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Vaccine Preparedness — Are We Ready for the Next Influenza Pandemic?

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The quest for a fully immunogenic vaccine against influenza H5N1 viruses has gone on for more than 10 years, since this family of potentially pandemic viruses emerged as a cause of human disease in Hong Kong in 1997. H5N1 has caused 381 human cases of influenza, with a mortality rate exceeding 60%. H5 strains have now been found in birds throughout much of the world (though not yet in the Americas), and human illness has occurred in 14 countries throughout Asia and in northern Africa.¹ The much-feared rapid spread through and between communities, however, has not occurred. Aside from small clusters of cases within families, each human case has been associated with close contact with poultry. The culling of poultry in the face of recognized bird disease has been a major defense strategy since the first outbreak.

Each human infection constitutes an opportunity for genetic modification of the virus through reassortment, mutation, or both — modifications that could enable the virus to overcome the remaining barrier to a pandemic by gaining the capacity for efficient person-to-person transmission. The fact that no epidemic has yet occurred has prompted questions about whether H5 viruses face some insurmountable barrier of viral fitness that renders them

incapable of causing widespread illness in humans. Yet all agree that history is a powerful teacher and that future influenza pandemics caused by novel strains are highly probable.

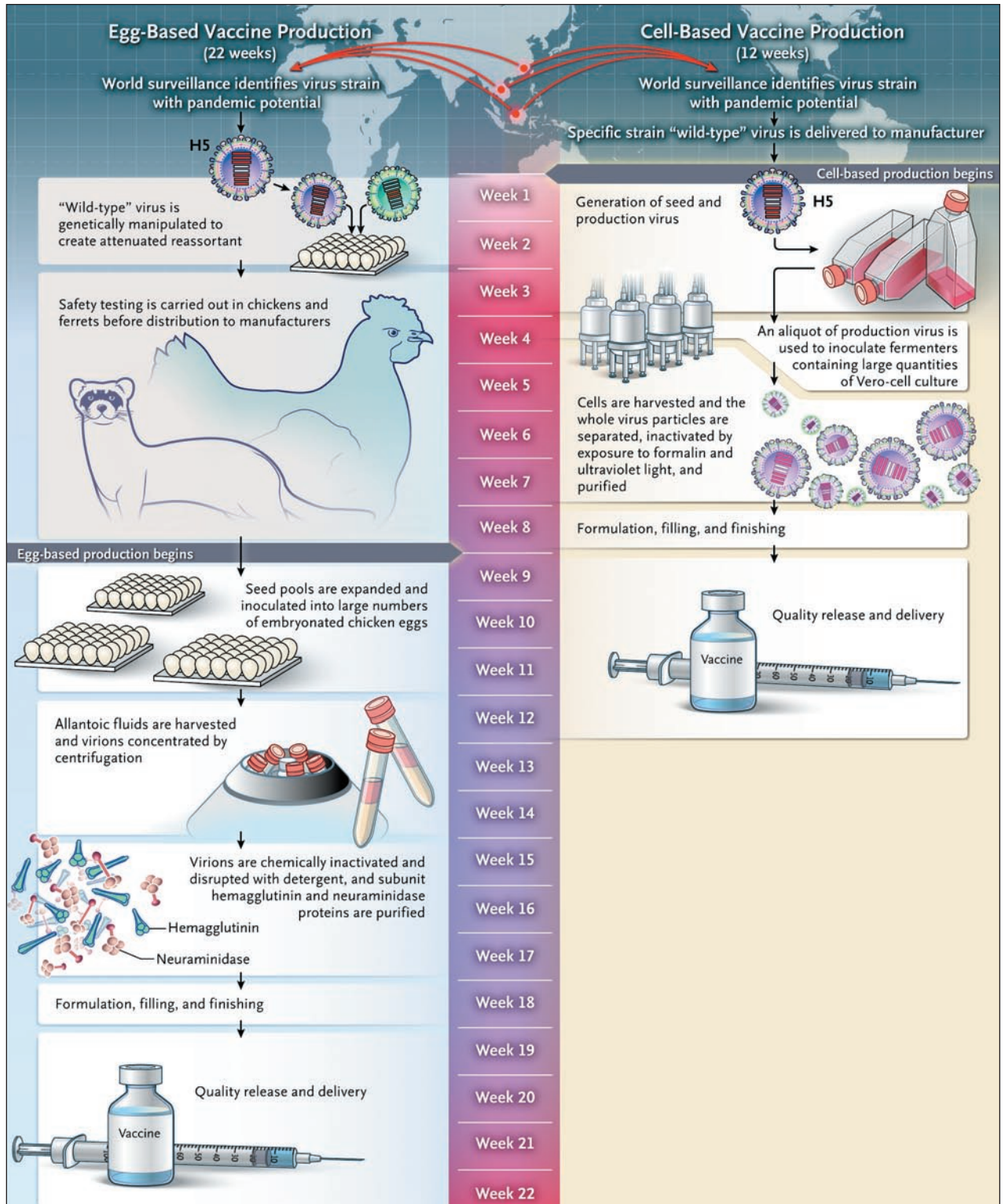
So where do we stand with vaccines against emergent influenza strains? The preparation of a vaccine against H5 influenza has not proved as simple as adhering to the standard manufacturing techniques used to create yearly influenza vaccines. The H5 strains have had to be modified, since their virulence in chicken eggs causes rapid death of the embryo, precluding the generation of an acceptable antigen yield. Assays that are used to evaluate potential vaccine efficacy have also had to be modified, since horse erythrocytes have proved more sensitive than the commonly used chicken or turkey cells in measuring responses to the H5 hemagglutinin antigen (HA). Attempts have been made to standardize a neutralization assay in the hope that it would be a more sensitive reflection of the functional activity of the vaccine. The difficulties in producing and standardizing conventional H5 vaccines have prompted innovative and extensive examinations of options for improving all influenza vaccines.

During the pandemics of Asian influenza in 1957 and Hong Kong influenza in 1968, there were ef-

forts to explore possible vaccines, but the first systematic attempt to develop vaccines against an influenza virus representing a pandemic threat was made in the face of the swine influenza of 1976. Both pediatric and adult trials were conducted, studying both whole-virus and subvirion vaccines. These trials showed that whole-virus vaccine was not only more immunogenic but also more reactogenic than subvirion vaccine; that with a new immunogen, two doses were needed; and that immunogenicity was roughly doubled with a 10-fold increase in the vaccine's HA content.

These lessons, coupled with epidemiologic data on the seasonal impact of influenza, have formed the basis for the broadening use of influenza vaccine in the United States for yearly epidemic influenza. The relatively poor immunogenicity of the 1976 vaccines in recipients who had not previously been exposed to the vaccine's influenza virus strain also presaged the difficulties of developing an effective vaccine against H5 influenza. This history suggests that H5 may not be a uniquely poor immunogen; rather, limited responses are to be expected whenever people are given an entirely new influenza vaccine.

The first efforts to develop an H5 vaccine involved the testing of a subvirion vaccine both with and without MF-59, a squalene con-



The Vaccine Production Process, with the Egg-Based Method (Left) and the Cell-Based Method (Right).

taining an oil-in-water emulsion. Limited immunogenicity of short duration was seen with the subvirion vaccine, though MF-59 enhanced the antibody response. The next study increased the dose of the subvirion vaccine to 90 μg of HA in each of two doses. It was only at this high dose that researchers achieved a titer that was predicted to be effective in more than 50% of those vaccinated.² This vaccine was approved by the Food and Drug Administration, is being stockpiled, and has become the benchmark against which new vaccines are judged. A vaccine incorporating another oil-in-water adjuvant has elicited the best immunologic responses to date and worked well even with dose-sparing methods. As little as 3.8 μg of HA was found to induce a response in 80% of those inoculated. Conversely, baculovirus-expressed HA, a vaccine made with alum adjuvant, and live attenuated H5 vaccines have not increased immune responses.

The article by Ehrlich et al. in this issue of the *Journal* (pages 2573–2584) extends our understanding of influenza vaccines in three key ways. Perhaps most important, it introduces the concept that influenza vaccines may be produced in substrates other than embryonated eggs. The idea that a vaccine might be grown in tissue culture under controlled conditions has excited people in the field for a number of years. Embryonated eggs are available only seasonally, which creates a time constraint in the manufacturing of yearly vaccine and certainly could influence preparedness for a pandemic. The timeline for year-

ly vaccine production currently requires decisions to be made in February about the subsequent winter's vaccine strains, but with tissue-culture–grown vaccine, this schedule could be altered to permit incorporation of late-emerging threats (see diagram). Adaptation to efficient growth in eggs

With tissue-culture–grown vaccine, the production schedule could be altered to permit incorporation of late-emerging threats.

requires modifications that are typically accomplished by inserting into the vaccine strains internal genes from older, egg-adapted influenza strains. In the case of an H5 vaccine, it also requires modification of the HA to remove a key virulence factor. Passage through eggs rapidly selects for changes in the HA that have been shown to alter immunogenicity. It is difficult to put this problem into perspective when considering an avian virus such as H5: the vaccine's starting strain (A/Vietnam/1203/2004), though human in origin, was egg-adapted and is at heart an avian virus, so passage through avian eggs may not change its immunogenicity. For nonavian strains, however, it is appealing

to consider the idea that mammalian cell culture could let us circumvent egg adaptation and the resultant alteration in antigenicity.

Second, the vaccine that was produced was not disrupted to form a subvirion vaccine, and Ehrlich et al. suggest that immunogenicity was stronger as a result. Such a finding would be consistent with those of 1976 trials, but it is difficult to draw this conclusion on the basis of comparison with published results on the H5 subvirion vaccine² because of differences between the assays used and the ways in which the data are presented. Something as potentially critical to global health as the development of an H5 influenza vaccine demands a free exchange of serologic specimens, if not head-to-head clinical trials, so that vaccines can be directly compared. I would also caution that given that the 1976 whole-virion vaccines caused the most marked reactions in children, the safety data in adults cannot be directly extrapolated to children.

Third, the study raises a key biosafety question about large-scale production of vaccine from a wild-type virus: Could virus spread from a production facility and initiate an epidemic? Wild-type poliovirus strains are still used in producing inactivated polio vaccine, and the experience with poliovirus is reassuring. In general, the closed systems in which vaccines are produced protect the vaccine's sterility and, in doing so, greatly limit the opportunities for spread.

Are we prepared for pandemic influenza? We are not ready to put

a vaccine in the field should H5 gain person-to-person transmissibility or should another strain emerge. The work on novel vaccine approaches, however, suggests that we may still make it, if influenza continues to stay in its lair and largely confine itself to avian hosts.

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