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ISSUE BRIEF

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OCTOBER 2006

PREVENTING EPIDEMICS. PROTECTING PEOPLE.

Pandemic Influenza: THE STATE OF THE SCIENCE

AN ISSUE BRIEF FROM TRUST FOR AMERICA'S HEALTH AND THE INFECTIOUS DISEASES SOCIETY OF AMERICA

PART I: Introduction, Background, and Overview

Most Americans are familiar with seasonal flu, a respiratory illness that strikes annually. Seasonal flu kills approximately 36,000 people in the United States every year and hospitalizes more than 200,000, but experts generally consider it a predictable public health problem, since many people have some form of immunity to it, and a yearly vaccine is available.[1]

Pandemic (from the Greek, meaning "of all of the people") flu, on the other hand, has the potential to pose a serious global health threat. Pandemic influenza typically is a virulent new strain of human flu that causes a global outbreak of serious illness. Because there is little natural immunity, the disease easily can spread from person to person. There have been at least ten recorded flu pandemics during the past 300 years.[2]

Three pandemics occurred during the 20th century.

- **1918-19 Pandemic** or **"Spanish flu"** was the most devastating flu pandemic in recent history, killing more than 500,000 people in the United States, and 20 to 50 million people worldwide, according to some estimates.
- **1957-58 Pandemic** or **"Asian flu"** was first identified in China and caused approximately 68,000 deaths in the United States.
- **1968-69 Pandemic** or **"Hong Kong flu"** caused roughly 34,000 deaths in the United States.

Scientific experts believe that another potentially deadly pandemic is inevitable. The only questions are when it will occur, how severe it will be, and whether the world will be ready for it. Pandemic influenza has received increasing attention in the past few years from scientists, public health officials, and the media. On November 1, 2005, recognizing the seriousness of the pandemic threat, President Bush announced a National Strategy for Pandemic Influenza and requested Congress to allocate $7.1 billion for preparedness efforts. These include expansion of domestic vaccine production capacity, increasing of stockpiles of antiviral medications, improving domestic and international surveillance, and investing in state and local public health preparedness.[3] Congress has responded by providing more than $5 billion to support these activities.

- The federal government's lead infectious diseases research agency, the National Institute for Allergy and Infectious Diseases (NIAID), budgeted $154.9 million in fiscal year 2006 for all influenza (including both seasonal and pandemic flu) research, and an additional $18 million was earmarked from the President's emergency supplemental funding for pandemic influenza.[4]
- Additionally, the U.S. Department of Health and Human Services (HHS) invested more than $1 billion in the research and development of new influenza vaccine technologies and has spent additional funds to purchase antiviral medications for the Strategic National Stockpile (SNS).[5]

This issue brief examines what is known scientifically about influenza viruses that scientists believe could pose a future pandemic threat. It also looks at the development of vaccines, therapeutics, and diagnostics that could be used in the event of a possible pandemic. Finally, it recommends further actions that need to be taken in order to translate the substantial public and private investment in science and research into practice.

A Primer on the Influenza Virus

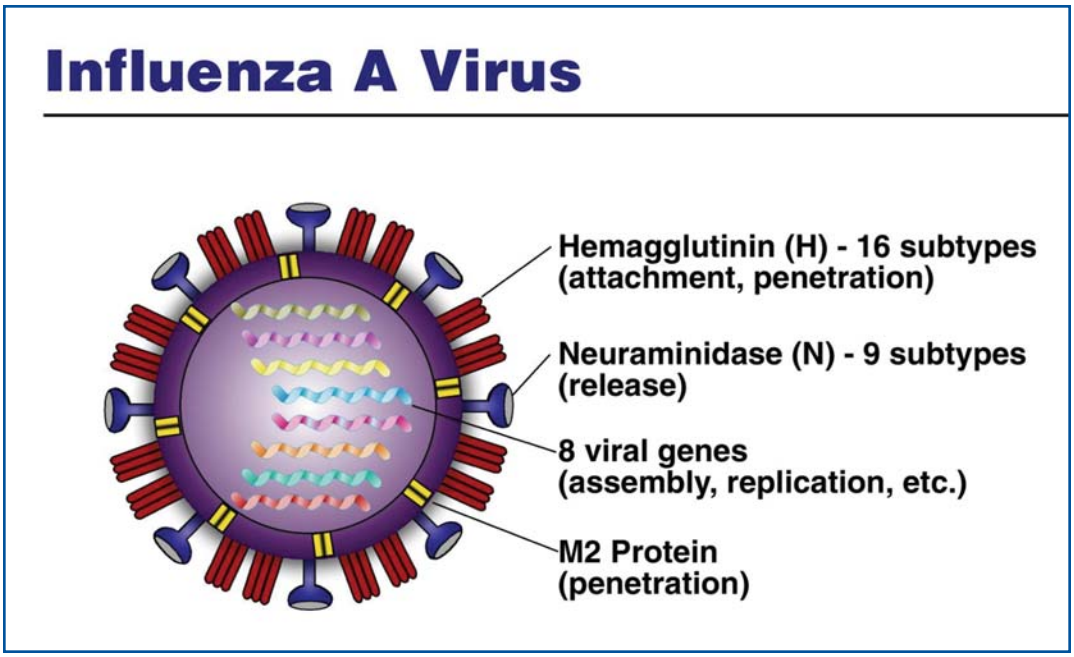
There are three types of influenza viruses, classified as type A, B, or C, based upon their protein composition.

- Type A viruses are found in many kinds of animals, including ducks, chickens, pigs, whales, and also in humans.
- The type B virus widely circulates in humans, but does not cause pandemics.
- Type C has been found in humans, pigs, and dogs, and causes mild respiratory infections, but does not cause epidemics or pandemics.[6]

Type A influenza concerns public health officials the most. Strains of influenza A virus were responsible for the 1918, 1957, and 1968 pandemics. Type A viruses are subdivided into groups based on two surface proteins on the virus, hemagglutinin (HA) and neuraminidase (NA). Scientists have characterized 16 HA subtypes and nine NA subtypes.[7] These are often represented as H1 through H16 and N1 through N9.

HOW DO FLU STRAINS GET THEIR NAMES?

Type A subtypes are classified by a naming system that includes the place the strain was first found, a lab identification number, the year of discovery, and, in parentheses, the type of HA and NA it possesses, for example, A/Hong Kong/156/97 (H5N1). If the virus infects non-humans, the host species is included before the geographical site, as in A/Chicken/Hong Kong/G9/97 (H9N2). The same convention of naming strains also is followed for influenza B and C viruses.



Courtesy of Anthony S. Fauci, MD, Director, National Institute of Allergy and Infectious Diseases

Influenza viruses are constantly changing and evolving. These genetic changes may be small and continuous or large and abrupt. Small continuous changes occur in type A and type B influenza as the virus replicates, that is, makes copies of itself. These types of changes are known as "antigenic drift" and result in new strains of the virus that are not entirely familiar to the human immune system. This is why a new vaccine must be produced annually as a protection against the year's most commonly occurring strains.

Type A influenza also undergoes infrequent and sudden changes called "antigenic shift." Antigenic shift occurs when two different flu strains infect the same cell and exchange genetic material. The novel assortment of HA or NA proteins in a shifted virus creates a new influenza A subtype. Because people have little or no immunity to such a new subtype, its appearance leads to a pandemic if the subtype is efficiently transmitted through the human population in a sustained fashion.[8] The pandemics of 1957 and 1968 were caused by a genetic re-assortment that occurred between human influenza viruses and low pathogenic avian influenza viruses. Scientists who in recent years have investigated the origins of the 1918 pandemic believe that virus might have evolved differently. They think it likely arose from an avian source that, in the absence of a gene re-assortment, underwent a series of mutations that gave it the ability to spread from human-to-human.[9]

Avian Influenza Viruses

Avian (or bird) flu is caused by influenza A viruses that occur naturally among wild birds and can affect a variety of domestic and wild bird species. Infection can range from asymptomatic to severe, depending on the virulence of the virus and the susceptibility of the avian host. Several different avian influenza strains have been shown to infect humans. These include viruses of the H5 subtype (H5N1), the H7 subtype (H7N2, H7N3, H7N7), the H9 subtype (H9N2), and the H10 subtype (H10N7).[10]

The degree to which viruses can cause disease is known as pathogenicity. A virus with a high pathogenicity can make its infected host very ill or even kill; a virus of low pathogenicity typically causes mild or no disease at all.

Global public health authorities are especially worried about a strain of avian flu known as H5N1 that in recent years has been circulating largely in Asia, and has proved especially dangerous to humans who become infected. This strain is lethal to domestic fowl and can be transmitted from birds to humans. There is no human immunity and no vaccine is yet available.

The chief concern is that H5N1 may be undergoing mutations that will make human-to-human transmission efficient and sustained, thus making a pandemic highly likely.

As of September 15, 2006, there were 246 laboratory-confirmed human cases caused by the H5N1 variant and 144 deaths -- a death rate of 58.5 percent.[11]

Global surveillance has not focused much on mild or asymptomatic H5N1 infections. They occur, but it is not known how common they are. If, in fact, epidemiologists determine that mild or asymptomatic infections are widespread, then the current mortality rate is "biased" upward. But if they are not, then the mortality rate for human disease with H5N1 is very high.

There continue to be many unanswered questions about the epidemiology of H5N1 in birds and in people. Research is still evolving with respect to how and why people become infected. For example, more needs to be learned about why some humans exposed to the virus become ill, while others do not.

> "We need to know more about the genetic susceptibility of people. You have to start looking at whether there is a susceptibility that makes some people vulnerable to infection, regardless of the exposure route."
>
> Tim Uyeki, MD, MPH, MPP, Epidemiologist with the Centers for Disease Control and Prevention

The World Health Organization (WHO), which uses a six phase pandemic alert system for determining the seriousness of the threat, sets the current pandemic phase at "phase 3" for H5N1, which means that a new influenza virus subtype is causing disease in humans, but is not yet spreading efficiently and sustainably among humans.

H5N1 first received widespread attention during a 1997 outbreak among poultry in Hong Kong that subsequently spread to humans. There were 18 identified human cases, and six deaths. Most of the human cases were believed to be the result of exposure to infected poultry. Since then, human H5N1 cases have been reported in ten countries: Cambodia, China, Indonesia, Azerbaijan, Djibouti, Thailand, Turkey, Iraq, Egypt, and Vietnam. By mid-September 2006, Vietnam has had the most reported cases, a total of 93, but Indonesia has had the most deaths.[12]

H5N1 is not a single virus, but a family of closely related viruses that differ by minor mutations, but share the H5N1 proteins. Moreover, there are at least two groups, known as clades, of H5N1 viruses that have been identified. They are distinguished by genetic and antigenic differences between the two.

Clade 1 viruses have been seen in Vietnam, Thailand, Cambodia, and Laos. Clade 2 viruses, which are much more widely distributed, have been found in China, Indonesia, and more recently in Eastern and Western Europe, the Middle East, and West Africa. There is no significant difference in mortality between the two clades.

NO SUSTAINED "BIRD FLU" H5N1 HUMAN-TO-HUMAN TRANSMISSION SO FAR

H5N1, like all influenza A viruses, continues to evolve. At this time the virus does not yet have the ability for sustained human-to-human transmission, although there have been some probable instances of limited human-to-human transmission, most of them among close family members.

One such case, for example, occurred in Thailand in 2004. A young girl who lived in a rural village with her aunt likely contracted the virus from infected poultry, became ill, and was hospitalized. The girl's aunt also became ill. The girl's mother, who lived in a Bangkok suburb, visited her hospitalized daughter and spent many hours in prolonged unprotected close contact with her. The mother became infected, developed symptoms, and subsequently died. The mother -- who had never been exposed to poultry -- almost certainly had been infected through contact with her daughter. Although there was never a formal diagnosis of avian influenza in the girl, it was assumed she had it because her close contacts (her aunt and mother) were confirmed to have had the virus.[13]

CLINICAL SYMPTOMS OF H5N1 HUMAN INFECTION

In many patients, the disease caused by the H5N1 virus can be very aggressive and quickly fatal. Like many emerging diseases, H5N1 influenza in humans remains poorly understood. Clinical data from cases in 1997 and the current outbreak are beginning to provide a picture of the clinical features of disease, but much remains to be learned. Moreover, the current picture could change given the nature of influenza A viruses to mutate rapidly and unpredictably.[14]

The incubation period for H5N1 avian influenza may be longer than that for normal seasonal influenza, which is around two to three days. Current data for H5N1 infection indicate an incubation period ranging from two to eight days and possibly as long as 17 days.[15]

The initial symptoms are like seasonal flu, with high fever, cough, and sore throat. Diarrhea, vomiting, abdominal pain, chest pain, and bleeding from the nose and gums also have been reported as early symptoms in some patients. Many patients develop lower respiratory symptoms early in the illness (cough, phlegm, chest pain on deep inhalation). After about five days, patients become quite sick with very severe respiratory disease. A high proportion experience respiratory failure and die.

Unlike seasonal flu strains, which bind to cells in the upper respiratory tract, H5N1 viruses probably bind preferentially to cells of the lower respiratory tract, which may contribute to their current inefficiency in human-to-human transmission. A recent study by Oxford virologist Menno D. de Jong, MD, Ph.D, however, did show heavy concentrations of virus in the throats of some H5N1 victims.[16] The virus could become more dangerous to humans if it develops the ability to infect the upper respiratory tract.

Some experts believe that young adults with healthy immune systems could be especially vulnerable during an H5N1 pandemic. A robust immune response could result in a dangerous overproduction of chemical messengers called cytokines that trigger inflammation. This is often referred to as a "cytokine storm." De Jong's study also showed high levels of fluid produced in the lungs, and high levels of cytokines and chemokines, indicating a dramatic inflammatory response.[17] Autopsies of H5N1 avian flu victims in Vietnam and elsewhere have revealed lungs choked with debris from excessive inflammation. Similar severe lung damage was frequently reported in victims of the 1918 pandemic, which disproportionately killed otherwise healthy young adults.[18]

THE LEGACY OF 1918

In the fall of 2005, using samples obtained from victims buried and preserved in the Alaska permafrost, scientists announced they had successfully reconstructed the influenza strain responsible for the deadly pandemic of 1918, known as the Spanish flu.[19] The goal of the work was to determine the set of genes in the virus that made it so lethal to humans.

The studies of the 1918 strain are helping scientists focus on detecting changes in the evolving H5N1 virus that might make widespread transmission among humans more likely. For example, at the time, the work showed that the H5N1 virus already had acquired five of the 10 gene sequence changes seen in the 1918 virus.

Other Avian Strains

While the biggest threat today appears to be the H5N1 virus, there are other avian influenza viruses circulating that have infected humans through direct contact with poultry. These include:

- **H2N2** which caused the 1957 pandemic. Concerns about H2H2 resurfaced in April 2005, when samples of the virus were mailed to laboratories in test kits used to check the ability of the labs to identify flu viruses. On May 3, 2005, the U.S. Centers for Disease Control and Prevention (CDC) reported that all samples of a potentially dangerous influenza virus that were sent had been accounted for and destroyed.

  First identified in China in late February 1957, the H2N2 virus spread to the United States within a few months. This pandemic of "Asian flu" caused about 70,000 deaths in the United States and over 1 million deaths worldwide. Similar H2N2 viruses continued to cause influenza in the U.S. each year until 1967. Flu shots have not included this type of influenza virus since that time. Nearly 40 years later, very few people are currently immune to H2N2 viruses.[20]

- **H9N2,** a low pathogenic virus in poultry and wild birds that is widely distributed. These strains can infect humans. There have been a small number of human infections, resulting in uncomplicated influenza illness, with no deaths. However, these strains share the same binding affinity as human influenza viruses. The concern is that these viruses could mix with human viruses to form a "reassortant" or hybrid virus. This process of genetic reassortment resulted in the pandemics of 1957 and 1968.

- **H7N7,** a virus highly pathogenic to poultry that can be transmitted to humans. A large outbreak among poultry occurred in the Netherlands in 2003, also resulting in 89 documented human infections and one death.

- **H7N3,** a virus highly pathogenic to birds. There were two human infections documented during a 2004 outbreak in British Columbia. The virus caused mild disease, but no deaths.

- **H7N2,** a low pathogenic virus. There have been two documented human infections in the United States, resulting in mild, uncomplicated influenza.

PART II: Vaccine Progress

Seasonal Flu Vaccine Status

The vaccines on the market today for seasonal flu contain three inactivated influenza viruses -- one A (H3N2) virus, one A (H1N1) virus, and one B virus. They are referred to as trivalent vaccines. The viruses in the vaccine may change each year based on international surveillance and scientists' estimations about which types and strains of viruses will circulate in a given year.

The ability of flu vaccine to protect a person depends on the age and health status of the person getting the vaccine, and the similarity or "match" between the virus strains in the vaccine and those in circulation. There are two types of seasonal vaccine products, those made from killed viruses, typically given with a needle in the arm, and those made from live but attenuated -- or weakened -- viruses administered through a nasal spray. Testing has shown that both the flu shot and the nasal-spray vaccine are effective at preventing the flu.

For its supply of seasonal flu vaccine, the United States is dependent on a handful of flu vaccine manufacturers, some located abroad, and any unexpected problems can disrupt the process, resulting in delays and vaccine shortages. In fact, the CDC reported in September 2005 that influenza vaccine distribution delays or vaccine supply shortages have occurred in the United States in three of the last five influenza seasons.[21] For example, in October 2004, several lots of Chiron's flu vaccine, produced in Liverpool, England were found to be contaminated, leading to suspension of Chiron's manufacturing license by Britain's Medicines and Healthcare Products Regulatory Agency. Subsequently, shipment of Chiron's 48 million doses of flu vaccine to the United States was halted by the U.S. Food and Drug Administration (FDA), which left public health departments scrambling to make up the shortfall.[22]

For the 2006-2007 flu season, the CDC expects manufacturers to produce and distribute more seasonal influenza vaccine than ever before in the United States. Thanks in part to the reentry of another flu vaccine manufacturer, GlaxoSmithKline, into the U.S. market, the agency estimates that there will be 100 million doses of flu vaccine available by January 2007 -- at least 17 million more doses than the previous high of 83.1 million in 2003 and 19 million more than were distributed during the 2005-2006 flu season.[23]

Influenza vaccines were first developed in the 1940s and consisted of partially purified preparations of killed (inactivated) influenza viruses grown in fertilized eggs. Because of substantial contamination by egg-derived components, these vaccines had undesirable side effects, such as high fever, and were not very effective. In the late 1960s, new technology improved purification, and the process remains the basis for the production of inactivated influenza vaccines today.[24]

The current egg-based technology requires about six months to produce an adequate supply of vaccine; the United States has a production capacity of about 60 million doses.[25] The remaining 40 million doses of this year's expected supply of 100 million doses will come from outside the United States.

Pandemic Vaccine Production

Overall, the world's current vaccine production capacity is limited. Today, manufacturers can produce a total of 300 million doses of the annual trivalent vaccine to combat seasonal flu. In theory, having to produce a single-strain or monovalent pandemic vaccine, rather than a three-strain product, might enhance production -- as many as 900 million doses could be produced. However, in practice, pandemic vaccine production faces two challenges: first, two doses would almost certainly be required to compensate for the lack of existing immunity within the world population (thus a production capacity of 900 million doses would only serve 450 million people), and second, at least based on current trials of pandemic vaccines, much higher concentrations of antigen might be needed to achieve an immune response, further limiting the number of people who can be vaccinated.[26]

To address the latter challenge, if the global supply of pandemic vaccines is to be adequate, its formulation must be "antigen-sparing," that is, each dose must contain a much smaller amount of HA antigen (the part of the virus that provokes an immune response). An "adjuvant" will almost certainly be necessary.[27]

An adjuvant is a substance that is added to a vaccine to improve the strength of the immune response; the use of an adjuvant could extend vaccine supply in order to treat more people. Such research into dose-sparing techniques is important because of the anticipated limited supplies of vaccines. Adjuvants, however, are known to produce side effects, including pain at the injection site. Research is now underway on candidate H5N1 vaccines using adjuvants, which include aluminum hydroxide, or alum, and MF59, an oil in water emulsion. MF59, developed by the Chiron Corporation, is said to produce fewer side effects than its aluminum salts counterpart and is the only adjuvant licensed for human use in combination with influenza vaccine in Europe.

GlaxoSmithKline, in testing its own candidate H5N1 vaccine, recently announced that its adjuvant produced a high immune response at a low dose of antigen. The vaccine, which uses a "proprietary" adjuvant -- that is, the details about it are a company secret -- produced a strong immune response in more than 80 percent of subjects.[28]

Even with the use of an adjuvant, however, it is important to remember that current production technologies can take up to six months to produce the seasonal vaccine supply. Therefore, it is doubtful at this time that enough H5N1 vaccine can be produced to meet global needs during the first wave of a pandemic.[29]

> "One of the big messages is that our current vaccine manufacturing capacity and infrastructure is not good. Our seasonal production is so fragile. This would multiply that much more in a pandemic. If we can't improve that infrastructure right now, it just won't be there for a pandemic when we need it."
>
> Scott Harper, MD, Centers for Disease Control and Prevention and New York City Department of Health, and Chair of the Infectious Diseases Society of America's Influenza Guidelines Panel

H5N1 and Other Avian Viruses' Vaccine Status

Several clinical trials currently underway in the United States and abroad are looking into potential H5N1 vaccines. In the United States, a trial sponsored by NIAID demonstrated that all doses of an experimental H5N1 vaccine induced immune responses in healthy adults, with the highest doses generating the largest responses. The vaccine, made from a killed H5N1 virus isolated in Southeast Asia in 2004 [A/Vietnam/1203/2004] was manufactured by sanofi pasteur,[30] of Swiftwater, Pennsylvania, under contract to NIAID. Because there are no manufacturers licensed in the United States to use adjuvants in inactivated influenza vaccines, NIAID's first step was to test an H5N1 influenza vaccine made in a way that mimics the process used to make conventional flu vaccines. The vaccine did work, but was poorly immunogenic; it required two doses, one month apart, of 90 mcg to get an immune response in 60-70 percent of subjects. This compares with the typical dose of 15 mcg that is needed to induce an immunogenic response in seasonal flu vaccine.[31]

NIAID-sponsored trials are now studying the vaccine using an adjuvant. They also are studying the immune response of the vaccine using different routes of administration (injection into muscle compared to injection under the skin), as well as dosing and safety in the elderly and in children.

This experimental vaccine is based on a clade 1 H5N1 strain; experts believe that vaccines also are needed against clade 2 H5N1 viruses -- or, better yet, a bivalent product that would offer cross-protection against both clades. Scientists at CDC and St. Jude's Children's Research Hospital have developed clade 2 viruses that are available for use in vaccine manufacturing. One aspect that NIH hopes to investigate in the future is testing the immune response after priming with clade 1 vaccine followed by subsequently boosting at a later date with clade 2 vaccine.

An NIAID-sponsored study of a live, but weakened, H5N1 nasal spray vaccine (based on the same strain) also is underway. The candidate vaccine was developed in a collaborative research effort by scientists at NIAID and scientists at MedImmune, Inc., of Gaithersburg, Maryland. It is currently in the earliest stages of clinical testing. Human data are not yet available but the vaccine protected mice and ferrets challenged with virulent H5N1.[32]

Another NIAID-sponsored study on the clade 1 H5N1 strain using both aluminum and MF95 as adjuvant also is underway. In this trial, doses as low as 1/6 of the seasonal flu antigen content are used. The candidate vaccine was manufactured by Novartis in its Liverpool facility under contract to NIAID. Initial results are expected in October 2006.

Furthermore, NIAID is sponsoring research into two candidate H9N2 vaccines. The first study uses an inactivated H9N2 strain with and without the MF59 adjuvant. In October 2005, researchers reported that all of the vaccine formulations containing MF59 were highly immunogenic, inducing antibody levels believed to provide protection. In comparison, doses without the adjuvant produced significantly lower antibody levels, and did not approach those containing MF59.[33] A second study, using a live attenuated H9N2 strain, is currently undergoing early clinical trials for safety, infectivity, and immunogenicity.[34]

NIAID also is funding research trying to develop at least one experimental live attenuated vaccine for each of the 16 HA strains and is supporting work using "reverse genetics" and classical re-assortment techniques to place HA genes from each subtype of influenza into live attenuated human influenza viruses to create live attenuated pandemic vaccine candidates.[35] Once generated, these vaccines could be scaled up and used to "pre-prime" individuals in an emergency situation while a more specific pandemic vaccine is being developed.[36]

> "Live attenuated influenza vaccines have several potential advantages. They induce both antibody and cellular immune responses at the local mucosal level and humorally, and they usually do not require a booster dose. Also, they may offer a wider breadth of cross-protection against different but related influenza viruses."
>
> Anthony S. Fauci, MD, Director, National Institute of Allergy and Infectious Diseases, in a 2005 interview with *Microbe Magazine*, a publication of the American Society for Microbiology.

Other companies outside of the United States are studying experimental H5N1 vaccines, as well as candidates against other avian viruses, including H9N2 and H5N3.[37]

Most of the trials underway currently involve vaccines made from "split" or subunit parts of the virus. A few other studies have begun to use whole-virus vaccines. Whole virus vaccines typically provoke a stronger immune response among those who have not been "primed" with an earlier dose of the vaccine. The splitting process contributes to inactivating the virus, however, which is why many manufacturers prefer it -- although viruses can be inactivated without splitting. [38]

Recently, Chinese scientists reported encouraging news from their study of a candidate whole-virus H5N1 vaccine made with an alum adjuvant. They demonstrated that using a whole virus with an adjuvant worked better at prompting an immune response and as a "dose-sparing" approach -- meaning less virus antigen is needed -- than previous experiments using split virus vaccines combined with adjuvants. It is important to note that this study did not compare adjuvanted vaccine to non-adjuvanted vaccine; it only tested different doses of adjuvanted vaccine compared to placebo.[39] The vaccine is made by Sinovac Biotech Ltd., a Beijing-based manufacturer.

Alternatives to Egg-based Technology for Vaccines

Many experts believe that the old egg production methods are time-consuming and inefficient. One new approach, cell-based vaccine production, uses mammalian cells (kidney cells are often used) to grow influenza viruses. Cell-based vaccine production has the potential to meet "surge capacity needs" because cells could be frozen and stored in advance of an epidemic or developed rapidly in response to an epidemic.[40]

Cell-based vaccine production may reduce the possibility of contamination. In place of eggs, cell-based vaccine production uses laboratory-grown cell lines that serve as "host" cells for a growing virus. The virus is injected into the cells where it multiplies. The cells' outer walls are removed, harvested, purified, and inactivated. Several vaccines, including those for polio, rotavirus, and varicella (chickenpox) are produced using the cell-based method.

One U.S. company, Baxter International, of Deerfield, Illinois, is conducting a clinical trial testing a killed H5N1 candidate vaccine produced using its vero-cell based technology. The study, using killed A/Vietnam/1203/2004, is underway in Austria and Singapore among several hundred healthy adults. Four different antigen concentrations are being tested in formulations with and without an alum adjuvant. NIAID is planning to initiate a similar trial with the same vaccine in the U.S. in the next several months.

Another company, the Swiss-based drug manufacturer Novartis, announced this summer that it plans to build what is believed to be the first U.S.-based plant to manufacture

cell-based vaccines. The facility will be built in Holly Springs, North Carolina, at a total cost of about $600 million. The company expects the plant to be able to produce about 50 million doses of seasonal trivalent flu vaccine annually. The plant is not expected to begin production until 2012.[41]

Genetic/DNA immunization is another new approach under study. DNA vaccine technology uses genes for the viral antigens – rather than the actual antigens themselves – to produce an immune response. The genes, composed of DNA, are directly injected into the skin. One British-owned company, PowderMed, has developed an experimental H5N1 DNA vaccine that is delivered without needles. Gold particles coated in the vaccine DNA are fired into the skin using helium. The DNA is translated into protein in the skin's immune system cells, prompting an immune response. The vaccine has not yet been tested in humans (although many other DNA vaccines have been) and the company has applied for permission to begin clinical trials in London.[42]

A Universal Flu Vaccine?

Scientists have long dreamed of designing a one-size-fits-all influenza vaccine that could protect against any and all strains of influenza virus, and convey lifelong protection. Such a product is a long way off, if it is possible at all. Nevertheless, researchers are searching for less variable parts of the influenza virus with the idea of using them to create broad-scale, longer lasting vaccines. NIAID is supporting a number of such universal vaccine development programs, including all of the ones discussed below, through its biodefense initiatives.

One stable element of the influenza virus is a coat protein called M2. At the Wistar Institute in Philadelphia, Pennsylvania, Walter Gerhard, MD, is using mice to test candidate vaccines containing many bioengineered versions of M2. He is studying how long the immunity provided by these vaccines lasts and whether the virus can find a way of evading these vaccines by developing mutations in their M2 proteins.[43] The Flanders Interuniversity Institute for Biotechnology, also studying the potential of M2, has teamed with vaccine company Acambis, of Cambridge, Massachusetts, to develop a universal vaccine candidate that would protect against both A and B strains. The vaccine has not yet been tested in humans.[44]

Gary Van Nest, PhD, a researcher at the biotechnology company Dynavax, has developed a vaccine candidate that combines an internal influenza protein that is less likely to be altered through mutation, NP, with a bioengineered molecule called an immunostimulatory DNA sequence, or ISS. He is testing the NP-ISS vaccine in mice that either have or have not previously been infected with influenza virus. He will examine whether the combination vaccine stimulates certain immune system cells that can fend off different influenza A strains. He hopes that some of the immune cells stimulated by the vaccine will become "memory" cells that can recognize influenza virus every year. Memory cells against an antigen that is less likely to change through mutation, such as NP, may provide broader protection against the flu than memory cells against an antigen that undergoes numerous changes, such as HA.[45]

Other investigators are working on yet another approach, trying to make HA-specific vaccines that protect against drift strains within the same HA family.[46]

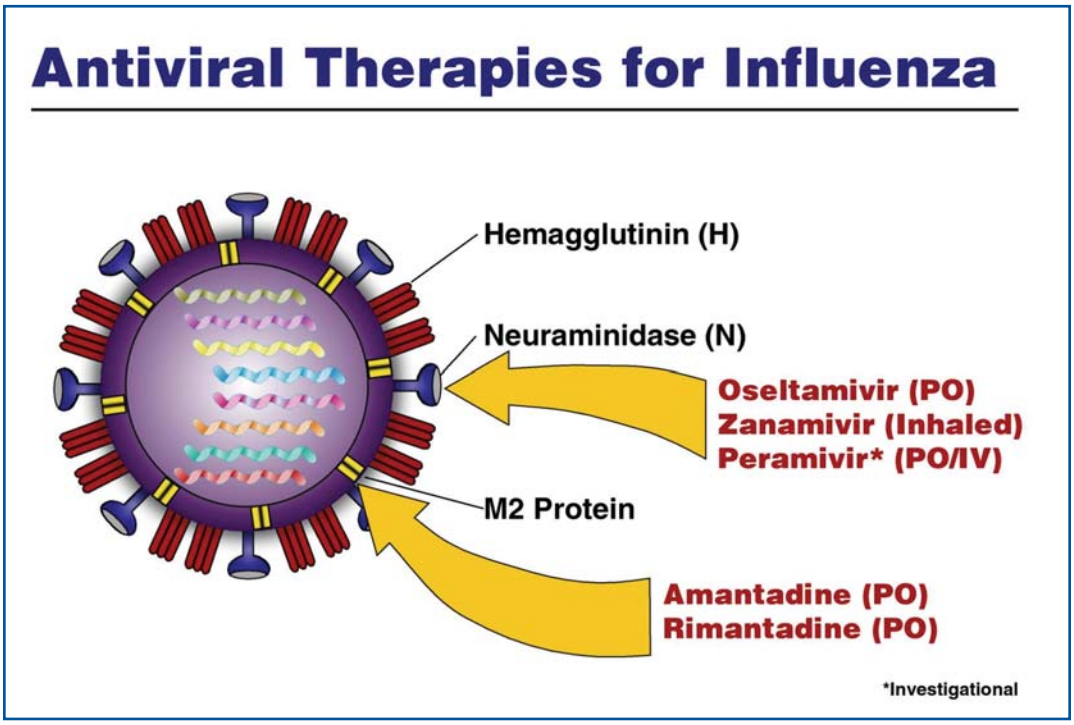
There are at least a half-dozen universal flu vaccine designs under development by companies and/or research institutes at this time, but none is considered a viable candidate for use if a pandemic occurred in the near future.[47]

PART III: Antiviral Drugs and Immunotherapeutics: Preventing and Treating the Flu

Drugs for Seasonal Flu

Currently, there are four drugs available to prevent and/or treat seasonal influenza. These are amantadine, rimantadine, zanamivir, and oseltamivir. The FDA has approved all of them to treat seasonal flu.

The first two drugs work by inhibiting the activity of the influenza virus M2 protein, making it impossible for the virus to make copies of itself once it enters a cell. These drugs are effective only against type A influenza. However, due to high levels of resistance, CDC currently recommends against the use of amantadine and rimantadine.[48] Resistance means that the virus has mutated (changed) in a way that makes a drug ineffective or less effective against it.



Courtesy of Anthony S. Fauci, MD, Director, National Institute of Allergy and Infectious Diseases

The second two drugs represent the first of a newer class of antiviral drugs known as neuraminidase inhibitors (NAIs). The surfaces of influenza viruses are sprinkled with neuraminidase proteins. Neuraminidase breaks the bonds that hold new virus particles to the outside of an infected cell; once these bonds are broken, new viruses are set free to infect other cells and spread the infection. These drugs stop the activity of neuraminidase, thus limiting the spread of infection. They are effective against both types of influenza, A and B.[49]

There are two neuraminidase inhibitors on the market that treat seasonal flu. They are oseltamivir, commonly known at Tamiflu, and zanamivir, commonly known as Relenza. Tamiflu is indicated for treatment and prevention of patients one year and older. Relenza is indicated for ages seven and older for treatment and five and older for prophylaxis (prevention). Tamiflu is taken orally as a capsule or as a liquid suspension which is important for use in children or adults who have difficulty in swallowing. Relenza comes in a dry powder and is inhaled using a device known as a "DISKHALER." Both can be prescribed for treatment or prophylaxis of seasonal influenza.

The drugs reduce the duration of flu symptoms by an average of one to one-and-one half days if taken within the first 48 hours after ill-

ness begins. As a preventive, zanamivir and oseltamivir also can significantly reduce the chances of getting the flu during a flu outbreak in a family or community. While this class of antivirals primarily has been studied in healthy populations where complications are rare, there are data from clinical trial results that show that NAIs decrease complications from pneumonia and resulting hospitalizations.

For persons (1) who live or work in institutions caring for persons at high risk for serious complications from influenza infection in the event of an institutional outbreak, and (2) at high risk for serious influenza complications if they are likely to be exposed to others infected with influenza, CDC recommends that NAIs be used as prophylaxis according to the following guidelines:[50]

- When outbreaks occur in institutions, prophylaxis should be administered to all residents, regardless of whether they received influenza vaccinations during the previous fall, and should continue for a minimum of two weeks.
- In addition to nursing homes, prophylaxis also can be considered for controlling influenza outbreaks in other closed or semi-closed settings (e.g., dormitories or other settings in which persons live in close proximity).
- Prophylactic use of antiviral agents is an option for preventing influenza among persons known to have anaphylactic hypersensitivity to eggs or to other components of the influenza vaccine.

Drugs for Pandemic Flu

Because vaccines are expected to be unavailable or in short supply during the first wave of an influenza pandemic, antiviral drugs and other therapeutics might be the only initial defense against illness. Antibiotics, which are effective only against bacteria, do not work against the viruses that cause influenza, although they could be useful against secondary bacterial infections that often can occur with flu.

The history of pandemic disease has shown us that many deaths are not due to the virus itself, but to bacterial pneumonia. It has been estimated that a large proportion of deaths in the three pandemics that occurred in the 20th century were due to bacterial complications of influenza. Increasing bacterial resistance to antibiotics, the significant reduction in available new antibiotics, and the reduced manufacturing capacity of existing antibiotics raises questions about the ability to deal effectively with secondary infections caused by pneumonia or other bacterial infections during an influenza pandemic. Among resistant bacteria that can cause pneumonia after influenza, methicillin-resistant *Staphylococcus aureus* is of particular concern.

Experts are interested in knowing more about the impact of existing influenza drugs on avian influenza viruses, especially against H5N1.

Some H5N1 viruses are reported to be resistant to amantadine and its sister drug rimantadine. Resistance of H5N1 viruses to these antiviral drugs means that they may not help by themselves in treating infected humans in the event of a pandemic. NIAID is sponsoring at least one study to see whether using amantadine and rimantadine in combination with oseltamivir and/or zanamivir could help reduce or prevent the emergence of drug-resistant strains.

Neuraminidase inhibitors have been shown effective against H5N1 in the laboratory, but until recently, no formal clinical trials have been conducted to evaluate how they might work in humans infected with the virus.

The Southeast Asia Influenza Clinical Research Network, led by NIAID, in collaboration with WHO and others, plans to begin a clinical trial in late 2006 of standard-dose and two-fold higher-dose Tamiflu among hospitalized children and adults in Thailand, Vietnam, and Indonesia. Researchers will be studying its impact on both seasonal severe flu and avian flu if they occur.

Some researchers suspect -- although there are not yet studies to prove it -- that humans infected with severe avian flu might require longer and/or higher doses of Tamiflu, which could raise serious concerns about whether there will be enough Tamiflu in the event of a pandemic.

Researchers, aware of the Tamiflu supply problem, are looking for new ways to "stretch" the drug. Lawrence Deyton, MSPH, MD, Chief of the Public Health and Environmental Hazards Office at the Department of Veterans Affairs (VA), working with a team of VA scientists in collaboration with the National Institutes of Health and the Department of Defense, is conducting a small study to see what happens when Tamiflu and the drug Probenecid are taken together. Probenecid often slows down the body's excretion of other drugs. If it can do this when taken with Tamiflu, it means Tamiflu will remain in the bloodstream longer, likely prolonging its impact -- or, put another way, less Tamiflu could be needed to achieve the same therapeutic effects. This could prove especially valuable if Tamiflu is needed for prophylaxis, for example, among front-line health care workers who might have to take the drug for longer periods of time to prevent the onset of disease.

Both Tamiflu and Relenza have been effective in preventing or disrupting seasonal flu outbreaks among family members and in nursing homes. There is little clinical data regarding their impact against H5N1, although, typically, if a drug works for treatment it usually works for prophylaxis. Even if it works as a preventive measure, most public health experts believe the current supply situation makes it unlikely that Tamiflu will routinely be used for prophylaxis during a pandemic.

> "THE KEY ISSUE IS THAT WE DON'T HAVE ENOUGH [TAMIFLU] FOR PROPHYLAXIS."
>
> Andrew T. Pavia, MD, University of Utah Medical Center, Division of Pediatric Infectious Diseases, and Chair, National and Global Public Health Committee, Infectious Diseases Society of America

Some experts have suggested that statins could have an important role in treatment and prophylaxis of pandemic influenza, particularly in reducing inflammation ("cytokine storm") that occurs with human H5N1 illness, and had been seen in lethal pandemics in the past. Statins are a class of drugs that lowers the level of cholesterol in the blood by reducing the production of cholesterol by the liver. Statins, which are plentiful, in part because they are safe, and low-cost, and available generically, have anti-inflammatory effects, and can help modify or adjust human immune system processes, such as cytokine dysfunction. There already exists literature that points to a decrease in mortality in patients with pneumonia who are being treated with statins.[51]

David Fedson, MD, former Director of Medical Affairs in Europe for the French pharmaceutical company Aventis Pasteur MSD, now sanofi pasteur, has called for an evaluation of administrative databases to search for reduced rates of hospitalization and death due to influenza-related conditions among people taking statins; this would be followed by laboratory studies of statins in animals and cell-based models of influenza infection, and, later, by clinical trials.[52]

De Jong's research also suggests that immediate antiviral treatment is critical with avian influenza -- to curb viral replication -- and should be supplemented with anti-inflammatory drugs to suppress a potentially dangerous immune response.[53]

> "WHEN THE NEXT PANDEMIC ARRIVES, PHYSICIANS WHO LIVE IN COUNTRIES WITHOUT ANTI-VIRAL STOCKPILES OR VACCINE COMPANIES WILL HAVE LITTLE OR NOTHING TO OFFER THEIR PATIENTS."
>
> David Fedson, MD, writing in Clinical Infectious Diseases, June, 2006

New Drugs

Several next-generation neuraminidase inhibitors are in various stages of development, although none would likely be available if a flu pandemic were to occur in the near future.

NIAID has provided funding for studies into at least two next-generation neuraminidase inhibitors. Biota, of Melbourne, Australia, has developed a long-acting inhaled product, which would be administered only once a week, compared to Relenza, which is inhaled twice daily, and Tamiflu, which is taken once daily. Clinical trials are planned for late 2006. This type of product would not only be easier to administer, but also could help reduce the storage bulk needed for possible pandemic drugs stockpiling.

BioCryst, of Birmingham, Alabama, is studying its own neuraminidase inhibitor, known as peramivir, also with support from NIAID. Preliminary studies indicate that the efficacy of a single injection into the muscle is comparable to five days of treatment with other existing agents. The drug also can be administered intravenously. Lab studies indicate that avian flu viruses are sensitive to peramivir.[54] Preliminary data from animal studies (in ferrets) show that peramivir protected the animals against a lethal challenge with at least one strain of H5N1.[55] Studies in mice are underway to compare intravenous with intramuscular delivery, and human safety studies are planned using both methods.[56]

There is additional government research ongoing into new influenza drugs, both for seasonal use and in the event of a pandemic. Some of these include:

- RNA interference (RNAi), a cellular phenomenon that scientists are just now starting to understand. Researchers at the Massachusetts Institute of Technology are exploring the possibility of using RNAi to prevent the flu virus from making copies of itself once inside a host cell. RNAi can selectively inhibit gene activity in cells; essentially, the technique allows researchers to "turn off" individual genes. It has worked in laboratory-grown cells, and in mice, the approach has both prevented and treated influenza infection, including infection from avian H5N1 and H7N7 strains. Scientists hope the research could point the way to new therapeutic or preventive drugs for flu. Moreover, it might be possible to create a "cocktail" targeting different influenza virus genes that could prevent the emergence of resistant virus strains.[57]
- Fusion proteins. These would disable receptors located on cells in the airway passages to render them inaccessible by flu virus particles, meaning the flu virus could not enter and infect human cells. Scientists at NexBio in San Diego have developed an experimental drug called Fludase that -- as an inhalant -- can be applied to the upper airway surface for both prevention and treatment of flu viral infections. Whereas most inhalants are systemic drugs that enter the bloodstream and travel throughout the body, Fludase sticks onto the surfaces of the respiratory tract, allowing the drug to function only in the desired areas. NexBio has completed animal studies and hopes to begin clinical studies in late 2006.[58]
- RNA polymerase inhibitors. Polymerase is an enzyme necessary for viral replication. In order for a virus to replicate, or make copies of itself, the virus requires a polymerase capable of recognizing the viral genome as a "template," and copying it. The experimental drug, T-705, is in preclinical development, meaning it has not yet been studied in humans.[59]

PART IV: Diagnostics

Background

Until recently, it was difficult to diagnose flu quickly and accurately. The way most outbreaks are recognized is when an astute front-line clinician notices that something strange is occurring and alerts public health authorities. More recently, epidemiologists have relied initially -- before diagnosis -- on a process known as "syndromic" surveillance to recognize the beginnings of an outbreak. This involves recognizing known health data -- a specific set of symptoms, for example -- as a harbinger. Syndromic surveillance sometimes has proved problematic in the case of influenza, where the early symptoms can resemble other illnesses.

There are rapid tests that can identify influenza A, but not the specific strain. Physicians' offices, emergency rooms, and health clinics -- especially those located in rural and isolated geographic settings -- typically are not close enough to the sophisticated lab equipment needed to perform such diagnostics as a viral culture, polymerase chain reaction (PCR), rapid antigen testing, or immunofluorescence, which are various tests that are used to identify specific flu strains. Also, the sensitivity and specificity of laboratory tests may vary by strain. Until recently, it could take days, or even weeks, between a throat or a nasal swab and a final reading. Moreover, only the CDC and a few other labs internationally have had the high-level biosafety facilities needed to perform specialized tests that reveal critical details about a virus's genetic origin and other features.

PCR Technology

Last February, however, the FDA licensed a new laboratory test that uses PCR technology -- a process that amplifies DNA sequences -- and can detect H5 strains of influenza within four hours after arriving at a laboratory. The test is called the Influenza A/H5 (Asian lineage) Virus Real-time RT-PCR Primer and Probe Set. The test provides preliminary results on suspected H5 influenza samples within four hours once a sample arrives at the lab and testing begins. Previous testing technology would require at least two to three days for results. If the presence of the H5 strain is identified, then further testing is conducted to identify the specific H5 subtype (e.g., H5N1). The use of this test is limited to laboratories designated by the Laboratory Response Network, which consists of about 140 labs in the United States.[60]

New Microchip Test

The influenza diagnostics field has been moving rapidly. Recently, NIAID announced that scientists from the University of Colorado at Boulder and the CDC have developed a microchip-based test that may allow more labs to diagnose influenza infections and learn more about the viruses causing illness. The so-called "FluChip" successfully distinguished from among 72 influenza strains -- including the H5N1 avian influenza strain -- in 11 hours.[61 62]

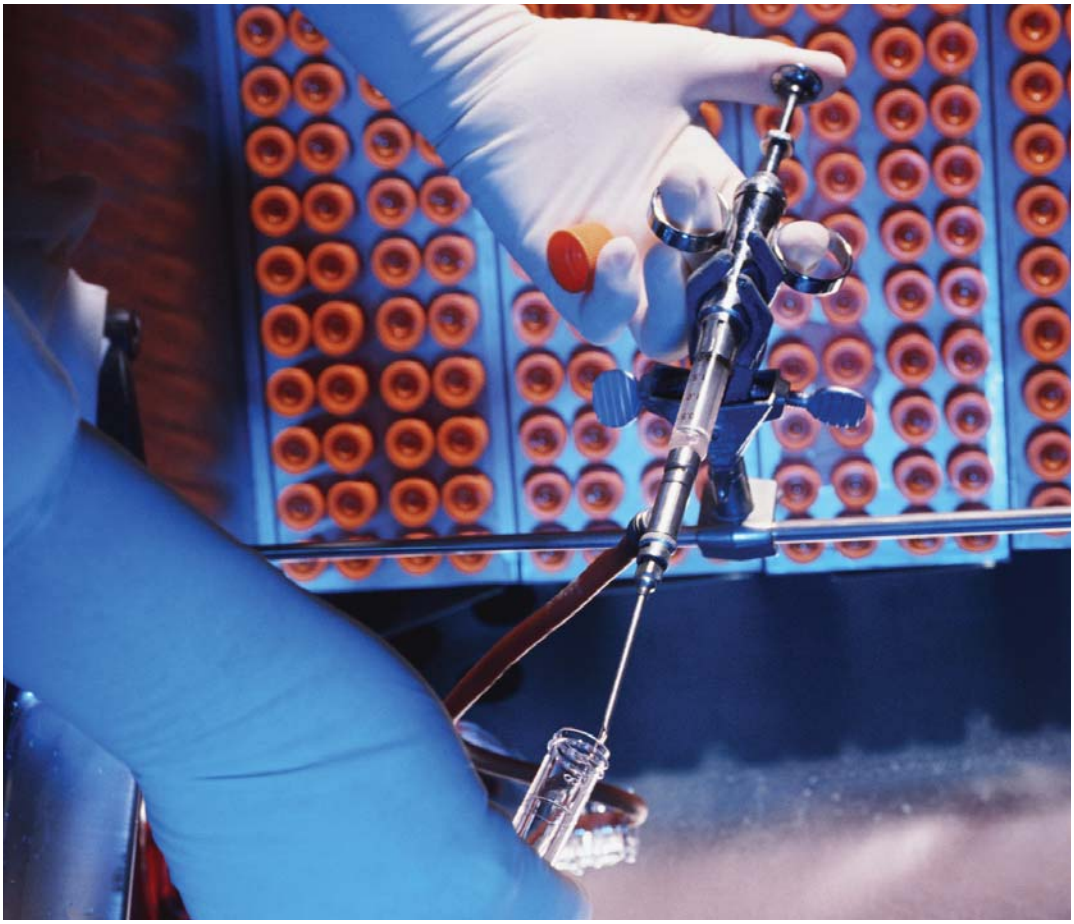
The FluChip is a type of microarray, commonly called a gene chip. Although there are numerous variations, microarrays can be made by using a robotic arm to drop hundreds or thousands of spots of genetic material -- DNA or RNA -- of known sequence onto a microscope slide. The spots, called probes, are then exposed to a sample of unknown composition: for instance, material taken from a person with an undiagnosed illness. Probes that match gene sequences of bacteria or viruses present in the sample result in capture of the target gene. By analyzing the pattern of captured targets, researchers can diagnose the cause of infection.[63]

Beginning with a pool of nearly 5,000 influenza gene sequences, the University of

Colorado investigators used the data mining process to select 55 influenza RNA sequences for use as probes on the FluChip. Among them were probes chosen to enable detection of two of the most common influenza strains currently circulating in humans, the H1N1 and H3N2 strains, as well as the avian influenza strain H5N1. Full information on type -- but only partial information on subtype -- was obtained for 13 percent of the samples. It took about 11 hours to conduct the tests and learn the identities of the strains.

This technology can be used by lower level bio-safety facilities, which could expand influenza diagnostic capacity by allowing more laboratories to determine whether its source is human or nonhuman. It also can help pinpoint how closely related a new virus is to ones that have circulated previously, and could tell scientists what genetic changes are underway that may signal that the virus is becoming more virulent. Experts point out, however, that developing improved gene chips for diagnosis depends, in part, on the immediate public availability of genomic sequence data.[64]

The work is not regarded as a major diagnostic breakthrough, however, but an important incremental step. Experts believe more tools are needed, specifically technology that could rapidly diagnose pandemic influenza strains on the spot; that is, at the point of care where patients are first seen and treated after they become ill. These would include rural clinics and health care centers and hospital emergency rooms, among other sites. Because the test now requires 11 hours, the FluChip will most likely be used as a surveillance tool, rather than a point-of-care diagnostic.



PART V: Translating Research into Practice -- Policy Recommendations

Over the last year, federal policy makers have paid considerable attention to pandemic influenza preparedness. The November 2005 National Strategy for Pandemic Influenza issued by the President outlined the responsibilities that individuals, the private sector, state and local governments, and the federal government should undertake to prepare for and respond to a pandemic. Concurrently, President Bush requested $7.1 billion to implement the strategies outlined in the document. The following day, the U.S. Department of Health and Human Services issued its revised Pandemic Influenza Plan. On May 3, 2006, the White House Homeland Security Council issued the National Strategy on Pandemic Influenza Implementation Plan, which outlines specific tasks and timelines for government-wide pandemic preparedness planning and a commensurate response. To date, the U.S. Congress has provided $5.6 billion to accomplish the tasks outlined in these documents.

While Trust for America's Health (TFAH) and the Infectious Diseases Society of America (IDSA) have individually issued recommendations and policy statements on a variety of pandemic influenza issues, including state and local public health preparedness and response, public education and communications strategies, community mitigation strategies (isolation, social distancing, quarantine), biosurveillance, medical surge and the public health workforce, the following policy recommendations are limited to matters discussed in this issue brief. They focus primarily on how to translate the substantial public and private investment in science and research into practice.

To better prepare the United States to respond to future interpandemic and pandemic influenza events, TFAH and IDSA recommend that the federal government support and/or adopt the following recommendations. These recommendations reflect the views of TFAH and IDSA and do not necessarily reflect the views of those individuals interviewed for this paper or those who served as peer-reviewers.

VACCINES

The widespread use of a pandemic vaccine should be the central strategy for the protection of human health. We must modernize our approach to vaccine production and delivery, and we must recognize that the Unites States has a responsibility to help assure that all people of the world have access to pandemic vaccines. This is both a moral responsibility and a practical one; in a highly interdependent society, mitigating the impact of a pandemic requires that all corners of the globe are protected equally.

Pandemic Vaccine Research and Development Master Program

An effective U.S. vaccine research and development (R&D) strategic program must be much larger in scale than current funding permits, in addition to being multinational in scope. Current U.S. and international pandemic vaccine R&D efforts are a patchwork, which while broad in focus, may not produce rapid progress. The U.S. must lead the international effort to develop the formulation of pre-pandemic vaccines and to prepare for the development, production, and distribution of a global supply of suitable pandemic vaccines. As part of this effort, the U.S. must coordinate activities in both the public and private sectors. To effectively harness the scientific expertise potentially available to this effort, the program must be open and transparent to ensure that government experts, industry and academics from around the world have access to vital information.

TFAH and IDSA propose the **"Pandemic Vaccine Research and Development Master**

Program" -- to systematize and greatly enhance the current U.S. and international vaccine R&D strategies. The program should provide a comprehensive approach to vaccine development, production, and delivery, utilizing new vaccine science and delivery approaches. The program should identify all relevant issues that must be explored (e.g., pathogenesis of disease, strain(s), formulation, antigen, adjuvant, dose, and route). It should identify activities currently in progress targeting each issue as well as those activities that are proposed, and should clearly delineate: which sectors (government, industry, academic, others) are responsible for completion of the activities; funding requirements for each activity; and benchmarks against which Congress and the public can measure progress. There should be regular and frequent (short cycle - every six to 12 months) review and reporting on progress toward those benchmarks, including obstacles encountered that require revision of the research and development program. A substantial increase in funding will be required to match the scale and critical importance of this effort.

Additional Vaccine Policy Recommendations

Also related to vaccine policy, TFAH and IDSA recommend that:

- The CDC implement a nation-wide, real-time tracking system to maintain and strengthen surveillance to assess vaccine efficacy; distribution and re-distribution, if required; uptake; and impact. This will make most efficient our use of what may be a scarce supply of vaccine.
- The U.S. expand and strengthen the working relationships with other countries, particularly within Southeast Asia, through the World Health Organization and bilaterally, in order to strengthen surveillance for a novel influenza virus. This will enable us to begin production of a pandemic vaccine sooner and possibly intervene with other preventive measures.
- The U.S. adopt policies to increase inter-pandemic influenza vaccinations, so as to reduce the morbidity and mortality of annual influenza and to help stabilize vaccine manufacturing capacity. This includes:
  - Increasing annual influenza vaccination rates among health care workers with direct patient care contact at hospitals, clinics, and other health care facilities. Licensing and accreditation agencies should track vaccination rates. Vaccinations should be paid for by the employees' health insurance or employers. This would improve patient safety and prevent many needless deaths due to transmission from infected health care workers to vulnerable patients.
  - Developing detailed national standardized templates for conducting mass vaccinations and countermeasure distribution. The templates should be based on supporting evidence and should be vetted, refined, and publicized. State and local governments should adapt the templates and implement and test them during annual flu seasons. The federal government should provide resources for proper deployment of these templates and states should be required to communicate the results of their tests.
  - Encouraging state and local health departments to use federal pandemic preparedness funds to purchase annual flu vaccine in order to test mass vaccination protocols.
- The FDA continue to streamline the licensure process for pandemic influenza vaccines, thereby accelerating the availability of vaccine for the public good. Specifically, pandemic vaccine should be evaluated differently than seasonal flu vaccine, and there needs to be flexibility in interpreting meaningful differences between alternate products.
- The FDA should adopt appropriate criteria that will allow foreign clinical trial data to be acceptable for registering influenza vaccines in the U.S. to speed access and reduce development costs.

ANTIVIRALS

Antivirals are likely to play a critical role in both preventing and treating a pandemic influenza. Accordingly, TFAH and IDSA recommend:

- The Department of Health and Human Services accelerate the development of an adequate stockpile of antiviral agents in the Strategic National Stockpile, which should at a minimum, be enough to treat 25 percent of the U.S. population.

  - TFAH and IDSA remain concerned that the Department of Health and Human Services expects state governments to purchase 31 million courses of antiviral medications. The states are expected to cover 75 percent of the purchase price, with a 25 percent federal subsidy to cover the remaining costs. Initial reports indicate that not all states have the fiscal resources to purchase their share or have determined that antiviral stockpiles held at the state level are not a priority. This will lead to geographic inequities in terms of antiviral treatment during a pandemic.

PROMOTING PUBLIC-PRIVATE PARTNERSHIPS

A comprehensive and effective approach to pandemic preparedness must harness both public and private resources. The private sector can be the source of innovation in product development; the private sector also will be critical in ramping up production of diagnostics, treatments, and vaccines to meet the heightened demand associated with a pandemic. While many policies can contribute to a more positive climate for private sector investment, TFAH and IDSA want to emphasize the importance of Congress moving rapidly to pass and implement the ***Pandemic and All-Hazards Preparedness Act***, which improves public health response capabilities and reauthorizes and expands programs critical to supporting innovation in the private sector with regard to influenza and other threats to the public's health.

PART VI: Glossary of Terms and Acronyms

Adjuvant: An *adjuvant* is a substance that helps and enhances the pharmacological effect of a drug or increases the ability of a vaccine antigen to stimulate the immune system. When used in vaccines, it can result in fewer or lower doses, thus helping to conserve a vaccine's overall supply.

Antigen: An *antigen* is any substance that is foreign to the body that evokes an immune response.

Antigenic drift: These are small, continuous changes that occur in type A and type B influenza as the virus replicates, that is, makes copies of itself. These changes, which typically happen with seasonal flu strains, mean that adjustments need to be made annually to seasonal flu vaccines.

Antigenic shift: These are infrequent and sudden changes in Type A influenza, when two different flu strains infect the same cell and exchange genetic material. These new viruses can be the source of severe influenza pandemics. Antigenic shift describes the establishment of a new subtype of influenza A – it can happen as a result of reassortment as described, but it could also happen if a non-human influenza A virus infects humans directly and is transmissible.

Antiviral: A drug used to combat viruses. These drugs typically work by targeting - and disrupting - specific functions of the virus in order to prevent or reduce infection, or treat illness.

Attenuated: *Attenuated,* when used to describe a live *attenuated* vaccine, means that the vaccine is made from live virus that is weakened, or *attenuated,* making it strong enough to prompt an immune response but too weak to cause disease.

Avian flu: A highly variable mild to severe influenza that typically afflicts domestic and wild birds and does not normally infect humans, but which can mutate and be transmitted to humans causing epidemics, or pandemics. *Avian flu* is also called bird flu.

CDC: The Centers for Disease Control and Prevention. A federal agency, based in Atlanta, is responsible for investigating disease outbreaks, preventing and controlling infectious and chronic diseases, injuries, and workplace hazards. www.cdc.gov.

Clade: A group of organisms, such as a species, whose members share certain features derived from a common ancestor.

DNA: Deoxyribonucleic acid, which is the material that carries genetic information in all organisms, except for some families of viruses that use ribonucleic acid (see RNA). The set of DNA molecules that contains all genetic information for an organism is called its genome.

Epidemic: An *epidemic* is an outbreak of an infectious disease that can spread rapidly and widely, but is regarded as less severe than a pandemic, which affects a global population.

Gene: A hereditary unit consisting of a sequence of DNA that occupies a specific location on a chromosome and determines a particular characteristic in an organism. Genes undergo mutation when their DNA sequence changes.

Hemagglutinin: A protein found on the surface of the influenza virus responsible for binding the virus to the cell that is being infected. There are 16 subtypes, labeled H1 to H16.

Host cell: A *host cell* is the cell that is infected by a virus. A virus infects a cell and uses the cell's machinery to make copies of itself, spreading the infection.

Imunofluorescence: Any of various techniques that use antibodies chemically linked to a fluorescent dye to identify or quantify antigens in a tissue sample.

In vitro: In an artificial environment, i.e., not inside a living organism.

In vivo: In a living organism, such as humans or animals.

Microarray: A semiconductor device that is used to detect the DNA makeup of a cell. It contains hundreds of thousands of tiny squares designed to mate with a particular gene. They react to the liquefied human cells poured over it and are detectable by a laser.

Mutation: A genetic or other change that occurs within living organisms, enabling them to adapt to certain conditions in order to survive.

NIH: The National Institutes of Health is the federal government's biomedical research agency and consists of 20 individual institutes and seven centers, each involved in a specific area of medical research. Information about the agency can be found at www.nih.gov.

NIAID: The National Institute of Allergy and Infectious Diseases is a research institute within the National Institutes of Health primarily concerned with studying infectious disease. NIAID conducts its own research and also financially supports research conducted by non-government scientists and companies. Information about NIAID can be found at www.niaid.nih.gov.

Neuraminidase: A protein on the surface of the influenza virus responsible for promoting the release of progeny viruses from infected cells. There are nine known subtypes, labeled N1 to N9.

Pandemic: An epidemic that covers a wide global area and affects a large population.

PCR: Polymerase Chain Reaction is a technique for amplifying DNA sequences in the laboratory (in vitro). The process can amplify a specific sequence of DNA by as many as one billion times and is important in biotechnology, forensics, medicine, and genetic research.

Polymerase: Any of several enzymes that catalyze the formation of DNA or RNA from precursor substances in the presence of preexisting DNA or RNA acting as a template.

Replication: The process by which a virus makes copies of itself after entering (infecting) a host cell.

Resistance: The capacity of a species or strain of microorganism to survive exposure to a toxic agent, such as a drug, formerly effective against it.

RNA: Ribonucleic acid is one of the two major classes of nucleic acid, mainly involved in translating into proteins the genetic information that is carried in deoxyribonucleic acid, or DNA. (see DNA)

Vaccine: A preparation of a weakened or killed pathogen, such as a bacterium or virus, or of a portion of the pathogen's structure that stimulates the production of protective antibodies or cellular immunity against the organism, but cannot itself cause a severe infection.

Virus: An agent that consists essentially of a core of RNA or DNA surrounded by a protein coat. Viruses, which often cause disease, cannot replicate without a host cell.

WHO: The World Health Organization. *WHO* is the United Nations specialized agency for health. Information about the *WHO* can be found at www.who.org.

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The Infectious Diseases Society of America (IDSA) is a professional organization of physicians, scientists, and other health care professionals dedicated to promoting human health through excellence in infectious diseases research, education, prevention, and patient care. The Society, which has nearly 8,000 members, is based in Alexandria, Va. For more information, visit www.idsociety.org.

Trust for America's Health is a non-profit, non-partisan organization dedicated to saving lives and making disease prevention a national priority.

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Endnotes

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