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 frequently 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 bio-safety 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
Rino Rappuoli1 and Philip R. Dormitzer2

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-
makes the population more vulnerable to severe
is so rare, the population has not been primed by
lated H1N1 antigens and were spared severe dis-
by infection and/or vaccination with distantly re-
H1N1 pandemic, most people had been primed
immune system is primed, the risk of a severe
enhancer of immune responses known as an
subjects with an H5 vaccine (combined with an
vaccine became available after the peak of viral infection. The options avail-
able 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]

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 quan-
ties of the pandemic vaccine became available. Data are adapted from
(22, 23); only qualitative data are shown. The figure shows that in 2009 the
disease caused by highly virulent H5N1 strains
and makes immunization more difficult, neces-
sitating the use of adjuvants, higher antigen con-
tent, and two doses to elicit sufficient antibody
titers (7).

Given that licensed H5N1 vaccines are avail-
able, we have the option to vaccinate individuals
at greatest risk or to vaccinate more broadly, in-
cluding 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 vac-
cination campaign. It is not impossible. With suf-
cient 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 manufac-
turing 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 trans-
missible strain (such as the 1918 pandemic strain),
in a population with little preexisting immunity,
and using vaccines that are incompletely effec-
tive, 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 dis-
tributed 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, dur-
ing 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 cor-
responds to 1.4 billion doses of monovalent vac-
cine (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 ca-
pacity to fill and distribute vaccine doses a limiting
factor. Therefore, start-to-finish manufacturing ca-
pacity 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 (15). 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 could implement today to reduce the risk of mass global mortality from the next influenza pandemic.

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Editor's Summary

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