The US pandemic influenza implementation plan at six months

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There has been great concern recently about pandemic influenza. The US government developed a National Strategy for Pandemic Influenza in November 2005, followed by an implementation plan in May 2006. A six-month progress report was published in late December. The current strategies are intended to improve preparedness and response for the next influenza pandemic. In comparison with the optimistic neglect that often characterized past planning for pandemic influenza, there has been considerable progress on a number of fronts in the past year. Despite this progress, major gaps remain. These include the coordination, encouragement and funding of international surveillance and cooperation; the need for new and more agile vaccine technologies; limitations in the use and distribution of antiviral agents; and communication with, and resources for, local responders and the public. One question is why, despite an estimated 36,000 seasonal influenza deaths annually in the United States alone, and a much greater number during pandemics, relatively little new basic research has been done for decades. This emphasizes both the need for and the difficulty of sustaining pandemic preparedness.

There is good reason to be concerned about a future influenza pandemic. There were three in the twentieth century, in 1918–1919, 1957 and 1968, and most virologists believe that pandemics are inevitable[1]. The greatest influenza pandemic, in 1918–1919, was also the worst natural disaster in recorded history, with an estimate of over 50 million deaths worldwide[2–4]. Concern about the state of pandemic preparedness and response has been increasing over the last decade. In 1999, when the World Health Organization (WHO) produced pandemic planning recommendations, only Canada and the UK already had plans. By 2007, 29 countries had submitted plans (available at http://www.who.int/csr/disease/avian_influenza/links/en/index.html) to WHO.

Next year will mark the 90th anniversary of the great pandemic of 1918, making it especially timely to take stock of our readiness for the next pandemic. On 1 November 2005, the President of the United States declared that "nature has presented us with a daunting challenge: the possibility of an influenza pandemic," and announced the government's National Strategy for Pandemic Influenza (http://www.pandemicflu.gov, under Federal Planning). This strategy is intended to address the next influenza pandemic, whichever influenza virus is the cause. Although we do not know whether the H5N1 avian influenza strain will ever develop the ability to spread readily from person to person and thus become pandemic, this virus has recently been getting close scrutiny. It has already caused serious human illness and deaths, primarily although not exclusively through close contact with infected poultry. There have also been tremendous economic losses for poultry farmers.

The US pandemic plan and progress in implementation

The national strategy delineated three critical goals, or 'pillars': "to detect and contain outbreaks before they spread across the world, to protect the American people by stockpiling vaccines and antiviral drugs and accelerating the development of new vaccine technologies, and to ensure that Federal, State and local communities are prepared for potential domestic outbreaks." The national strategy was followed in May 2006 by the National Strategy Implementation Plan (http://www.pandemicflu.gov, under Federal Planning), which enumerated a timeline for specific actions to be taken across the Federal government. The implementation plan also required reports on progress toward these specific tasks. The six-month progress report, National Strategy for Pandemic Influenza Implementation Plan: Summary of Progress (http://www.pandemicflu.gov, under Federal Planning), was released on 29 December 2006. The purpose of this Commentary is to evaluate progress thus far and to discuss further needs.

International surveillance and cooperation, crucial for dealing with global diseases, is the first pillar of the plan. In the past, international public health was often neglected and underfunded. The US government is contributing to international virus surveillance through WHO, providing funding and technical assistance. The high-level political backing and visibility of the current effort may also have helped to galvanize other actions. A number of countries have now developed pandemic plans. Meetings, such as the US government–initiated International Partnership on Avian and Pandemic Influenza, have been convened for international fundraising. Almost $2.4 billion has reportedly been raised through other donor conferences jointly sponsored by the United Nations and the World Bank. Over $300 million of this was disbursed by the end of 2006 (http://siteresources.worldbank.org/INTTOPAVIFLU/Resources/Framework06-2006.pdf), although it remains to be seen what total amounts are ultimately disbursed and how the funds are used. The funding is intended to be used for a variety of purposes, including compensation to farmers whose poultry flocks need to be culled, as well as support of public health and medical needs. Given the current situation with

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H5N1 as an avian disease, control in poultry is an essential measure and requires adequate compensation for farmers.

Closely tied to this is diagnostic capacity. There are several promising technologies for multiagent identification, including PCR, dipsticks and array-based devices. However, any diagnostic test must be inexpensive, easy to use and relatively accurate if it is to be used in field settings, especially in developing countries, and it must reliably identify and differentiate a new strain (which may be yet another influenza virus in addition to H5N1) from the circulating seasonal influenza subtypes. The Department of Health and Human Services (HHS) and HHS components, including the National Institutes of Health's National Institute of Allergy and Infectious Diseases (NIH/NIAID) and the Centers for Disease Control and Prevention (CDC), have financed several efforts in diagnostic development, and they are anticipating commercial products in about 2–3 years.

The second leg of the plan includes vaccines and antiviral agents. For over 50 years, the mainstay of our defense against influenza has been vaccine[1,5]. Manufacturers (seemingly fewer in number each year) produce new influenza vaccines annually, a process that must start months before the 'flu season'. Producing influenza vaccine in eggs was a major breakthrough. However, it is difficult to switch production on short notice. A major limitation is the supply of suitable fertilized eggs. The plan assumes that new vaccine production would require about six months, a realistic assessment under current conditions. To facilitate rapid production, the government is providing funding for vaccines in which the influenza viruses are grown in cell culture instead of in eggs. Viruses grown in cell culture have been used to make many other viral vaccines for decades, leading one to wonder why cell culture vaccines could not have been introduced years ago. The most recent vaccine innovation in the last decade has been the introduction of live attenuated influenza vaccines (FluMist). The production process is similar to conventional influenza vaccines, in eggs or cell culture, but the final product consists of live attenuated viruses, administered as a nasal spray. In vaccine development, liability has historically been another major concern for manufacturers[6]. The Public Readiness and Emergency Preparedness (PREP) Act, passed by Congress last year, is intended to address this problem.

A second part of this pillar is acquisition and stockpiling of antiviral drugs. Effort has focused on the neuraminidase inhibitors, the main class of antiviral agents that has shown therapeutic efficacy against influenza[7]. Much of the attention has revolved around oseltamivir (Tamiflu), because it can be administered orally and is active systemically. In order to diversify the stockpile, the US government is including a second neuraminidase inhibitor, zanamivir (Relenza), expected to comprise 20% of the stockpile. This is an ongoing program, and it continues to evolve. However, as of this writing, the current federal goal is 75 million treatment courses, sufficient quantities (by government estimates) to treat all of the US population who are anticipated to become ill and are likely to benefit from antiviral treatment. This comprises 25% of the US population. Of the 75 million drug courses, states have the option to purchase 31 million using state funds, at a 20% federal subsidy. This has led to varying decisions by states on how much they wish to buy (or can afford). Assuming sufficient supply continues, adding prophylactic use, such as for patients' families and healthcare workers, has been suggested. Targeted antiviral prophylaxis in schools and other high-transmission settings has also been advocated as a strategy for reducing transmission[8]. Finally, another 6 million courses in the national stockpile are held for targeted containment of identified early outbreaks anywhere in the world. Perhaps to hedge bets in view of limited supplies and the expected development of viral resistance, in January HHS awarded a $102.6 million contract to BioCryst Pharmaceuticals for advanced development of their injectable neuraminidase inhibitor, peramivir.

The third pillar of the strategy is domestic preparedness. Over the last year, HHS Secretary Leavitt has met with government officials in every state and territory throughout the United States. These state summits have been an impressive effort to engage municipalities and state authorities. Many municipalities believe, however, that despite federal aid they still do not have sufficient resources to support local preparedness. They are especially concerned about the need to have the resources and medical surge capacity. Supporting and building local capacity, and coordinating different jurisdictions, is probably the greatest single operational issue within the United States.

Gaps and future needs

Influenza seems to be getting serious consideration at last. Having a coherent national strategy is itself significant. Though a number of the activities listed in the implementation plan, such as interagency meetings, are administrative, there are many broader accomplishments as well. The plan is ambitious and represents the most comprehensive attempt at pandemic preparedness so far. It recognizes the interdependency of systems and communities, and the need for flexibility. Flexibility is essential, as influenza pandemics have been unpredictable, each one unique[1].

Many alliances have also been developed at the international level; these need continual reinforcement. However, many of these laudable international efforts remain largely *ad hoc*. Although the US progress report discusses a mandate and new systems for international surveillance, there is insufficient detail to judge their effectiveness. Will the system be a single network or (as seems more likely) a 'network of networks'? If the latter, will the systems all be able to share information readily using common standards (in the current jargon, will they be interoperable)? For that matter, how will human health and veterinary systems be linked, if at all? The gaps between animal and human health systems remain dangerously wide. The training of veterinarians to recognize and control influenza in fowl and to understand its natural history, cross-training between human and animal health personnel, and information sharing should be greatly accelerated and improved. Recent initiatives have improved information sharing for influenza surveillance, at least at the official level, but need to be strengthened and greatly expanded.

A workable real-time global system of outbreak reporting and response has long been a 'holy grail' for those working on emerging infectious diseases[9]. Systems being developed for pandemic influenza surveillance could form the foundation of a generic system that can also be applied to unanticipated future threats. These systems should also support the new International Health Regulations (http://www.who.int/csr/ihr/en/), which are scheduled to begin implementation in June 2007, and which mandate rapid, and preferably electronic, international disease reporting. This will require considerable funding, as well as other incentives.

Effective diagnostics are essential, but diagnostic capacity still remains a shortcoming. Time lags in diagnosis and reporting can still be considerable, exacerbated by a lack of fast, reliable and inexpensive point-of-care or field diagnostics. The consequences can be enormous, especially if one hopes to quell a pandemic by treating and isolating the first clusters of human cases, which are likely to be outside the United States or western Europe[10,11]. Rapid response requires rapid recognition. An extreme example of delayed recognition was a human H5N1 death in 2003 that was not reported until almost three years later[12]. More typically, based on WHO reports examined by the author, laboratory confirmation of human H5N1 cases has usually required

about a week (although sometimes less) after the case is recognized by health authorities, but it often took two weeks to a month. Even a week could allow a pandemic virus to generate a number of new, possibly dispersed, cases before a response is initiated. Another recent concern was Indonesia's decision against sharing new H5N1 isolates. Although this issue now appears settled, the incident served to highlight the inequities in the distribution of vaccine and access to care that a number of developing countries fear will occur in a pandemic. The incident also demonstrates how dependent we all are on availability of isolates and sequence data, which will often come from developing countries, and emphasizes the importance of global capacity building and resource sharing in the face of a truly global disease problem.

For a number of years, limited vaccine capacity and disequilibrium between supply and demand have been serious concerns. Ways to stabilize demand (such as by government-guaranteed minimum purchases) are essential. So is a concerted strategy for bringing more rapid vaccine production online. Current vaccine capacity is sorely limited, and manufacture is slow in comparison with the speed with which a pandemic influenza strain can traverse the globe. Additional technologies must be encouraged and tested. The long timeline and high cost of new vaccine development are themselves worrisome, if we are to have adequate vaccine capacity for pandemics.

There is currently little incentive to develop new vaccine technologies and bring them to market. One collateral benefit of the attention to pandemic influenza may be to encourage consideration of new strategies, as in the use of a new adjuvant in a human H5N1 vaccine candidate. The most widely used human influenza vaccines contain the hemagglutinin (and sometimes also the neuraminidase) surface proteins extracted from virus that has been grown and then inactivated—basically, one purified protein each from the three current strains believed most likely to cause the major seasonal epidemics in the coming year. If the object is to produce a protein, why not simply clone the desired viral hemagglutinin proteins and produce them in suitable eukaryotic cell culture systems? As early as 2001, Treanor *et al.* tested a recombinant vaccine containing the H5 hemagglutinin[13]. Human antibody response was modest but, in retrospect, results seem similar to the results reported for the first conventional H5 vaccine recently produced by Sanofi[14]. This approach therefore merits revisiting, especially in combination with newer adjuvants. Kilbourne has suggested producing inactivated vaccines against all 16 known hemagglutinin types, as a 'universal' vaccine[1].

Many other experimental approaches for new vaccine and therapeutic technologies are also in the research stages, many of them funded by HHS, NIH/NIAID or CDC[5,15–18]. However, even if some of these are successful, it is likely to be a decade or more before they reach the clinic. Of equally grave concern, HHS had solicited proposals for new vaccine development in 2005 and did not judge any of the new proposals mature enough to warrant funding. HHS plans to reissue this solicitation in 2007; it is to be hoped that the results will be more promising.

Until a vaccine is produced, which may well be 4–6 months, we will need to rely on stocks of antiviral agents such as the neuraminidase inhibitors; and on nonpharmaceutical measures such as staying home when sick, possibly closing schools and mass gatherings (collectively known as 'social distancing'), and 'respiratory etiquette' (covering coughs and sneezes)[19]. One difficulty with oseltamivir and other neuraminidase inhibitors is that, public perceptions to the contrary, we still are learning how to use these drugs most effectively. A related problem is our limited armamentarium of antivirals. At present the most effective therapeutic agents for influenza are the neuraminidase inhibitors. Although most influenza viruses remain susceptible, there have already been reports of resistance to oseltamivir in a few human cases of H5N1 avian influenza. Advanced strategies (such as interfering RNAs) are in the research stages, but these are likely to be years away. Thus new antiviral drugs, such as protease inhibitors, that can capitalize on known successes with other viruses to allow relatively rapid development should also be encouraged.

Regarding nonpharmaceutical measures, interim Federal guidance from the CDC was released in early 2007, and it is still evolving. Unfortunately, the science base is less than robust[19]. CDC has funded several projects to develop better evidence on effectiveness of various interventions. This is welcome, and long overdue. Additional research is needed to develop a firmer scientific foundation, even for such fundamental questions as primary modes of transmission.

It appears that determining who is in charge among the various federal agencies, long a stumbling block, is being resolved. In December, Congress passed the Pandemic and All-Hazards Preparedness Act (PAHPA, Public Law 109-417), which states that HHS is now the lead federal agency for response to public health emergencies. The act also establishes the Biomedical Advanced Research and Development Authority (BARDA) within HHS, which could help to accelerate advanced development of new vaccines and antivirals. However, it is too soon to determine the effect of this law. The bill also requires HHS to set preparedness standards for states. Interestingly, it also requires HHS to establish within two years a nationwide electronic information-sharing system to enhance detection of and response to disease outbreaks and other public health emergencies, although (as of this writing) additional funds have not yet been allocated for this purpose. A national or, better, international integrated surveillance system would be an enormous step forward.

Much of the actual execution of any plan will need to occur at the local level, and there is considerable variation in local capacity and plans for mass distribution of antivirals and vaccine. Continued development of standard procedures, and local and regional exercises, are essential. Local implementation of nonpharmaceutical countermeasures may also be a concern. Therefore, strengthening local public health remains a high priority. Many consider this area to be insufficiently funded. As D.A. Henderson and colleagues have noted, it is essential to inform the public and involve the community in planning[20]. Community planning to ensure sufficient hospital capacity and medical care is essential.

One of the strongest lessons, as we consider 1918, is that despite considerable progress in the last century, much of the basic science is still simply lacking[19,21]. Fundamental questions of environmental stability, reasons for seasonality and many other properties remain largely unanswered. We lack the ability to predict transmissibility across species or from human to human. Much of what we know about influenza is based on limited inferential evidence, often developed decades ago. Thus there is an urgent need to develop an integrated research agenda that includes special attention to the basic science and epidemiology, as well as to accelerate applied research such as vaccine and diagnostic technologies.

Perhaps most important of all is sustainability. For pandemic preparedness, we have only a few historical examples to rely on and limited data from which to draw[4,10,19]. If, as we hope, the pandemic does not come within the next year or two, how can we maintain momentum and encourage funding for public health efforts? One essential step is public outreach. There has been a great deal of attention in the media; this has served mostly to raise awareness. The public will eventually lose interest in an imminent threat that does not immediately materialize. Past history suggests that it is possible to sustain some momentum by more directly involving the public. In this respect, the seasonal influenza can be a useful opportunity.

Even though we may take it for granted, 'ordinary' seasonal flu kills about 36,000 Americans annually (by CDC estimates). It provides an excellent target and practice opportunity for both clinicians and the public.

Recent past emergencies, such as the response to Hurricane Katrina, indicate that there is an urgent need to think through the desired outcomes and prepare long before the event. A pandemic may be an emergency comparable to a Katrina, yet far more widespread and protracted. Evacuating people to 'safe' ground will not be an option. Pandemics may come in prolonged and often unpredictable waves that will put great stress on our medical systems and general infrastructure. Great progress has been made, but a great deal remains to be done before the next pandemic strikes.

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COMPETING INTERESTS STATEMENT

The author declares no competing financial interests.

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