

measures for work on select agents (including certain highly pathogenic influenza viruses). Principles for biosafety are laid out in the widely used *Biosafety in Microbiological and Biomedical Laboratories* (25). We recommend that compliance with these measures and principles be actively monitored by the Centers for Disease Control and Prevention (CDC) on a basis more frequent than the current requirement for federal inspection of BSL-3 laboratories, which is every 3 years and when a new select agent is added (27, 29). These requirements apply only within the United States; we share the concern expressed by many experts about variation in biosafety practices worldwide (27). For experiments on the evolution of viral or bacterial transmissibility to mammals, there should be an explicit requirement to justify why the research must be done with virulent strains.

Traditional peer-reviewed funding decisions evaluate scientific merit first and then undertake risk mitigation if it is considered necessary; the dual-use research of concern (DURC) policy in the United States (3) does not specify how, if at all, this approach would change. We propose that the decision about whether research on mammalian-transmissible H5N1 viruses or agents with similar potential for damage to public health should be funded or should proceed with restrictions should not be left to each department or agency, because some may lack the relevant expertise to evaluate risks and benefits in light of the overall portfolio of studies already approved or under way. A single interagency committee, including experts in fields such as evolutionary microbiology and bio-defense as well as virology, needs to review the small number of proposals identified by grant administrators or scientific review committees that involve pathogens whose accidental or deliberate release would represent a major threat to public health. In contrast to the National Science Advisory Board on Biosecurity, which is only advisory, this committee should have decision-making authority. The U.S. government is actively considering options to strengthen DURC governance, including a possible review group to provide independent assessments of research proposals. Similar considerations should motivate policies outside the United States (27).

Each additional study of mammalian-transmissible, highly pathogenic influenza will improve our understanding and may move us closer to an ability to control such viruses, but will also increase the risk of an accident that could trigger a global public health disaster, especially if evolution proceeds in an unfavorable direction. This exceptional level of risk should motivate exceptional caution by scientists, funders, and regulators worldwide.

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#### POLICY FORUM

## Influenza: Options to Improve Pandemic Preparation

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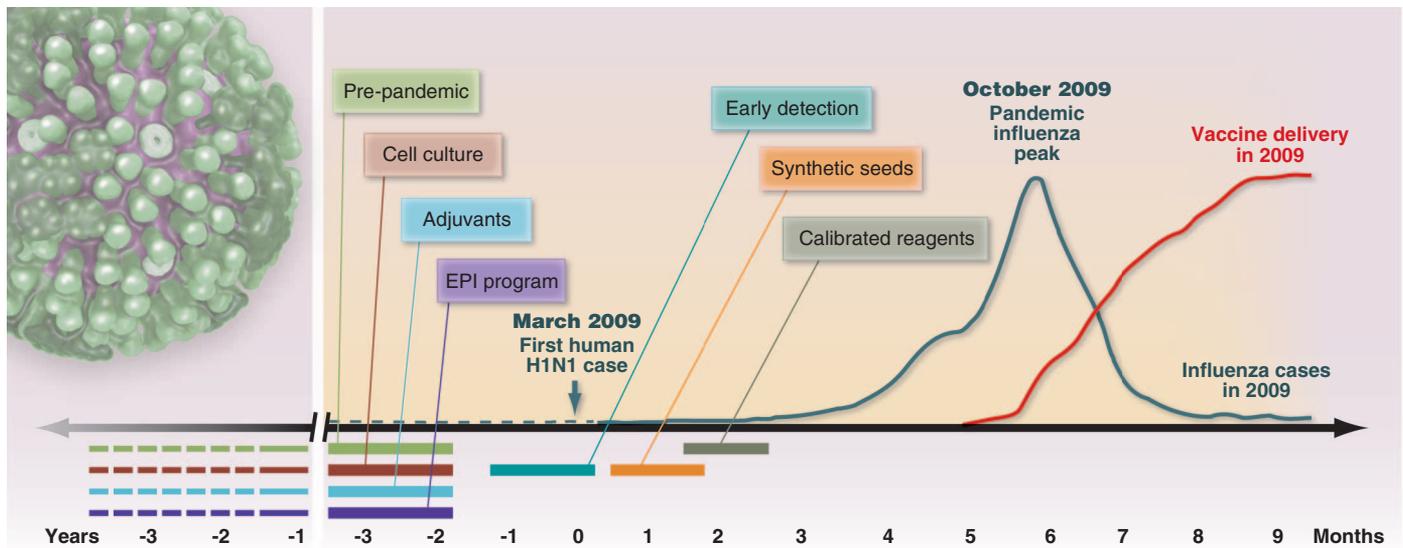
Science and society have been struggling to find a way to protect humankind from recurring epidemics and pandemics of influenza. Here, we review the options available in the short term and also briefly address the solutions that research may make available in the long term.

Every year, seasonal influenza causes several hundred million cases and 250,000 to 500,000 deaths, of which 90 million cases and 28,000 to 111,500 deaths occur in children (1, 2). Pandemic influenza strikes periodically, infecting billions of people and potentially causing millions of deaths. Recently, two studies showing that, in the laboratory, pathogen-

ic H5N1 influenza strains can evolve to be transmissible in ferrets divided the scientific community between those saying that the studies should not have been done and/or should not be published in their entirety and those saying that the studies are useful and should be published in their entirety (3–6). Because influenza in ferrets so closely models the disease in humans, the findings of H5N1 transmissibility between ferrets suggest that transmission of such strains between humans also could occur. The controversy continues, and it is evident that the studies have reminded us that a deadly H5N1 pandemic is not impossible. Therefore, it is important to discuss what options

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**Fig. 1.** Summary of the activities that occurred in 2009 from day 0 of the pandemic on 18 March 2009, when the first case of H1N1 virus was reported in Mexico, to November and December (months 8 and 9), when large quantities of the pandemic vaccine became available. Data are adapted from (22, 23); only qualitative data are shown. The figure shows that in 2009 the

vaccine became available after the peak of viral infection. The options available today to improve pandemic preparation are shown above the graph. The four options on the left are preparations in advance of a pandemic; the three on the right are elements of executing a pandemic response. [Source: Doug Jordan/CDC]

are available and whether we are ready to invest to reduce or eliminate the risk.

The experience of the 2009 H1N1 pandemic showed that pandemic vaccines could be successfully developed and deployed; however, they became available in significant quantities only after the peak of viral infection and only in high-income countries (Fig. 1). The figure also shows a summary of the activities that occurred during the 8 months between March 18, when the first case was reported in Mexico, and November, when the vaccine started to be distributed in large quantities. In the figure, we list options for improved pandemic responses.

The first option is prepandemic vaccination, which can circumvent the daunting logistics of developing, manufacturing, and distributing a new vaccine more rapidly than an advancing pandemic wave can spread. Vaccination of human subjects with an H5 vaccine (combined with an enhancer of immune responses known as an adjuvant) elicits protective antibody titers in the short term and primes the immune system for the long term against any H5 virus variant (7). The experience of 2009 indicates that, once the immune system is primed, the risk of a severe pandemic is eliminated, and the worst that can happen is a mild pandemic. During the 2009 H1N1 pandemic, most people had been primed by infection and/or vaccination with distantly related H1N1 antigens and were spared severe disease (8–10). Because H5N1 infection of humans is so rare, the population has not been primed by previous exposures. This lack of prior exposure makes the population more vulnerable to severe

disease caused by highly virulent H5N1 strains and makes immunization more difficult, necessitating the use of adjuvants, higher antigen content, and two doses to elicit sufficient antibody titers (7).

Given that licensed H5N1 vaccines are available, we have the option to vaccinate individuals at greatest risk or to vaccinate more broadly, including the populations of individual countries, of continents, or even of the entire globe. It is just a question of evaluating the cost, the logistics, and the risk of implementing such a large vaccination campaign. It is not impossible. With sufficient investment and political will, the global population could probably be vaccinated with one or two doses of a prepandemic vaccine in a period of 3 to 5 years, which would dramatically reduce the risk of a devastating H5N1 influenza pandemic.

The second option is increasing manufacturing capacity so that we can produce enough vaccines to protect the 7 billion people on our planet. The proportion of the population that must be immunized to quell a pandemic through herd immunity varies with the transmissibility of the strain, the level of preexisting immunity, and the efficacy of available vaccines. With a highly transmissible strain (such as the 1918 pandemic strain), in a population with little preexisting immunity, and using vaccines that are incompletely effective, modeling indicates that the proportion of the population that must be immunized for effective immunity is likely to be greater than 80% (11). The introduction of cell culture technologies can eliminate the current dependence on egg supply,

potentially shorten production time, and increase capacity. Although most of the vaccine doses distributed in the 2009 pandemic response were produced in eggs, a vaccine produced in cultured mammalian cells was at the leading edge of the vaccine supply (12). Cell culture production is more rapidly scalable than egg production and is not vulnerable to decimation of poultry flocks by a pandemic avian influenza strain. In the medium term, production of influenza vaccine antigens from recombinant platforms, such as *Escherichia coli*, insect cells, or plants, also could increase the global vaccine supply (13). However, in the present environment, capacity would be available only for rich countries, where it is sustained by the seasonal influenza business. Although, during the 2009 pandemic, the calculated capacity may have reached a peak of ~900 million doses, to be sustainable, capacity must be supported by the seasonal influenza business. As of 2009, the northern hemisphere seasonal influenza vaccine markets supported production of ~470 million doses of trivalent influenza vaccine (targeting three varieties of influenza) during a 6-month northern hemisphere manufacturing campaign, which corresponds to 1.4 billion doses of monovalent vaccine (14). The capacity to make sufficient bulk vaccine could be doubled or even quadrupled by the use of an adjuvant, on the basis of the reduced antigen dose needed in influenza vaccines with adjuvant (12). Reduced bulk vaccine requirements with dose-sparing adjuvants could make the capacity to fill and distribute vaccine doses a limiting factor. Therefore, start-to-finish manufacturing capacity is still too little by far compared with the

need of 7 billion doses in 6 months to vaccinate the global population during a pandemic (such as the 2009 H1N1 pandemic) in which one dose of vaccine is required or 14 billion doses in 6 months for a pandemic (such as a highly pathogenic H5N1 pandemic) in which two doses are required.

A win-win solution to the problem of insufficient influenza vaccine manufacturing capacity is possible. Today, influenza vaccines are used only in rich countries, and outside of the United States, routine influenza immunization is usually not recommended for children and infants. Recently, it has been shown that influenza vaccines with adjuvant are highly efficacious in infants and prevent 86% of the infections (15). Introducing influenza vaccines in the Extended Program on Immunization (EPI) and vaccinating all children and pregnant women globally against influenza (16) could save the lives of up to 28,000 to 111,500 infants annually, prevent 90 million cases, and enable a sustainable increase in vaccine manufacturing capacity to levels close to those required for an effective global pandemic response. Because much of the new capacity would be built in low-income countries, the expansion would end the embarrassing and inequitable situation in which influenza vaccines are only available for rich countries, as occurred during the 2009 H1N1 pandemic.

The next option is acceleration of vaccine manufacturing during a pandemic. In 2009, it took nearly 3 months from March 18, when the first case occurred, to June 7, when vaccine manufacturing started. This could probably be reduced to a couple of weeks by early detection of the first case and the use of fully synthetic seed viruses for vaccine production. Today, once the sequence of the virus is available, we can synthesize the genes and make a synthetic virus to seed vaccine manufacture in less than a week. To implement synthetic seed generation in influenza vaccine manufacturing, several changes are necessary, including a rethinking of the regulations and more rapid and widespread sharing of sequence and antigenic information about new influenza strains. Preoptimized and preapproved influenza virus backbones (sets of influenza gene segments other than those that encode the strain-specific antigens) can be designed for high yields in cell culture and eggs, as well as for attenuation, thereby increasing the vaccine supply while allowing manufacture in biosafety level 2 containment. The ability of manufacturers to synthesize vaccine seed viruses would allow them to begin developing a pandemic vaccine at their own risk, at the first hint of a potential pandemic, rather than waiting for a vaccine virus to arrive in the mail from a World Health Association (WHO)-associated laboratory. Early development activities for potential pandemic vaccines can occur on a rolling basis, even as seasonal vaccine production continues. The combination of early

detection of new strains with pandemic potential, more rapid and open sharing of surveillance data (including the results of antigenic testing), and synthetic vaccine seeds could hasten the start of pandemic vaccine manufacturing by months. Increased yields from higher-producing seed viruses could hasten the ramp-up of the vaccine supply and improve global access to pandemic vaccines.

In 2009, the distribution by regulatory authorities of the calibrated reagents required to formulate and release the pandemic vaccine was a rate-limiting step, with clinical trials starting on the basis of manufacturers' surrogate assays (12). To accelerate pandemic response and to realize the benefits of more-rapid vaccine seed virus generation, we need to eliminate the need for calibrated reagents distributed by regulatory agencies. Today, these reagents are obtained by immunizing sheep with research-grade vaccine antigen, and they are used to determine the quantity of influenza hemagglutinin (HA) in vaccines, using single radial immunodiffusion (SRID), an assay that is more than 35 years old (17). Producing and calibrating SRID reagents requires nearly 2 months. Today, there are numerous techniques (including reversed-phase high-pressure liquid chromatography and isotope dilution mass spectrometry) that can quantify vaccine antigen content with better precision than SRID (18, 19). If coupled to a simple physical technique to separate misfolded from native HA, the assay adjustments needed to formulate and release a new pandemic vaccine could be available in hours rather than months. These two technological innovations, synthetic vaccine seeds and physical release assays, could transform the WHO system for pandemic response from a mid-20th-century system of producing and distributing materials from centralized laboratories at a pace dictated by sheep seroconversion, manipulation of influenza viruses in chicken eggs, and shipping logistics, into a 21st-century system of instantaneous electronic information exchange followed by immediate production at manufacturing sites around the globe. If the above changes had been introduced before the 2009 pandemic, the vaccine would have been available in large quantities before the peak of viral infection.

Finally, in the long term, we may think of universal vaccines (13). Although these are not an immediate solution, recent findings on the molecular mechanisms of human immunity to influenza have shown that antibodies directed against the stem of influenza HA can be broadly neutralizing (20). This finding raised the expectation that, by studying these antibodies and their crystal structures in complex with HA, we may learn how to make universal vaccines. However, to date, the progress in designing universal immunogens by using conserved regions of virulence factors has been limited, which suggests that, although this is a possibility in the long term, in

the short term we should not rely only on this approach. A promising way to improve the quantity of antibodies against the conserved region of the stem seems to be a prime-boost regime, in which a DNA vaccine primes and a conventional vaccine boosts the immune response (21). This approach, possibly coupled with the use of adjuvants, has the potential to improve cross-protection by influenza vaccines in the medium term, although adjuvants and priming alone are unlikely to produce a truly universal vaccine. Finally, there are many other approaches to universal vaccines, including the use of conserved antigens that do not elicit neutralizing antibodies, such as parts of the M1, M2, and NP proteins (13). Nevertheless, these approaches have been in the research-and-development pipeline with little progress for more than two decades, and it would be surprising if they succeeded in the near term.

In conclusion, while we wait for the development of a universal influenza vaccine, we have practical options that we could implement today to reduce the risk of mass global mortality from the next influenza pandemic.

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