V. The role of the Office of the Assistant Secretary for Preparedness and Response (ASPR), within the U.S. Department of Health and Human Services, in global preparedness and response to pandemic influenza

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Resumen

Cuando los virus de influenza en animales desarrollan la capacidad de infectar y transmitirse en poblaciones humanas inmunes sin exposición, pueden diseminarse rápidamente en el mundo con niveles significativos de morbilidad y mortalidad. Para prepararse y atenuar las consecuencias, se realizan esfuerzos de preparación en muchos países. El gobierno de Estados Unidos, incluyendo el Departamento de Salud y Servicios Humanos de Estados Unidos (HHS), participa en iniciativas internacionales sobre preparación en influenza. A través de estos mecanismos proporciona ayuda financiera y asistencia técnica a los países; contribuye a investigación, vigilancia, capacidad de producción y a la respuesta. México y Estados Unidos colaboran extensamente en el Plan de Norte América para la Influenza Aviar y Pandémica *y en una iniciativa de transferencia de tecnología para incrementar la capacidad de producción de vacuna contra la influenza. La oficina de HHS de la Subsecretaría para Preparación y Respuesta (ASPR) tiene la responsabilidad de la preparación y respuesta a emergencias en salud pública. Dentro de la ASPR, el* Biomedical Advanced Research and Development Authority *(BARDA) apoya la innovación, desarrollo, reserva y fortalecimiento de la infraestructura para producir medidas, tales como vacunas, antimicrobianos y pruebas diagnósticas para influenza pandémica, enfermedades infecciosas emergentes y amenazas químicas, biológicas, radiológicas y nucleares.*

Palabras clave:
Pandemia de influenza, Departamento de Salud y Servicios Humanos de los Estados Unidos, emergencias en salud pública

Summary

When animal influenza viruses evolve the capacity to infect and transmit among immune-naïve human populations, they may rapidly spread throughout the globe, resulting in significant levels of morbidity and mortality. To prepare for and mitigate the consequences of such an event, extensive preparedness efforts are underway in many nations. The U.S. Government, including the U.S. Department of Health and Human Services (HHS), is involved in a number of international initiatives on influenza preparedness. Through these mechanisms, the United States provides financial support, and technical assistance, to partner countries; and contributes to research, surveillance, manufacturing capacity, and response. Mexico and the United States collaborate extensively on preparedness; resulting in, for example, the North American Plan for Avian and Pandemic Influenza *and a technology transfer initiative to increase influenza vaccine manufacturing capacity.*

The HHS Office of the Assistant Secretary for Preparedness and Response (ASPR) has the responsibility of preparing for, and responding to, public health emergencies. Within ASPR, the Biomedical Advanced Research and Development Authority (BARDA) supports the innovation, development, stockpile building, and building of infrastructure to manufacture medical countermeasures, such as vaccines, antimicrobial drugs, and diagnostics for pandemic influenza, emerging infectious diseases, and chemical, biological, radiological, and nuclear threats.

Key words:
Influenza pandemic, U.S. Department of Health and Human Services, medical countermeasures, public health emergencies

Pandemic influenza

The emergence and spread of novel influenza viruses are a pressing concern to the global public health community due to their potential to cause a pandemic. While seasonal human influenza viruses circulate widely each year and cause epidemics with moderate levels of morbidity and mortality,[1] the appearance of a novel and highly-pathogenic strain of influenza in humans could be devastating. Of the many infectious diseases which have emerged in the past century, few have had as acute and widespread an impact as that of new influenza strains. The emergence of the H1N1

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subtype in the human population in 1918 resulted in an estimated 50 million deaths worldwide. The subsequent emergence of the H2N2 subtype in 1957 and H3N2 in 1968 had smaller, yet significant, global tolls on the human population, resulting in up to two million and 700,000 deaths, respectively.[2] Some models suggest that if the currently circulating H5N1 avian influenza virus or another equally pathogenic subtype evolves the capacity to spread easily from one human to another, it could lead to the deaths of two to 70 million[3] people and cost the global economy up to $3 trillion.[4]

Seasonal influenza viruses are those which have become established in the human population and reappear in the fall/winter months in the Northern Hemisphere. Currently, these include influenza A subtypes H1N1 and H3N2 (A/H1N1 and A/H3N2, respectively), and influenza B; therefore, the annual trivalent vaccine for seasonal influenza includes a strain of each. Due to the continuous generation of genetic variation within the immunodominant proteins of seasonal influenza types and subtypes (termed "antigenic drift"), however, immunity to the predominant A/H1N1, A/H3N1, and B variants may not be fully effective against A/H1N1, A/H3N1, and B variants circulating in subsequent years. Thus, the vaccine is updated annually to protect against the newest variants.

The annual recurrence of seasonal influenza —and thus, an adequate degree of population-level immunity, to variants of A/H1N1, A/H3N2, and B— typically prevents severe seasonal morbidity and mortality. However, as in 1918, 1957, and 1968, novel influenza subtypes may emerge to which there is little or no population-level immunity. These novel subtypes are often generated via the replacement of the viral hemagglutinin (HA) and/or neuraminidase (NA) gene segments by the corresponding segments from a different subtype. This genetic reassortment, termed "antigenic shift", can result in the widespread absence of neutralizing humoral immunity.

Birds are the main reservoir for influenza A viruses. Collectively, they harbor viruses that may express sixteen known HA genes and nine known NA genes. Differences in human and avian biology typically prevent the infection of humans by avian-specific viruses, unless these viruses have acquired HA or NA gene segments from human influenza viruses, or changes to the receptor-binding domain of the avian influenza HA have rendered it capable of binding human cell receptors. If the strain can be passed efficiently from one human to another, and there is little or no population-level immunity, it may sweep through the human population very quickly, with little or no advance warning. The emergence of the highly-pathogenic avian strain, H5N1, is particularly significant and worrisome as it has acquired the ability to infect humans. The virus likely circulated prior to 1997, but mutated that year from a form that caused mild symptoms in poultry to its current, highly pathogenic form that is nearly 100 percent fatal to poultry.[5] The virus reemerged in 2003, and as of March 16, 2009, avian H5N1 has been detected in 50 countries, and has infected at least 6,601 birds.[6] As of March 19, 2009, officials have confirmed human cases of H5N1 in 15 countries. Though only 411 people have had confirmed infections, the estimated case-fatality rate is currently 62.3 percent,[7] which is extremely high when compared to case fatality rates of 0.35 and 2.5 percent for seasonal influenza and the 1918 influenza epidemic, respectively.[8] Most cases are thought to have occurred via direct and significant contact with birds; however, relatively few genetic adaptations may be required to achieve sustained and efficient human-to-human transmission in the immunologically-naïve human population. The consequences of an H5N1 pandemic could be catastrophic, and it is essential that the global public health community prepare in order to mitigate the impact of such an event.

The role of the U.S. Government, the U.S. Department of Health and Human Services, and the Office of the Assistant Secretary for Preparedness and Response

A pandemic will impact multiple segments of society including the healthcare system, the economic sector, transportation, and critical infrastructure services. Therefore, planning for a pandemic necessarily must involve all sectors and levels of society. In preparing for an influenza pandemic, the *U.S. Government* issued the *National Strategy for Pandemic Influenza*[9] in November 2004, which involves Federal, State, local and Tribal authorities, the private sectors and communities. It expends significant and complementary resources and human capital for pandemic preparedness, both domestically and internationally. The U.S. Department of Homeland Security and the U.S. Department of State play key roles in coordinating overall U.S. Government efforts on pandemic influenza preparedness and response with foreign Governments, and the U.S. Agency for International Development manages programs that promote international preparedness. *Pandemicflu.gov*, a U.S. Government website, provides a comprehensive, Government-wide overview of these efforts for the general public, health and emergency preparedness professionals, policy makers, government and business leaders, school systems, and local communities.

The *U.S. Department of Health and Human Services (HHS)* is the U.S. Government lead for preparedness and response to public health and medical emergencies, including pandemic influenza. HHS is the U.S. Government's principal agency for protecting the health of all Americans and providing essential human services. In the field of pandemics, the HHS Centers for Disease Control and Prevention (CDC) leads programs that focus on training, laboratory strengthening, capacity building (particularly for the early detection of novel pathogens), and rapid response,[10] and the HHS National Institutes of Health supports extensive influenza research both intramurally and extramurally.[11] The HHS Food and Drug Administration regulates drugs, biological products, and medical devices, and is responsible for determining their safety and efficacy.

The *Office of the Assistant Secretary for Preparedness and Response* (ASPR), within HHS, was established on December 19, 2006, under the Pandemic and All-Hazards Preparedness Act (PAHPA),[12] to lead the United States in preventing, preparing for, and responding to public health emergencies and disasters.[13] ASPR serves as the principal advising office on public health threats, including bioterrorism and public health emergencies, such as pandemic influenza, and coordinates intra- and inter-department preparedness

and response efforts. It aims to achieve its mission through three goals:

1. Promote preparedness to prevent and address the public health, medical, and human services effects of a disaster on individuals, families, and communities.
2. Enable public- and private-sector partners to prevent and address the effects of disasters on the healthcare and public health systems.
3. Lead HHS' emergency preparedness and response capabilities to prevent and address the public health, medical, and human services effects of disasters, both natural and man-made.

ASPR undertakes public health and medical emergency preparedness, policy and program development, analysis and evaluation. In addition, ASPR develops operational strategies and procedures, carries out training and simulations, coordinates plans nationally and internationally, provides public health advice on domestic and international programs and activities, and supports the development and acquisition of biomedical countermeasures against chemical, biological, radiological, and nuclear agents, and emerging infections such as pandemic influenza or other emerging infectious diseases.

Responsibility for the latter activity, the advanced development and building of a stockpile for medical countermeasures, such as vaccines, therapeutics, diagnostics, and non-pharmaceutical medical devices for public health and medical emergencies, lies within the *Biomedical Advanced Research and Development Authority (BARDA)*, one of the multiple offices in ASPR. To establish the manufacturing infrastructure, expand surge capacity, and provide new products necessary to mitigate the effects of severe influenza pandemics, HHS investments facilitate research and development of influenza vaccines, antiviral drugs, diagnostics, and other countermeasures.

Vaccines

The uncertain nature of the next pandemic virus, and the speed with which it will spread across the globe, pose unique problems for the development and stockpiling of new pandemic influenza countermeasures, particularly prepandemic vaccines (vaccines, made prior to the onset of a pandemic, against currently circulating influenza virus strains with high pandemic potential). In the event of a pandemic, these challenges to vaccine development would be accompanied by supply shortages, and vaccine manufacturing capacity would likely be inadequate to initially meet demand. To meet domestic and global pandemic vaccination challenges, ASPR/BARDA supports the advanced development of cell-based vaccines, antigen-sparing vaccines formulated with new adjuvants, and next-generation recombinant vaccines. By retrofitting existing manufacturing facilities and building new manufacturing facilities for cell-based influenza vaccine in the United States, ASPR/BARDA is expanding domestic vaccine manufacturing infrastructure multifold to provide pandemic vaccines for the entire U.S. population.

Presently, all seasonal influenza vaccines licensed in the United States are produced in embryonated hen's eggs. While this process serves domestic seasonal influenza vaccine needs, it is vulnerable to avian pathogens such as H5N1 viruses, and dependent on the availability of eggs and specialized egg-processing equipment that may be limiting during an influenza pandemic. Cell-based influenza vaccines are produced with virus vaccine strains in secure closed tissue culture cell systems that are flexible, robust, and capable of rapid surge capacity. ASPR/BARDA also supports the development of recombinant vaccines that may be available sooner during an influenza pandemic than egg- and cell-based vaccines.

Additionally ASPR/BARDA supports the development of new adjuvants with H5N1 vaccine, which afford significant antigen-sparing effects (12-24 fold), broad cross-reactive immune protection against antigenically drifted virus variants, and prime-boost effects. These new vaccines may expand both stockpiles of pre-pandemic vaccines and pandemic vaccine manufacturing surge capacity.

The development and maintenance of the national pre-pandemic vaccine stockpile started in 2004, under the charge of ASPR/BARDA. The stockpile is comprised currently of four H5N1 vaccine strains using the manufacturers and the processes for U.S.-licensed seasonal influenza vaccines. The stockpile size is expected to reach its goal of 40 million doses by mid-2009.

Diagnostics

The ability to immediately and accurately diagnose those infected with the circulating novel pandemic strain would greatly facilitate the management of a pandemic. In recognition of this critical need, ASPR/BARDA and the CDC support the development of novel "point of care" rapid influenza diagnostics. These will enable healthcare providers to determine whether an individual is infected with influenza on-site for initial medical assessment, triage, and care.

Antivirals

To treat those infected with influenza, and improve their chances of survival, and/or prophylax those exposed or likely to be exposed, effective antiviral therapies are needed. Two adamantine-derived M2 inhibitors and two neuraminidase inhibitors are currently licensed as influenza antiviral drugs in the United States and ASPR/BARDA is supporting the advanced development of new and better influenza antiviral drugs including combination therapies and passive antibody therapies. ASPR/BARDA oversees the acquisition and management of Federal and State stockpiles of influenza antiviral drug for use during a pandemic.

Medical equipment

In the event of an influenza pandemic, there would also be an overwhelming demand for medical equipment, such as ventilators, which cannot be met with current technology and supplies. Thus, ASPR/BARDA sees a great need for the development of next-generation ventilators which are lightweight, portable and easy to use; have an extended battery

life and a closed-loop inspiratory pressure control system; and can accommodate a wide range of patients.

Global partnerships and initiatives

In addition to ASPR's activities related to medical countermeasures, the U.S. Government engages in a range of global initiatives and partnerships to mitigate the global impact of an influenza pandemic. The lead for initiatives on pandemic influenza is the U.S. Department of State, but HHS engages in a number of efforts as well. Though not a comprehensive list, below are some of the global partnerships and initiatives in which HHS, including the International Influenza Unit, engages.

The *International Partnership on Avian and Pandemic Influenza (IPAPI)* is an example of one of these. The U.S. Government has contributed substantially to the IPAPI which is comprised of approximately 120 countries and international organizations that strive to improve international surveillance, transparency, timeliness, and response capabilities and sharing of epidemiological information and samples critical for the response effort.

The United Nations also manages a number of programs aimed at preventing, preparing for, and responding to avian influenza. The *Central Fund for Influenza Action (CFIA)* is a multi-donor trust fund created in November 2006 by the United Nations. It enables donors to pool their resources and rapidly provide funding for urgent, unfunded and under-funded priority actions on avian influenza and influenza pandemics. Currently, the total portfolio of CFIA is $40,590,473, which has been donated by Norway, Spain, and the United States. Projects range from targeting communication to travelers, and social mobilization of poultry workers, to developing simulation exercises on preparedness and response, and building the capacity of communities to respond to avian influenza.

The *Global Health Security Initiative (GHSI)* is an international partnership between the Ministers of Health of the United States, the United Kingdom, Japan, France, Germany, Italy, Canada, Mexico, the European Union, and the World Health Organization (WHO), focused on public health emergency preparedness and response. The Initiative was launched in November 2001, as an informal group to address pressing health issues, such as global health security. It was not intended to replace, overlap or duplicate existing fora or networks, but provides an opportunity for scientists and policy-makers to collaborate on biological, chemical, radio-nuclear terrorism and pandemic influenza threats. The GHSI Pandemic Influenza working group, co-chaired by an HHS representative and a representative from the United Kingdom, addresses topics such as pre-pandemic vaccine, antiviral drug use and stockpiling, border management and screening, health care surge capacity, and medical management.

In addition, the U.S. Government participates in the *Security and Prosperity Partnership (SPP)*, a collaboration among Canada, Mexico and the United States. The SPP was launched in March of 2005 as a trilateral effort to increase security and enhance prosperity among the three neighboring North American countries, through greater cooperation and information sharing. One of the Partnership's key health deliverables, the *SPP North American Plan for Avian and Pandemic Influenza*, was released in August of 2007. This is a comprehensive plan that outlines ways in which Canada, Mexico and the United States intend to work together to combat an outbreak of avian influenza or an influenza pandemic in North America. Currently, the three countries are working together to implement the Plan.

In October 2006, the WHO established a program on international development of pandemic influenza vaccines, the *Global Pandemic Action Plan for Influenza Vaccine Supply*.[14] The original supporters of this effort to increase vaccine supply, particularly in developing nations, included the Governments of Japan and the United States, as well as the WHO. In FY 2006-2008, ASPR/BARDA provided significant financial support for the accelerated development and production of an H5N1 vaccine for humans in Vietnam, Thailand, Indonesia, India, Mexico and Brazil. In addition, ASPR/BARDA has also provided subject matter expertise to assist nations to build their influenza vaccine production capacity. The ASPR/BARDA funding addresses global and country-specific needs for training, laboratory equipment, manufacturing process development, development and validation of product release assay methods, clinical sample analysis, manufacturing of clinical investigational lots, scale-up development for vaccine manufacturing, vaccine production equipment, and eventual commercial scale manufacturing of pandemic vaccines. A grant was awarded to Mexico through its laboratory, *Laboratorios de Biológicos y Reactivos de México* (BIRMEX), which is collaborating with technology-transfer partner Sanofi Pasteur to increase in-country vaccine manufacturing capacity.

Finally, throughout all of its activities, the U.S. Government closely adheres to the *Revised International Health Regulations (IHR) (2005)*, an international legal instrument spearheaded by the WHO, binding in 194 countries, which aims to help the international community prevent and respond to acute public health risks that have the potential to cross borders.

Conclusions

A severe influenza pandemic is a catastrophic public health emergency that will have global consequences. The rapid development of effective medical countermeasures, along with collective action and coordinated international preparedness and response efforts, are essential to mitigate the possible consequences of this threat.

HHS, and ASPR in particular, participates in global initiatives, creating partnerships to prepare and respond to pandemic influenza internationally. In addition ASPR, through BARDA, promotes and supports the advanced research and development of countermeasures for influenza. Developing medical countermeasures is an exceedingly complex and resource-intensive endeavor which requires a large commercial market. Investments in new technologies, such as those being made by the U.S. Government, will expand

the global market and result in further improvements of these tools. The use of such countermeasures may save countless lives across the globe.

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