled clinical trial of a subvirion influenza A (H5N1) vaccine are important and informative. Enrolled in the study were 451 healthy adults 18 to 64 years of age who received two doses of the vaccine without adjuvant, each of which contained 90, 45, 15, or 7.5  $\mu\text{g}$  of hemagglutinin antigen, or placebo. The vaccine was produced from a human isolate (A/Vietnam/1203/2004 [H5N1]) of a virulent clade 1 influenza A (H5N1) virus with the use of a plasmid rescue system, with only the hemagglutinin and neuraminidase genes expressed. The rest of the genes were derived from an avirulent egg-adapted influenza A/PR/8/34 strain. The hemagglutinin gene was further modified to replace six basic amino acids associated with high pathogenicity in birds at the cleavage site between hemagglutinin 1 and hemagglutinin 2. Immunogenicity was assessed by microneutralization and hemagglutination-inhibition assays with the use of the vaccine virus, although a subgroup of samples were tested with the use of the wild-type influenza A/Vietnam/1203/2004 (H5N1) virus.

The results of the vaccine in the study by Treanor et al. (referred to here as the “1203 vac-

“give pause. Although the 1203 vaccine was safe, with an unremarkable adverse-event profile, its immunogenicity was poor to moderate at best. In fact, in only one group did more than 50 percent of the subjects reach the immunogenicity threshold (defined a priori) of an antibody titer of 1:40 or greater (typically thought of as seroprotective) — the subjects who received two doses of 90  $\mu\text{g}$  each 28 days apart — a total dose 12 times that of seasonal influenza vaccines. Notably, the current worldwide manufacturing capacity for influenza vaccine is estimated at only 900 million doses (at the dose level of 15  $\mu\text{g}$ ). The requirement of two doses of 90  $\mu\text{g}$  per person means that only 75 million persons (1.25 percent of the world's population) could be fully immunized, and of those, only half would achieve seroprotection. Thus, vaccines must contain much less influenza hemagglutinin to be widely useful as a global public health measure.

And there are some additional provisos. An antibody titer of 1:40 does not guarantee protection from infection. People with lower titers show protection against influenza, and people with higher titers can have symptomatic infection. Moreover, the assumption that a titer of 1:40 is seroprotective is based on circulating strains of seasonal influenza. Whether the same will prove to be true for new influenza viruses in people whose immune systems have not been primed is unknown. However, even moderate levels of seroprotection could be useful for the public health by preventing or decreasing transmissibility, severe symptoms, complications, or death.

An important issue is whether the 1203 vaccine offers cross-protection against other H5N1 strains of influenza A. A lethal human infection with an antigenically distinct influenza A (H5N1) strain is discussed elsewhere in this issue of the *Journal*.<sup>8</sup> From an immunologic standpoint, it is probable that more than one H5N1 vaccine will be needed. We know that the Indonesian clade 2 influenza A (H5N1) viruses are antigenically distinct from the clade 1 viruses from which the 1203 vaccine was developed. Preliminary evidence from serologic studies of laboratory-confirmed cases of influenza A (H5N1) infection also suggests that cross-protection between these two influenza A (H5N1) clades may be limited (Katz J: personal communication). Therefore, further studies are warranted to establish the level of cross-neutralizing antibody against heterologous influ-

enza A (H5N1) viruses, such as those in clade 2, that is generated by vaccination with the 1203 vaccine. Such cross-neutralization is of great importance, because at the current time, the 1203 vaccine is being stockpiled for use in the event of an influenza A (H5N1) pandemic. In any case, one candidate for a clade 2 vaccine is now available, and others are being developed by the WHO Influenza Network.

Additional factors for which data are needed include differences in vaccine-induced immunity according to age, sex, immune status, and ethnic group. Some of these data could be derived from the results of Treanor et al. on further analysis. Age may be particularly important; those who have died in past pandemics and from influenza A (H5N1) infection are disproportionately children, adolescents, and young adults.

Studies of different dose levels of vaccines administered with MF59 (a licensed adjuvant in Europe), aluminum hydroxide, or other adjuvants are urgently needed. We know from previous work that new hemagglutinin proteins (including H5) in people who have not been primed are poorly immunogenic.<sup>9,10</sup> In recognition of this fact, the Department of Health and Human Services and the National Institutes of Health have funded studies of more than 30 candidate vaccines. Early results from some of these trials should be available in the next 6 to 12 months. Previous studies of a new influenza A (H5N3) vaccine administered with MF59 adjuvant showed that vaccine administered without adjuvant was poorly immunogenic but that vaccine administered with MF59 adjuvant in two doses, each as low as 7.5  $\mu\text{g}$ , was highly immunogenic and resulted in cross-neutralizing antibodies against influenza A (H5N1).<sup>11,12</sup> Studies of an influenza A (H2N2) vaccine administered with alum adjuvant had similar results: hemagglutination-inhibition titers increased significantly at doses as low as 1.9  $\mu\text{g}$ .<sup>9</sup>

The immediate development and testing of such antigen-sparing vaccines administered with adjuvant are imperative both to improve immunogenicity and to increase the number of doses available (if lower doses are effective). In addition, live attenuated cold-adapted influenza vaccines are safe, are immunogenic, and have the relevant advantage of cross-protection against heterologous influenza strains — suggesting a promising avenue to the development of pandemic vaccines. A contract for the development of such vaccines

has been awarded to MedImmune. Other approaches to vaccine development involve DNA, adenovirus vectors,<sup>13</sup> and cell-culture manufacturing techniques to increase the speed and capacity of vaccine production. These approaches are promising, particularly since reverse-genetics reassortant vaccine candidates can be generated within weeks.<sup>14</sup>

Thirty years ago, the United States attempted to respond to the threat of pandemic influenza with a vaccine approach. Now, armed with a greater understanding of the science, we have the capacity and the responsibility to embark on multiple, parallel avenues of vaccine development. In addition, we need efficient, rapid, high-yield, low-cost manufacturing innovations; the rapid generation of candidate vaccines for other, potentially pandemic influenza viruses (including emerging clade-2 influenza A [H5N1] viruses); and the rapid movement of those vaccines into clinical trials. In turn, this effort will require creativity along the entire pipeline: in the development and manufacture of candidate vaccines; the synchronization among countries of regulatory approaches; the resolution of issues concerning liability and intellectual property; ensuring the efficiency of clinical trials; and the use of methods to stockpile and rapidly deploy these vaccines. To do otherwise, with the pandemic clock ticking, could prove to be too little, too late.

Dr. Poland reports serving as the chair of a data monitoring and safety board for an investigational trial of an influenza peptide vaccine being conducted by Merck Research Laboratories. No other potential conflict of interest relevant to this article was reported.

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## Serious Adverse Drug Effects — Seeing the Trees through the Forest

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The medical community and the public have been buffeted by a steady stream of news linking the use of widely prescribed medications with serious health risks. The latest in this barrage of unsettling reports is an article by Park-Wyllie et al. that

appears elsewhere in this issue of the *Journal*<sup>1</sup> regarding the association of the fluoroquinolone gatifloxacin with dysglycemia.

The authors describe the findings of two population-based, nested case-control studies involv-