Seasonal and Pandemic Influenza Preparedness: Science and Countermeasures

Anthony S. Fauci

National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland

Influenza has not been treated with the degree of medical attention that the disease warrants. As such, there is not an adequate baseline of preparedness in the United States to deal with the potential of pandemic influenza. The National Institute of Allergy and Infectious Diseases (NIAID) has been working to enact measures to deal more effectively with a potential influenza pandemic and also to assist in the management of seasonal influenza. The majority of the NIAID's efforts have been dedicated to basic research aimed ultimately at developing and testing, in clinical trials, countermeasures in the form of antiviral drugs and vaccines. Some of the NIAID's current and planned antiviral projects include the (1) assessment of oseltamivir therapy in infants, (2) conduct of clinical trials of higher doses of osteltamivir for avian influenza, (3) appraisal of combination therapies, and (4) evaluation of the next generation of neuraminidase inhibitors. In addition, the NIAID is screening potential new antiviral drugs and evaluating novel drug targets. Similarly, significant funding has been committed to vaccine preparedness, and numerous novel candidate influenza vaccines are in various stages of development. Importantly, there is an integral relationship between preparation for seasonal influenza and preparation for pandemic influenza. Until these approaches are firmly linked, the community will not have optimized its preparedness for a pandemic.

There are multiple subtypes of influenza type A virus based on the 16 hemagglutinin (HA) (H1–H16) and 9 neuraminidase (NA) (N1–N9) proteins that are present on the surface of the different virus strains. Influenza A viruses are subject to a high degree of genomic mutation during replication, which can result in changes in HA and NAs. With regard to seasonal influenza, patterns of changes are the consequence of antigenic drift whereby the virus, particularly the HA gene, changes slightly from year to year. These changes are enough to necessitate a change in the vaccine but not so great as to precipitate a global pandemic, because the new viral strains are related enough to the preceding ones that a substantial degree of cross-reacting immunity exists within the general population.

Seasonal influenza is a relatively predictable annual event resulting in ~36,000 deaths and 200,000 hospitalizations in the United States [1, 2] and a global burden of ~500,000 deaths every year. One of the challenges of seasonal influenza, like so many global diseases, such as malaria and tuberculosis, is that there is a consistent disease burden from year to year. Thus, the world has accepted this disease burden, and a general assumption exists that there is little that can be done about it. In contrast, the anticipation of pandemic influenza brings up the possibility of a far greater disease burden than that associated with seasonal influenza. It is this perception of greater threat that prompts a reexamination of the adequacy of our seasonal influenza preparedness. Pandemic influenza occurs because, periodically, there is an antigenic shift or such a substantial change in viral antigens that the human population is left immunologically "naive" to the new virus. Such a shift has happened 3 times in the past century: (1) H1N1 in 1918, (2) H2N2 in 1957, and (3) H3N2 in 1968, each of which precipitated a pandemic. How-

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Reprints or correspondence: Dr. Anthony S. Fauci, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bldg. 31, Rm. 7A03, 31 Center Dr., MSC 2520, Bethesda, MD 20892 (af10r@nih.gov).

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Table 1. Confirmed cases of H5N1 infection in humans, by country (2003–August 2006).

Country	Cases, no.	Deaths, no.
Azerbaijan	8	5
Cambodia	6	6
China	21	14
Djibouti	1	0
Egypt	14	6
Indonesia	60	46
Iraq	2	2
Thailand	24	16
Turkey	12	4
Vietnam	93	42
Total	241	141 (58%)

NOTE. Data are from [3].

ever, the range of the severity of these pandemics is significant, ranging from 700,000 deaths in 1968 to >50 million in 1918. The 1918 H1N1 influenza pandemic is easily the most important pandemic of the 20th century and certainly one of the most catastrophic public health crises in recorded history.

Avian influenza cases caused by H5N1 have been detected in numerous countries of Southeast Asia and Europe and, more recently, in a growing number of countries in Africa and the Middle East. Spread of the disease to domesticated poultry continues to occur through migratory birds via their traditional flyways and, in some cases, through the legal and illegal transport of birds. Since 2003, the World Health Organization has confirmed 241 cases of H5N1 infection in humans in 10 countries, which resulted in 141 deaths (table 1) [3].

SEASONAL PREPAREDNESS

Table 2 details the historical production and distribution of influenza vaccine in the United States. Since 1980, there has been a progressive increase in attempts to vaccinate more people, including young children. Apart from the vaccine shortage in 2004 secondary to a contaminated production plant of a major supplier, the number of people vaccinated has generally increased each year. In reality, the medical and public health communities have not done an adequate job of either educating the public on influenza morbidity or providing medical interventions. As such, an adequate baseline of preparedness has not been developed that would serve as the infrastructure for a response to pandemic influenza. However, progress has been achieved. For example, as many as 120 million doses of influenza vaccine will be produced for the 2006–2007 influenza season. This increase in production volume represents a start but remains less than optimal, and further increase is needed.

PANDEMIC PREPAREDNESS

The US Department of Health and Human Services released an updated draft of the Pandemic Influenza Plan in November 2005 [4], at which time the US Homeland Security Council released the National Strategy for Pandemic Influenza. These documents focus on 6 main areas of preparedness:

- International surveillance
- Domestic surveillance
- Vaccine development and production
- Antiviral therapeutics
- Communications
- State and local preparedness.

Subsequently, the US Homeland Security Council issued a detailed implementation plan for the strategic plan, to clarify the roles and responsibilities of government and nongovernment bodies and to provide further preparedness guidance to the US population [5].

What are the measures that can be put into place to deal with a potential pandemic influenza, and how do they relate to seasonal influenza? Preparedness can be categorized into broad public health measures and countermeasures. Public health measures are discussed further in another article in this supplement, by Julie Gerberding [6]. In the present article, the basic research efforts and countermeasures of antiviral drugs and vaccines will be highlighted.

Basic research. Influenza research funding at the NIAID has increased dramatically (~10-fold) over the past 5 years, to >$150 million in 2006. Most of this funding has been dedicated directly or indirectly to developing countermeasures, particularly vaccines. An example of the scientific advances that have emanated from NIAID-supported research include the now

Table 2. Historical production and distribution of influenza vaccine.

Year	Doses produced (millions)	Doses distributed (millions)
1980	15.7	12.4
1985	23.1	20.1
1990	32.3	28.3
1995	71.5	54.9
1999	77.2	76.8
2000	77.9	70.4
2001	87.7	77.7
2002	95.0	83.0
2003	86.9	83.1
2004	61.0	56.5
2005	86.0	>80.0

NOTE. Data are from the Centers for Disease Control and Prevention.

widely applied reverse-genetics capability. This technology has enabled more reliable and predictable development of a reference vaccine by eliminating chance in the generation of appropriate reassortments. Furthermore, it reduces the time required for vaccine reference virus generation. In addition, the NIAID has established the Influenza Genome Sequencing Project, in which genetic information has been collected on a large number of influenza isolates. As of 28 August 2006, the full genomic sequences of 1465 human and avian influenza virus isolates had been made available to the scientific community for use in research.

Antivirals. Currently, there are 2 major targets for antiviral drugs: NA and the M2 protein. A number of the H5N1 influenza viruses isolated in Southeast Asia in early 2004 were sensitive to oseltamivir and zanamavir (NA inhibitors) but were resistant to amantadine and rimantadine (M2 inhibitors). However, some of the second clade of H5N1 appears to be sensitive to both classes of drugs, which indicates the variability and drift of these viruses. Further, this observation reiterates the need to perform drug sensitivity testing on available viral isolates to define the potential utility of all available antiviral agents.

Different strategies exist for the deployment of antiviral drugs. Modeling studies suggest various options for intervention with antiviral drugs as a pandemic evolves [7, 8]. Drug interventions will likely not stop a full-blown pandemic, but antiviral drugs could, potentially, contain local outbreaks. Regardless, effort needs to be devoted to assessing the full potential of antiviral therapy. Some of the NIAID's current and planned projects include an assessment of the appropriate use of oseltamivir in infants <1 year of age, the conduct of clinical trials of different dose regimens (i.e., higher doses) of osteltamivir in Southeast Asia, studies of the efficacy of combination therapy, and the evaluation of the next generation of NA inhibitors, such as peramivir. In addition, the NIAID is screening potential new antiviral drugs and evaluating novel drug targets (i.e., viral entry, replication, and HA maturation). The current goal of the national antiviral stockpile strategy is to have 81 million courses of therapy, including 6 million to contain an initial outbreak and 75 million to treat 25% of the US population.

The impact of antiviral drugs on the treatment of a pandemic influenza is unclear at present. The development of promising new antiviral candidates should be accelerated because of the limitations of the current drugs, such as the need for them to be taken within 24–48 h of onset of symptoms.

Vaccines. A significant component of the $3.8 billion approved by Congress in 2005 for pandemic influenza preparedness has been committed to vaccine development and production by increasing surge capacity and generating alternative vaccine methodologies, such as cell-based systems. The NIAID is currently working with Sanofi Pasteur and Novartis to evaluate a prepandemic vaccine based on a strain of H5N1 virus that was isolated in Vietnam in 2004. Preliminary results from a study evaluating this vaccine in 451 healthy adults demonstrated that a high dose of vaccine (2 doses of 90 μg each) is required to induce a level of immunity that would be predictive of being protective, a dose that is considered to be impractical [9]. Studies are also ongoing in elderly and pediatric subjects. Methods under study to improve immunogenicity include additional booster doses, use of adjuvants, and intradermal immunization. Results with an alum-adjuvanted vaccine (Sanofi Pasteur) have demonstrated that protective antibody levels can be achieved with 2 doses of 30 μg [10]. However, the need for a booster with a dose as high as 30 μg is still impractical. Another study, utilizing an H9N2 vaccine with MF59 as the adjuvant (Novartis), demonstrated that an adequate immune responses was induced using a regimen as low as 2 doses of 3.75 μg [11]. GlaxoSmithKline has reported similar results with low doses of an H5N1 vaccine with a proprietary adjuvant.

The national vaccine strategy is to stockpile 20 million courses of prepandemic vaccine and to accelerate vaccine production capacity within the United States substantially, to produce intrapandemic vaccines. Since the currently circulating H5N1 virus continues to evolve by mutation, prepandemic vaccine production for the entire US population is not an optimal strategy. Nonetheless, it is important to develop the vaccine-manufacturing capacity to produce, within a reasonable period (4–6 months), 300 million doses of a vaccine that matches the virus strain, should it ultimately develop the capability of being transmitted efficiently from human to human and, hence, cause a pandemic. One way of achieving this goal is to accelerate the development of new production platforms, such as cell-based vaccine technology to obviate dependency on egg production. In addition, researchers must identify novel vaccine approaches, such as DNA vaccines, and develop dose-sparing strategies, particularly through the use of adjuvants. The NIAID has joined forces with MedImmune to develop potential pandemic influenza live attenuated vaccines by preemptively developing at least 1 vaccine for each of the 16 HAs.

The ultimate goal is to have a universal influenza vaccine. Although studies of natural infection suggest that effective cross-protection among related influenza strains does not occur readily, the weak natural response may be enhanced through the use of conserved antigens such as the M2 protein in a highly immunogenic form. Areas in vaccinology that require further exploration include the following:

- The molecular basis of the ability of the influenza A viruses to drift and/or shift and thus evade immune detection
- The lack of broadly cross-protective, highly functional antibodies and $CD8^+$ T cell responses in influenza A virus infection

- The paucity of conserved epitopes
- Inadequate protection conferred by previous infection(s) with an influenza virus of a different subtype—that is, weak "heterosubtypic" immunity
- The need for mucosal immune responses that restrict replication in the upper and lower respiratory tract.

In conclusion, there is an integral relationship between preparedness for seasonal influenza and preparedness for pandemic influenza. Until these approaches are unified, the community will not have optimized its preparedness for an influenza pandemic and will not be able to get beyond crisis mode.

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