

ISSUE BRIEF



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OCTOBER 2007

PREVENTING EPIDEMICS.
PROTECTING PEOPLE.

Pandemic Influenza: WARNING, CHILDREN AT-RISK

AN ISSUE BRIEF BY TRUST FOR AMERICA'S HEALTH AND THE
AMERICAN ACADEMY OF PEDIATRICS

“ IT IS CRITICAL THAT THE HEALTH AND WELFARE OF CHILDREN ARE CONSIDERED IN ALL ASPECTS OF INFLUENZA PLANNING, INCLUDING PREPARATION FOR A POSSIBLE PANDEMIC INFLUENZA OUTBREAK. ”

— JAY BERKELHAMER, MD, FAAP, President, American Academy of Pediatrics, October 26, 2006.

PART I: Introduction, Background, and Overview

Scientists around the globe have been warning about the risk of a potential pandemic influenza outbreak. Pandemic flu is caused by a new, severe strain of the flu virus capable of producing severe disease and spreading rapidly person-to-person worldwide. Unlike the seasonal flu, a pandemic flu virus poses a novel threat since humans would have no previously developed immunity against this new virus strain, putting most people at high risk for infection. This could result in a large percentage of the world's population being infected by a rapidly spreading virus in a very short period of time.

Experts predict a severe pandemic flu outbreak could result in up to 1.9 million deaths in the United States, approximately 9.9 million Americans needing to be hospitalized, and an economic recession with losses of over \$680 billion to the U.S. Gross Domestic Product.¹

How to treat and care for the nation's 73.6 million children and adolescents during an influenza pandemic is a significant concern.²

Children are not “small adults.” Special consideration needs to be given to complicated issues ranging from:

- Child-appropriate doses of vaccine and medications;
- Management and treatment of children who are ill;
- Including children in strategies to slow the spread of influenza in communities; and

- Caring for and supervising healthy children if schools and childcare facilities are closed for extended periods of time.

It is difficult to predict the impact of a future influenza pandemic on children, although children are known to suffer a significant burden from seasonal flu. Statistics regarding children in past pandemics are elusive, although children certainly became sick and died. In the 1918 “Spanish flu” pandemic, healthy young adults were the hardest hit, rather than the usual high-risk groups (i.e., young infants and the elderly) seen with the seasonal flu. More recently, children have been disproportionately affected by the avian flu virus that is circulating in Asia and elsewhere.

The American Academy of Pediatrics (AAP) and Trust for America’s Health (TFAH) recommend specific actions to ensure that the health and welfare of the nation’s children are protected in the event of an influenza pandemic.

This issue brief examines strategic approaches for containing the spread of a pandemic in children and adolescents, which include limiting social interaction, developing potential medical interventions such as vaccines and anti-viral medication, the use of masks and respirators, and educating children, families, and communities on what to do and how to do it.

“AT THE MOMENT, THERE ARE MORE QUESTIONS THAN THERE ARE ANSWERS. WE KNOW WHAT THE ISSUES ARE. WE JUST DON’T KNOW WHAT THE ANSWERS ARE.”

– JOHN S. BRADLEY, MD, FAAP, Children Hospital San Diego, California.

SEASONAL VS. PANDEMIC INFLUENZA

Seasonal Influenza -- Most Americans have had some experience with seasonal flu, a respiratory illness that strikes annually. Seasonal flu is not a benign illness -- it kills about 36,000 and hospitalizes over 200,000 people in the United States every year.³ Yet some experts generally regard it as a manageable public health problem, since many people have some form of immunity, and a yearly vaccine is available.

Pandemic (from the Greek, meaning “of all of the people”) **Influenza** has the potential to pose a far greater threat to global health. It typically is a novel human flu that causes a worldwide outbreak of serious illness and death. Because there is little natural immunity, the disease can easily spread from person to person, one of the key characteristics that defines a pandemic.

There have been at least 10 recorded flu pandemics during the past 300 years.⁴ Three of these occurred during the 20th Century.

1. The 1918-1919 “Spanish Flu” was the most devastating flu pandemic in recent history. It killed more than 500,000 Americans and as many as 50 million people globally, according to some estimates. It proved especially lethal to young adults.

2. The 1957-1958 “Asian Flu” was first identified in China and killed approximately 1 million people worldwide, including 68,000 Americans.

3. The 1968-1969 “Hong Kong Flu” caused about 34,000 deaths in the United States.⁵

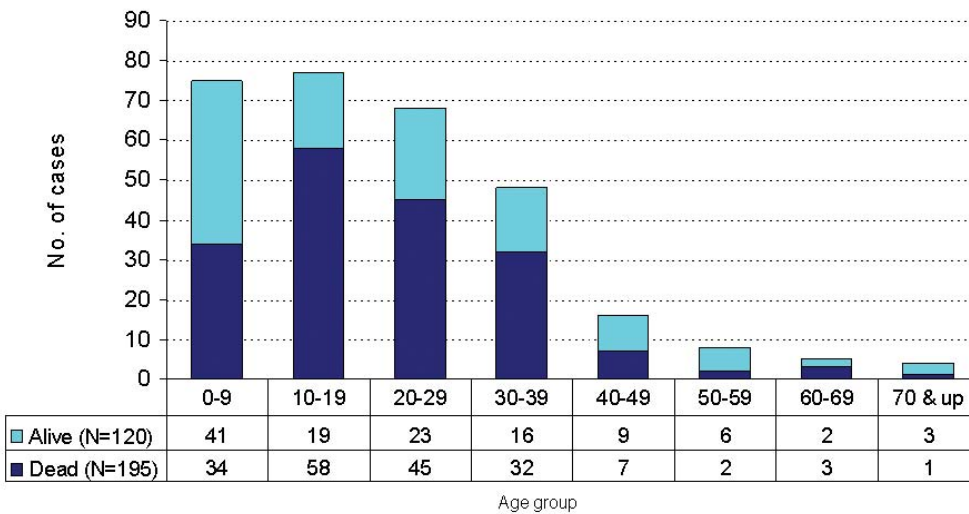
Scientific experts believe that another potentially deadly influenza pandemic is inevitable. Unanswered questions include when it will occur, how severe it will be, and whether the world will be prepared to cope with it.

AVIAN FLU (H5N1) IN HUMANS

Fears about pandemic influenza have intensified in recent years with the emergence of a deadly strain of avian (bird) flu. The virus, H5N1, has mainly circulated in Asia, although cases in birds have been reported as far north as England, while human cases have been reported as far west as Nigeria.

As of October 2, 2007, there have been 329 laboratory-confirmed human cases caused by the H5N1 virus and 201 deaths, which represents a staggering 61 percent mortality rate.⁶ Most alarming is the high number of cases resulting in death in children and adolescents. Children and teens between the ages of 0-19 account for nearly 46 percent of all H5N1 “bird” flu deaths.⁷

Human Avian Influenza A (H5N1) Cases by Age Group and Outcome
(as of 10 September 2007)



As of 10 September 2007, total of 328 cases were reported officially to WHO. The 12 cases in Turkey were excluded.



SEASONAL FLU AND CHILDREN

Seasonal flu is regarded as predictable and poses an important threat to the unvaccinated, especially young children. In evaluating the potential needs of children should a global pandemic begin, it is instructive to understand how vulnerable they are during seasonal episodes of flu -- and how important it is to prevent them from becoming infected.

In recent years federal health officials have expanded the age range for recommended seasonal flu vaccination of children. Currently, CDC recommends that all children between the ages of 6-59 months of age receive the annual flu vaccine and that previously unvaccinated children from 5 through 8 years of age receive 2 doses of vaccine the first time they are vaccinated.⁶⁸

Children younger than 2 years old, even if they are otherwise healthy, are more likely than older children to be hospitalized with serious complications if they become ill with influenza. These complications can include pneumonia, dehydration, worsening of long-term medical problems like heart disease or asthma, encephalopathy, and other bacterial infections, including sinus and ear infections. In some cases, these complications can lead to death. It is estimated that each year in the U.S., there are more than 20,000 children younger than 5 years of age hospitalized due to flu. Also, there is an under-recognized burden of influenza in young children, with outpatient visits 10 to 250 times as common as hospitalizations, with the highest rates in children 24-59 months of age.⁶⁹

CDC began collecting reports of seasonal influenza-associated deaths among children in 2003. Influenza-associated deaths in children became a nationally reportable condition in 2004, meaning that health professionals are required to report such cases to the federal government.

The annual number of deaths among children reported to CDC for the past 4 influenza seasons has ranged from a low of 44 during 2004-2005 to a high of 153 during 2003-2004, but probably represents an underestimate of the true number of deaths due to a lack of recognition and underreporting.⁷⁰

Of 153 laboratory-confirmed influenza-related pediatric deaths reported during the 2003-2004 influenza season, 96 deaths were in children younger than 5 years of age, and 61 in children younger than 2 years of age. Among the 149 children who died and for whom information on underlying health status was available, 100 did not have an underlying medical condition that was an indication for vaccination at that time.⁷¹ These statistics represent the highest mortality rate for a vaccine-preventable illness in recent years.

In California during the 2003-2004 and 2004-2005 influenza seasons, 51 percent of children with laboratory-confirmed influenza who died, and 40 percent of those who required admission to an intensive care unit, had no underlying medical conditions. These data indicate that, although deaths are more common among children with risk factors for influenza complications, the majority of pediatric deaths occur among children of all age groups with no known high-risk conditions.⁷²

Vaccine Coverage Rates for Children

Vaccination rates among children at increased risk for influenza complications remain low. Coverage among children aged 2-17 years with asthma for the 2004-05 influenza season was estimated to be 29 percent. However, one study reported 79 percent vaccination coverage among children attending a Cystic Fibrosis treatment center.⁷³

During the first season that CDC recommended that all children aged 6-23 months be vaccinated, only 33 percent received more than one dose and 18 percent received 2 doses of influenza vaccine.⁷⁴

Among children enrolled in Health Maintenance Organizations (HMOs) who had received a first dose during 2001-2004, second dose coverage varied from 29 to 44 percent among children aged 6-23 months and from 12 to 24 percent among children aged 2-8 years.⁷⁵

Data collected in February 2005 indicated a national estimate of 48 percent vaccination coverage for more than one dose among children aged 6-23 months and 35 percent coverage among children aged 2-17 years who had one or more high-risk medical conditions during the 2004-05 season.⁷⁶

PART II: Strategies to Limit Social Interaction in Children to Contain the Spread of an Influenza Pandemic

“CHILDREN ARE INHERENTLY MORE AT RISK BECAUSE THEY CONGREGATE IN GROUPS. THEY LIKE TO ‘SHARE’ THEIR SECRETIONS. THEY WON’T SHARE THEIR TOYS, BUT ARE HAPPY TO SHARE THEIR GERMS. WE CAN EXPECT THEM TO BECOME INFECTED -- AND TO INFECT OTHERS.”

– MARGARET C. FISHER, MD, FAAP, Chair of the Department of Pediatrics and Medical Director, The Children’s Hospital at Monmouth Medical Center, Long Branch, New Jersey.

Studies have indicated that school children are the population group most responsible for transmission of contagious respiratory viruses, including influenza. They have a high attack rate of influenza infection because they have limited pre-existing immunity and once infected, transmit influenza viruses to many others even before they themselves have recognizable symptoms.⁸ Moreover, numerous studies have demonstrated the extent to which children act as efficient disease vectors, spreading infection not only throughout classroom settings, but secondarily at home. In turn, there is tertiary spread from the parent to the workplace and from the siblings to daycare and school settings.⁹

Public health experts agree that children infected with influenza are major transmitters of the disease. Children gather in groups – in school, in daycare settings, on playgrounds, in households – and often are unintentionally careless when it comes to their personal hygiene. They cough and sneeze, often without using a tissue. Many children

cough into their hands, and then touch other objects -- a door knob, a computer mouse or keyboard, toys -- or other people, including other children, rather than coughing or sneezing into their sleeves, which many pediatricians consider the next best alternative to using a tissue. Not surprisingly, it is challenging to try to teach very young children “cough etiquette,” and to get them to wash their hands frequently.

Children also shed higher levels of influenza virus for longer periods of time than adults.¹⁰ All of these factors place family members and others with whom children have contact, such as other children, daycare providers and teachers, and vulnerable groups, such as elderly grandparents, at an increased risk of infection. The risk of secondary transmission of seasonal flu within households is known to be inversely proportional to the age of the person who brings influenza into the household: the younger the person, the greater the risk to other family members.¹¹



SOCIAL DISTANCING

“ WE KNOW THAT GATHERING PEOPLE TOGETHER IS A GOOD WAY TO TRANSMIT RESPIRATORY VIRUSES, SO ALL OF THESE SOCIAL DISTANCING SUGGESTIONS MAKE PERFECTLY GOOD EPIDEMIOLOGICAL AND INFECTION-CONTROL SENSE. HOWEVER, THE QUESTION IS WHETHER OR NOT THEY MAKE PRACTICAL SENSE -- AND HOW DO WE DEAL WITH THAT? ”

--Lorry Glen Rubin, MD, FAAP, Schneider Children's Hospital, New Hyde Park, New York.

Social distancing is a term used by public health experts to describe measures such as school and daycare closures, telecommuting or staggered shifts for the workforce, and cancellation of public gatherings to minimize the transmission of disease. Community mitigation strategies and nonpharmaceutical interventions are terms also used by public health officials when referring to community-based interventions intended to limit disease transmission in the absence of vaccines or medications.

In the event of an influenza pandemic, communities likely will have to make difficult decisions about the most effective ways to reduce transmission of the virus -- actions that will have profound social and educational ramifications on children. For example, children faced with extended school or daycare closings could become increasingly isolated, experiencing serious disruption of their social and educational development during a time in their lives when they are already vulnerable. Parents will have to stay home from work to care for their children, limiting their productivity and contributions to the economy.

The extent of the community response will depend on how serious any pandemic turns out to be. The U.S. Centers for Disease Control and Prevention (CDC) has created a Pandemic Severity Index (PSI) using case fatality ratios to determine the severity of a pandemic. Using the PSI as a guide, CDC

recommends what communities should do to reduce transmission of the virus.

The severity levels range from 1 to 5, with 1 being the least severe. At the lowest level, health officials recommend voluntary measures, including isolation and quarantine, but do not recommend that schools or workplaces be closed, or that public gatherings be canceled. Suggestions for containment increase with the severity of the pandemic. At level 5, for example, the government recommends schools and daycare facilities be closed and public gatherings canceled for as long as the transmission of the pandemic virus is occurring, possibly for as long as 3 months. In addition, at level 5, businesses should modify workplace schedules to keep people separated and implement telecommuting alternatives to workplace attendance.¹²

In September-October 2006, a Harvard School of Public Health public opinion poll was conducted to explore the willingness of Americans to comply with community mitigation or social distancing measures. More than three-fourths of the almost 1,700 respondents indicated that they would cooperate if public health officials recommended that they curtail various activities in their daily lives like attending religious services, going to the mall, or using public transportation for one month.¹³ Respondents were not asked about their willingness to comply with these recommendations for longer time periods.

Summary of the Community Mitigation Strategy by Pandemic Severity¹⁴

Pandemic Severity Index			
Interventions* by Setting	1	2 and 3	4 and 5
Home Voluntary isolation of ill at home (adults and children); combine with use of antiviral treatment as available and indicated	Recommend	Recommend	Recommend
Voluntary quarantine of household members in homes with ill persons (adults and children); consider combining with antiviral prophylaxis if effective, feasible, and quantities sufficient	Generally not recommended	Consider	Recommend
School Child social distancing -dismissal of students from schools and school based activities, and closure of child care programs -reduce out-of-school social contacts and community mixing	Generally not recommended Generally not recommended	Consider: ≤4 weeks Consider: ≤4 weeks	Recommend: ≤12 weeks Recommend: ≤12 weeks
Workplace / Community Adult social distancing -decrease number of social contacts (e.g., encourage teleconferences, alternatives to face-to-face meetings) -increase distance between persons (e.g., reduce density in public transit, workplace) -modify postpone, or cancel selected public gatherings to promote social distance (e.g., postpone indoor stadium events, theatre performances) -modify work place schedules and practices (e.g., telework, staggered shifts)	Generally not recommended Generally not recommended Generally not recommended Generally not recommended	Consider Consider Consider Consider	Recommend Recommend Recommend Recommend

Legend:

Generally Not Recommended = Unless there is a compelling rationale for specific populations or jurisdictions, measures are generally not recommended for entire populations as the consequences may outweigh the benefits.

Consider = Important to consider these alternatives as part of a prudent planning strategy, considering characteristics of the pandemic, such as age-specific illness rate, geographic distribution, and the magnitude of adverse consequences. These factors may vary globally, nationally, and locally.

Recommended = Generally recommended as an important component of the planning strategy.

**All of these interventions should be used in combination with other infection control measures, including hand hygiene, cough etiquette, and personal protective equipment such as face masks. Additional information on infection control measures is available at www.pandemicflu.gov.*

SCHOOL CLOSURES

“ ISOLATING FAMILIES IS BETTER THAN PEOPLE CONTINUING TO MEET. BUT THE QUESTION IS: HOW DOES THAT HAPPEN? HOW CAN PEOPLE MISS WORK? HOW CAN CHILDREN MISS SCHOOL? THOSE ARE THE MILLION DOLLAR QUESTIONS. ”

– HENRY H. BERNSTEIN, DO, FAAP, Chief, General Academic Pediatrics,
Children’s Hospital at Dartmouth, Lebanon, New Hampshire

Preventive school closures, which might last weeks or even months, would halt the operation of the educational system as currently structured, leaving millions of displaced students in need of alternative means of formal education. Additionally, in a pandemic, many daycare and childcare centers may be required to follow the lead of the local school system and close to limit disease transmission among their populations. Closing schools or childcare centers once a pandemic is widespread in a community may not significantly halt the spread of disease.¹⁵ Therefore, identifying the optimal time to initiate preventive school closures will be challenging for government officials because “implementation needs to be early enough to preclude the initial steep upslope in case numbers and long enough to cover the peak of the anticipated epidemic while avoiding intervention fatigue.”¹⁶

At the onset of a pandemic, many parents may voluntarily choose to keep their children at home even if schools remain open in order to reduce possible exposure to infection in a school setting. However, it is uncertain how families might respond during prolonged disruptions in their daily lives and if adherence rates can be sustained over several months.¹⁷

There could be significant social and educational implications for children and adolescents who are out of school for an extended period of time. Despite evidence that social distancing may be a good strategy to reduce the spread of infection, there are additional concerns about the behavioral, cognitive, and social impact on children and adolescents that could result from closing their

schools and daycare facilities. Schools not only educate children but also socialize them. School and day care settings are places where developmental skills are honed and where children learn to interact with others. For many, it is also a site of nurturing and growth, and where friendships are formed.

Many children of lower socio-economic status also rely on school as their major source of nutrition. The National School Lunch Program operates in approximately 100,000 public and private schools and residential childcare institutions, and the School Breakfast Program operates in about 80,000 schools. School lunch and breakfast are free for students at or below 130 percent of the poverty level and are available at reduced price for students between 130 percent and 185 percent poverty level. Half of the 30 million students that participate in the National School Lunch Program received free meals in 2006.¹⁸ If a flu pandemic resulted in school closures, steps would need to be taken to ensure that children continue to receive proper nutrition.

Could children continue their education during an extended school closure? A combination of planned extended lessons and home schooling may supplement formal education and allow students to maintain skills while schools are closed. This will require extensive planning by the school system and a “learning compact” between school and home. Assuming that communication, mail, and other critical infrastructure systems remain intact, tests, e-lessons, supplementary materials, and teacher-student interaction may support this process.

However, distance-learning models for ongoing education are not likely to be within reach of all school systems and all households, especially those in disadvantaged areas. For school districts that can implement this option, distance learning may take advantage of Internet technologies that support real-time interaction between students and teachers, sharing of educational materials, submission of assignments, and automated grading of certain types of assignments in real time. Consideration must be given to the amount of time required to implement distance-learning software, create Internet access to the software for students and teachers, and train students and teachers to use these programs.¹⁹ Also, there is increasing concern that there may not be sufficient bandwidth to support telecommuting, educational activities, and continuity of business operations in the private sector.

Long-term school closures would impact entire families. Young children unable to attend school will be in need of adult supervision during the day. Some working parents may be able to make arrangements with friends, family, or alternative childcare facilities. However, childcare alternatives may not be available to a large proportion of working parents due to physical, emotional, economic, medical, or other factors.

Working parents may be forced to take extended leave from work to provide childcare during a severe flu pandemic. When the 2006 Harvard School of Public Health public opinion survey questioned respondents about possible financial difficulties due to missed work, three-quarters (74 percent) believed that they could miss work for 7-10 days without having serious financial problems. However, more than half (57 percent) believed they would have serious financial problems if they had to miss work for 1 month, and three-quarters (76 percent) of respondents thought they would experience serious economic hardship if they were out of work for 3 months due to a severe pandemic.²⁰ The disruption of school and work for children and adults alike can lead to physical, mental, social, economic, psychological, and financial stress as individuals struggle to ensure a balance between protecting and providing for their loved ones.

Additionally, in the event of a pandemic, it is likely that restrictions on social gatherings and extensive community-wide closures will follow. Closures will lead to significant economic losses across a large number of industries. Curtailing social interactions can lead to social unrest and feelings of loneliness and isolation. Crime and participation in violent, unhealthy behaviors might be pursued by individuals who are deprived of regular social and recreational activities.

FAST FACTS: Schools and Early Childhood Education in the U.S.

- In the U.S., there are over 54.5 million primary and secondary school students.²⁵
- Approximately one-fifth of the U.S. population attends or works in schools.²⁶
- Sixty percent of the 20.7 million children ages 0-5 nationwide are enrolled in center-based early childhood learning programs.²⁷
- In 2005, 6.9 percent of K-8 pupils nationwide participated in academic after-school activities.²⁸
- In 2006, 101,000 schools participated in the National School Lunch Program and served 30 million children each school day.²⁹
- Nearly 22 million school days are lost annually due to the common cold alone.³⁰

“YOU MAY BE ABLE TO CLOSE SCHOOLS, BUT YOU CAN'T ALWAYS CONTROL WHERE KIDS GO. IF THEY CONGREGATE ON PLAYGROUNDS, ALL YOU'VE DONE IS MOVED THE SITE OF TRANSMISSION.”

-- JOHN S. BRADLEY, MD, FAAP, Children's Hospital of San Diego, California.

LIMITING SOCIAL INTERACTION - TIME IS OF THE ESSENCE

There is evidence that strategies to limit social interaction in communities can be a very successful tool in reducing transmission during a pandemic -- if these measures are imposed quickly.

During the 1918 flu pandemic, in cities where public health officials took measures to limit public gatherings within a few days after the first local cases were identified, peak weekly death rates were up to 50 percent less than cities that waited just a few weeks before responding. Two historical analyses published in April 2007 showed that non-pharmaceutical interventions, such as restricting social gatherings, limited the spread of the virus.²¹ These studies demonstrated that public health interventions limiting social interaction effectively curbed the transmission of influenza virus in 1918, and death rates were reduced more dramatically the sooner these measures were put in place.²²

For instance, St. Louis took quick action compared with the city of Philadelphia. St. Louis introduced a broad series of public health measures to contain the flu within 2 days of the first reported cases. Philadelphia used similar measures, but took more than 2 weeks to implement them; a city-wide parade took place prior to imposing its ban on public gatherings. The peak mortality rate in St. Louis was only one-eighth that of Philadelphia.²³

In addition, schools, theaters, churches, and dance halls were closed in various cities. Kansas City banned weddings and funerals if more than 20 people were to be in attendance. New York required that factories stagger shifts to reduce rush hour commuter traffic. Seattle's mayor ordered citizens to wear face masks.²⁴

A World Health Organization (WHO) expert panel found that during the relatively mild 1957-1958 pandemic, infections increased in some countries following public gatherings, such as conferences and festivals. This panel also concluded that, in many countries, pandemic influenza spread most rapidly in camps, army units, and schools, suggesting that avoiding crowds can help reduce transmission.



PART III: Medical Interventions to Limit the Spread of a Pandemic in Children

This section examines the status of medical strategies -- vaccines, anti-viral medications, masks and respirators, and isolation in

health care facilities -- for trying to contain the spread of a pandemic influenza in children and adolescents.

VACCINES

“CHILDREN WILL BE THE MAJOR VECTORS, JUST LIKE THEY ARE EVERY SINGLE YEAR. ANY VACCINE STRATEGY THAT DOESN'T INCLUDE THEM IS FOOLISH.”

-- MARGARET C. FISHER, MD, FAAP, Chair of the Department of Pediatrics and Medical Director, The Children's Hospital at Monmouth Medical Center, Long Branch, New Jersey.

Since the best way to reduce the role of children in spreading influenza is to ensure that they do not become infected, many public health experts believe that mass immunization of children would be an effective tool in curbing widespread community transmission. However, a pandemic flu vaccine well-matched with the circulating strain is not likely to be widely available for at least 6 months after the onset of a pandemic outbreak. That is why the federal government is undertaking pre-pandemic activities to address the initial critical 6 month period.

For example, in April 2007, FDA approved a vaccine for the H5N1 “avian flu” virus for use in adults; however, this vaccine is expected to primarily protect against one of the virus strains predicted to have the potential to cause pandemic flu. It is administered through 2 intramuscular injections given 1 month apart.³¹

The pre-pandemic vaccine is meant to offer some protection during the early months of a pandemic while a more precise vaccine -- tailored to the specific pandemic strain -- is developed and manufactured. Should the virus undergo changes that would acceler-

ate its spread among people, a new vaccine must be created and produced, which could take 6 months or longer before sufficient production of a new vaccine is possible.

The newly approved vaccine is manufactured by sanofi pasteur,³² but will not be sold commercially. Instead, the vaccine has been purchased by the U.S. government for the Strategic National Stockpile for distribution by public health officials to states when needed. The federal government expects to have enough of the pre-pandemic vaccine for an estimated 20 million of the nation's 300 million people. The government currently has 12 million doses, or enough for 6 million people, assuming that 2 doses will be required to stimulate the appropriate immune reaction.³³

However, at this time, the pre-pandemic vaccine is approved only for use in persons 18-64 years of age. A government-sponsored study looking at safety and immunogenicity in children ages 2-9 years of age currently is underway at 3 National Institute of Allergy and Infectious Diseases-sponsored Vaccine Treatment Evaluation Units. So far, the vaccine has been well-tolerated in children. The final data analysis is continuing.³⁴



“FOR SEASONAL FLU, THE DOSE FOR AGE 3 AND ABOVE IS THE SAME AS IT IS FOR ADULTS, WHILE THE DOSE FOR AGES 6 MONTHS THROUGH 35 MONTHS IS HALF THE DOSE AS ADULTS. WE DON'T KNOW YET IF THE SAME THING WILL BE TRUE FOR AVIAN FLU. ALSO, IF ADULTS NEED 2 DOSES, KIDS PROBABLY WILL NEED 2 DOSES TOO.”

-- LORRY GLEN RUBIN, MD, FAAP, Schneider Children's Hospital, New Hyde Park, New York.

The National Institutes of Health plans to study the pre-pandemic vaccine in children younger than 2 years, as this group would likely to be at high risk for hospitalization with pandemic influenza as they are with seasonal influenza. There are no plans to study the vaccine in children 10-17 years because the data in adults, elderly and -- thus far -- in children 2-9 years of age suggest they would respond similarly to the same doses of vaccine.

Typically, those with underlying medical conditions, the elderly, children from 6 months through 59 months of age, as well as health care workers and other essential personnel are given higher priority for vaccination. When vaccines are in short supply, healthy children over 5 years of age usually fall near the bottom of vaccine priority lists -- despite some studies that point to the value of mass immunization of schoolchildren in reducing community-level infection.

The federal government has a strategic response plan for pandemic flu, but no final decisions have been made regarding vaccine priorities. The plan includes recommendations from 2 federal advisory committees -- the Advisory Committee on Immunization Practices (ACIP) and the National Vaccine Advisory Committee (NVAC). Both groups have proposed that medically high-risk individuals and front-line emergency personnel receive immunizations first, should a vaccine become available. Otherwise healthy individuals ages 2-64 years -- an estimated 179.3 million people -- are at the bottom of the initial priority lists.³⁵

Later this year, the Department of Health and Human Services (HHS) will make final recommendations regarding pandemic vaccine priority groups after a series of town meetings and other public forums. The HHS recommendations will then be sent to state public health officials, who will ultimately decide who gets the vaccine first.³⁶

“A PHYSICIAN RECOMMENDATION FOR VACCINATION AND THE PERCEPTION THAT HAVING A CHILD BE VACCINATED 'IS A SMART IDEA' WERE ASSOCIATED POSITIVELY WITH LIKELIHOOD OF VACCINATION OF CHILDREN AGED 6-23 MONTHS.”

-- FROM CDC'S ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES SEASONAL INFLUENZA RECOMMENDATIONS FOR 2007-08.

“I THINK THAT, IN THE EVENT OF A REAL PANDEMIC, VACCINE SHOULD BE GIVEN TO INFANTS BASED ON THE IMMUNOGENICITY DATA THAT WE HAVE IN ADULTS, YOUNG CHILDREN AND THE ELDERLY...AND THE FACT THAT PANDEMIC FLU VACCINES ARE NOT MANUFACTURED DIFFERENTLY THAN THE SEASONAL VACCINE, WHICH IS LICENSED FOR KIDS DOWN TO 6 MONTHS OF AGE. THAT IMPLIES THAT SAFETY IS NOT LIKELY TO BE AN IMPORTANT ISSUE IN INFANTS. THE REAL ISSUE IS THAT THE CURRENTLY LICENSED H5NI VACCINE IS ONLY MODESTLY IMMUNOGENIC, REGARDLESS OF AGE, AND, OF COURSE, WE HAVE NO EFFICACY DATA. REGARDLESS, IN AN ACTUAL PANDEMIC, MODEST IMMUNOGENICITY BEATS NO IMMUNOGENICITY AT ALL.”

-- KEN ZANGWILL, MD, Division of Pediatric Infectious Diseases, UCLA Center for Vaccine Research, Harbor-UCLA Medical Center, Torrance, California.

ADDITIONAL FLU VACCINE RESEARCH

- In December 2006, NIH began clinical trials of another H5NI vaccine candidate. Clinical trials will continue throughout this year.³⁸
- The government also is funding research into more rapid and flexible alternatives to the chicken egg technology currently used to produce seasonal influenza-related vaccines. As an example, use of cell cultures to produce vaccines is already standard practice with many other modern vaccines. This cell-based technology is being studied for seasonal and pandemic vaccine production and it may allow enough influenza vaccine to be made for every American within 6 months after developing a product tailored to the specific pandemic viral strain. HHS plans to ask commercial vaccine manufacturers to look at other promising approaches, including the development of recombinant vaccines.³⁹
- In January 2007, the federal government awarded \$132.5 million to 3 vaccine manufacturers to develop adjuvanted vaccines against the H5NI influenza virus.⁴⁰



“SOME PUBLIC HEALTH OFFICIALS SPEAK OF UNIVERSAL VACCINATION AGAINST INFLUENZA, MEANING A RECOMMENDATION FOR ALL AGE GROUPS -- BUT SCHOOLCHILDREN, AGED 5 TO 18 YEARS, ARE A PRIME TARGET AS THEY ARE GENERALLY CONSIDERED TO BE THE MOST IMPORTANT SOURCE OF COMMUNITY-WIDE TRANSMISSION.”³⁷

-- M.E. HALLORAN AND I.M. LONGINI, “Community Studies for Vaccinating Schoolchildren Against Influenza,” *Science*, February 2006.

CHILDREN AND SEASONAL FLU VACCINATIONS

“Based on what we know about the role kids play in seasonal flu -- and the impact -- we can only extrapolate that it is going to be magnified during a pandemic.”

-- HENRY H. BERNSTEIN, DO, FAAP, Chief, General Academic Pediatrics, Children’s Hospital at Dartmouth, Lebanon, New Hampshire

Several studies underscore the potential importance of mass immunization of schoolchildren in preventing influenza infection in the community:

- A study conducted in Tecumseh, Michigan showed that immunization of 85 percent of all schoolchildren against influenza resulted in a 3-fold reduction in the infection rate in other age groups, compared with a neighboring community where schoolchildren were not the focus of vaccination.⁴¹
- A Japanese study published in 2001 demonstrated that immunization of 50-85 percent of schoolchildren was associated with a significant drop in deaths among unvaccinated elderly during influenza epidemics. The vaccination of Japanese schoolchildren prevented about 37,000 to 49,000 deaths per year, or about one death for every 420 children vaccinated. When vaccination of schoolchildren was discontinued, the excess death rates in Japan once again increased.⁴²
- A 2005 pilot study compared the impact of FluMist (a vaccine delivered by a nasal spray) administered to children in one Maryland elementary school with 2 other demographically similar schools where the vaccine was not offered. Again, the results showed a significant reduction in fever and/or respiratory illnesses within households of pupils who received the vaccine.⁴³
- A Russian study published in 2006 analyzed the impact of mass vaccination of children on unvaccinated elderly people living in their homes, and found 3 to 4 times fewer episodes of influenza-like illnesses, as well as a decrease in conditions that often result as complications from the flu.⁴⁴ This study concludes that “although these findings may not be applicable immediately in many developed countries, where a high proportion of elderly people are vaccinated on an annual basis, the finding may be far more relevant in a pandemic situation where there is insufficient vaccine available to cover both children and the elderly and some form of prioritization has to be introduced. Targeting children for vaccination against influenza may protect the unvaccinated elderly and may contribute towards preparing pandemic vaccination strategies.”⁴⁵

ANTIVIRAL MEDICATIONS:

Because vaccines will likely be unavailable during the first wave of an influenza pandemic, antiviral drugs and other therapeutics will likely be the only initial defense against illness. Antibiotics are effective

only against bacteria. They do not work against the viruses that cause influenza, although they could be useful against secondary bacterial infections that sometimes occur with flu.

Two drugs, oseltamivir (known commercially as Tamiflu) and, to a much lesser extent, zanamivir (known commercially as Relenza), are neuraminidase inhibitors that may be used to treat people infected by the H5N1 virus, and public health officials are focusing on these drugs as primary treatments in the event of a pandemic.

Tamiflu and Relenza have been shown effective against H5N1 in the laboratory, but it is still unclear what impact they will have during a pandemic. A trial is currently underway in Southeast Asia studying the efficacy of different doses of Tamiflu among hospitalized children and adults diagnosed with either severe seasonal flu or avian flu. No preliminary data on this trial are yet available.⁴⁶

Pediatric infectious disease experts and others are concerned, however, because neither Tamiflu nor Relenza is licensed at this time for children younger than 1 year of age. There also have been a few reports, mostly from Japan, of children causing self-injury or experiencing delirium (confusion, hallucinations, speech problems) while using Tamiflu – although the drug has not been proved to be the cause.⁴⁷ At the same time, infants are at high risk for complications if they become ill with influenza and will be especially vulnerable during a pandemic if a vaccine is delayed or unavailable.

The National Institute of Allergy and Infectious Diseases (NIAID) has a study underway examining the safety and efficacy of Tamiflu in children from birth through 23 months of age. The study is starting with the older children and working its way down to infants. Researchers hope to find out whether the drug is safe in infants and young children, and at what dose. The study is expected to continue until April 2009.⁴⁸

There are several doses and formulations of Tamiflu available, including a flavored liquid. The government recently approved 2 new lower dosage formulations of Tamiflu for children, at 30 and 45 milligrams. Roche, the company that manufactures Tamiflu, also makes a standard 75-mg capsule for adults.

Tamiflu has proved useful as a preventive measure during influenza outbreaks in group settings like nursing homes and dormitories. But, if the drug is in short supply, it will not likely be used routinely to prevent infections during a pandemic.

In January 2007, HHS awarded \$103 million to develop a new influenza antiviral drug, peramivir, which appears to be effective in laboratory tests against a number of influenza strains. Further studies will test whether this drug can treat seasonal and other life-threatening influenza viruses such as H5N1.⁴⁹ The drug is another neuraminidase inhibitor given by a single injection into the muscle and is comparable to 5 days of treatment with other existing agents. It also can be delivered intravenously.

As with vaccines, the federal government and the states have been buying antiviral drugs, mostly Tamiflu, with the goal of stockpiling enough treatment courses (81 million) for 25 percent of the U.S. population, a figure that includes children. The drug manufacturer has made the drug available at below market cost. HHS plans to buy 50 million treatment courses to distribute to states based on their population; the remaining 31 million will be purchased directly by the states, partially subsidized by the federal government. HHS has purchased or has on hand approximately 36 million antiviral treatment courses. Almost all of the states have taken advantage of a federal discount plan and, to date, have purchased more than 12 million treatment courses.⁵⁰

Also, HHS has thus far purchased 100,000 treatment courses of the flavored liquid Tamiflu specifically for children.⁵¹

On July 19, 2005, NVAC voted unanimously in favor of antiviral drug use priorities during a pandemic influenza outbreak. The recommendations were made considering pandemic response goals, assumptions on the impacts of a pandemic, and after thorough review of past pandemics, annual influenza disease, data on antiviral drug impacts, and recommendations for pandemic vaccine use.



Children between 12-23 months of age were included in the top 5 priority groups initially identified by NVAC as follows:

1. Patients admitted to hospitals (estimated 10 million individuals);
2. Health care workers with direct patient contact and emergency medical providers (estimated 9.2 million individuals);
3. Highest risk outpatients -- immunocompromised persons and pregnant women (estimated 2.5 million individuals);
4. Pandemic health responders (public health, vaccinators, vaccine and antiviral manufacturers), public safety (police, fire corrections), and government decision-makers (estimated 3.3 million individuals); and

5. Increased at-risk outpatients, including young children 12-23 months old, persons over 65 years of age and persons with underlying medical conditions (estimated 85.5 million individuals).⁵²

NVAC considered the primary goal of a pandemic response to decrease the impact on health, including severe morbidity and death. Minimizing societal and economic impacts were considered secondary and tertiary goals respectively.⁵³ Currently, there is an effort underway to revise these recommendations based on additional information and the possibility of increased antiviral supplies.

CHILDREN AND ANTIVIRAL MEDICATIONS FOR SEASONAL FLU

Currently, there are 4 drugs available to treat and/or prevent seasonal influenza. These are amantadine, rimantadine, zanamivir (Relenza) and oseltamivir (Tamiflu). The FDA has approved all of them to treat, and most of them to prevent, seasonal flu caused by influenza A, while only zanamivir and oseltamivir are able to treat and prevent seasonal flu caused by influenza B.

However, during recent flu seasons -- and for the coming 2007-2008 flu season -- CDC has recommended against using amantadine and rimantadine for the treatment or prevention of seasonal flu because influenza A viruses are becoming increasingly resistant to both drugs. Resistance develops when the virus has mutated (changed) in a way that makes a drug ineffective against it. CDC has urged that these 2 drugs not be used again until circulating influenza A viruses once again become susceptible to them.⁵⁴

The first 2 drugs work by inhibiting the activity of the influenza virus M2 protein, making it difficult for the virus to make copies of itself once it enters a cell. These drugs are effective only against type A influenza.

The second 2 drugs represent the first of a different class of antiviral drugs known as neuraminidase inhibitors. The surfaces of flu 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.⁵⁵

The FDA has approved oseltamivir to treat children one year and older and prevent influenza among children 13 years and older. Zanamivir is licensed to treat children 7 years of age and older, but is not licensed for the prevention of influenza.

All of the drugs except zanamivir are taken orally in pill or suspension form. Zanamivir comes in a dry powder and is inhaled using a device known as a "Diskhaler."

On average, the drugs reduce the duration of flu symptoms by about one day if taken within the first 48 hours after illness begins. As a preventive, antivirals also can significantly reduce the chances of becoming ill during a flu outbreak in a family or community.

A recent analysis of data from previous studies of oseltamivir in children showed that earlier use of the drug results in a greater reduction in the length of illness, its symptoms, and secondary infections. Treatment begun within 24 hours of the onset of symptoms provided "clinically meaningful improvements."⁵⁶

FACEMASKS AND RESPIRATORS

On May 3, 2007, CDC issued *Interim Guidance for the Use of Facemasks and Respirators in Public Settings during an Influenza Pandemic*. While there is very little specific research about the value of masks to protect people in public settings, CDC's interim recommendations are based on the best judgment of public health experts who relied in part on information about the protective value of masks in healthcare facilities.⁵⁷

Facemasks are loose-fitting, disposable masks that cover the nose and mouth. These include products labeled as surgical, dental, medical, isolation, and laser masks. Facemasks help stop droplets from being spread by the person wearing them. They also help keep splashes or sprays from reaching the mouth and nose of the person wearing the facemask. They are not designed to protect the person wearing them against breathing in minute particles, such as the flu virus itself. Facemasks should be used once and then thrown away, but if there is a shortage, this recommendation may need to be reconsidered.⁵⁸

CDC recommends that people consider wearing a facemask during an influenza pandemic if:

- They are ill with the flu and think they might have close contact with other people, i.e., within about 6 feet;
- They live with someone who has flu symptoms; or
- They are in a crowded public place where they might be in close contact with infected people.

A respirator is designed to reduce the exposure of the wearer to airborne particles, including particles containing flu virus. The term "N95" is used to refer to a half-facepiece filtering respirator designed, when used correctly, to filter out 95 percent of the particles that could pass through. The filters are tested with approximately a 0.3 micron particle, which is the most penetrating size. Particles smaller or larger than this will be filtered more efficiently. Most of the time, N95 respi-

rators are used in industrial manufacturing, construction and other jobs that involve dust and small particles. Health care workers, such as nurses and doctors, also use respirators when taking care of patients with diseases that can be spread through the air, like tuberculosis. At present, there is no federal-approved respirator for use by children.

To be most effective, these types of respirators need to fit tightly to the face so that the air is breathed through the filter material. Respirators generally are not designed to form a tight fit on people with very small faces, such as children.⁵⁹ In addition, respirators are not recommended for anyone with lung, heart, or other conditions which interfere with breathing.

CDC recommends that individuals should consider wearing a respirator during an influenza pandemic if they are well, but will be in close contact with people who are thought to be sick with pandemic flu. This recommendation also applies to those taking care of an ill person at home. If a respirator is unavailable, CDC recommends that a facemask should be considered.⁶⁰

Masks and respirators will not likely be able to prevent all disease transmission. They are only one step in disrupting the chain of transmission. Individuals likely will be infectious before they have symptoms, so it may not be sufficient to simply put on a mask once flu symptoms appear. Also, there will likely be "contact" contagion, that is, infection transmitted by handling contaminated items, in addition to droplets spread through the air by coughing or sneezing. Perhaps most importantly, there are serious questions about how available facemasks and respirators will be during a global flu pandemic due to manufacturing constraints and off-shore production issues.

Safety, design, and compliance are 3 of the concerns with respect to facemask and respirator use by children. Currently, there are no NIOSH-approved or FDA-cleared respirators designed for children. However, some



small-sized respirator facepieces may adequately fit older children. While surgical masks are not required to fit as tightly to the face, they should not interfere with eyesight and gaps should be minimized.

The likelihood that a child would use a face-mask or a respirator properly is a significant concern. Facemasks and respirators will not serve their intended purpose if they are not worn during appropriate times. Children may

not understand the importance of wearing a mask and they may not be tolerant of having it on their face for an extended period of time. Because handling used facemasks and respirators could also transmit the flu virus, wearers should be trained in how to remove and dispose of them safely. Careful handling of a contaminated mask or respirator may not be a reasonable expectation of young children.

“WHAT MAKES YOU THINK CHILDREN WOULD EVER KEEP THEM ON? OLDER CHILDREN -- A MATURE 8-YEAR-OLD -- MAYBE, BUT MASKS ARE VERY UNCOMFORTABLE. HAVING SOMETHING ON YOUR FACE IS SOMETHING CHILDREN DON'T LIKE.”

-- MARGARET FISHER, MD, FAAP, Chair of the Department of Pediatrics and Medical Director, The Children's Hospital at Monmouth Medical Center, Long Branch, New Jersey.

“HAVE YOU EVER TRIED TO PUT A MASK ON A 3-YEAR-OLD? THE PLACE WHERE A MASK MIGHT BE VALUABLE IS IN A HOSPITAL SETTING WHERE IT COULD BE ENFORCED. YOU CAN'T ENFORCE IT ELSEWHERE BECAUSE, IF IT'S UNSUPERVISED, THE MINUTE YOU TURN YOUR BACK ON A CHILD, THE MASK COMES OFF. AND I DON'T BLAME THE KIDS -- THEY'RE UNCOMFORTABLE.”

-- JOHN S. BRADLEY, MD, FAAP, Children's Hospital of San Diego, California.

INFECTION CONTROL IN HEALTH CARE FACILITIES

CDC recommends that all health care facilities, including pediatricians' offices and clinics, take extra precautions in the event of an influenza pandemic.

Public health experts believe that human influenza is primarily spread through large respiratory droplets. Given the current uncertainty about the exact modes by which avian influenza may first be transmitted among humans, CDC recommends additional precautions for healthcare workers who may confront suspected human cases of avian flu.

These include standard precautions, such as hand hygiene before and after all patient contact, particularly with items that might have become contaminated. CDC also recom-

mends that health professionals use gowns and gloves, N95 respirators, eye protection, such as goggles and face shields, as well as “dedicated” equipment, such as disposable blood pressure cuffs and thermometers. They also urge physicians to place patients in specially equipped airborne isolation rooms with monitored negative air pressure in relation to corridor, with 6 to 12 air changes per hour, and rooms that exhaust air directly outside or have recirculated air filtered by a high efficiency particulate air (HEPA) filter.⁶¹

Pediatricians often have separate “well” and “sick” waiting rooms for their young patients. No one knows yet whether separate waiting rooms will provide enough protection during a pandemic and few pediatric

practices or clinics would have sufficient isolation rooms. When separate isolation rooms are not feasible, physicians should make masks available to symptomatic patients who are able to wear them (adult

and pediatric sizes should be available) and provide facial tissues, receptacles for their disposal, and hand hygiene materials in waiting areas and examination rooms.⁶²

“HAVING WELL AND SICK WAITING ROOMS MIGHT BE SUFFICIENT, BUT THE BIG PROBLEM IS THAT PEOPLE ARE CONTAGIOUS A DAY BEFORE THEY GET SYMPTOMS. IN MOST OFFICES, THE AIR IS RECIRCULATED INTO EXAM ROOMS -- WE REALLY WOULD HAVE TO KNOW MORE ABOUT HOW LONG THE VIRUS STAYS ALIVE IN THE AIR. SEPARATE VENTILATION SYSTEMS ARE PROBABLY TOO EXPENSIVE. WE WILL NEED TO HAVE INFORMATION ABOUT THE SIZE OF THE VIRUS PARTICLES. BIG DROPLETS FALL TO THE GROUND BUT SMALL ONES STAY AIRBORNE. IF THEY TRULY ARE SMALL, AIRBORNE PARTICLES, THEN SYSTEMS DO MATTER.”

-- Margaret Fisher, MD, FAAP, Chair of the Department of Pediatrics and Medical Director, The Children's Hospital at Monmouth Medical Center, Long Branch, New Jersey.

If separate waiting rooms or separate ventilation systems became impractical or too expensive, pandemic flu could inspire the return of house calls, a practice which largely disappeared during the 1960s. Larger patient practice loads and managed care drove house calls into near-extinction. It became impractical, costly, and inefficient

for pediatricians to visit sick children in their homes, particularly if lab work needed to be performed. However, home visits could become a useful effective infection control approach in the event of influenza pandemic -- as long as pediatricians themselves take appropriate precautions when making home visits.

“HOUSE CALLS USED TO BE POPULAR BECAUSE PEOPLE DIDN'T HAVE TRANSPORTATION TO THE DOCTOR'S OFFICE. ONCE TRANSPORTATION BECAME AVAILABLE, IT BECAME MUCH EASIER TO SEE A CHILD IN THE OFFICE, ESPECIALLY SINCE A DOCTOR MAKING HOUSE CALLS DOESN'T HAVE THE BACKUP FACILITIES TO DO LAB TESTS AND BLOOD WORK. BUT IF PEOPLE ARE WORRIED ABOUT VECTORS (INFECTED CHILDREN) GOING OUT, HOUSE CALLS COULD BECOME USEFUL AGAIN. WE COULD TAKE A PLACE LIKE KANSAS CITY, AND DIVIDE IT INTO GRIDS, THEN ASSIGN GRIDS AMONG THE TOTAL NUMBER OF PEDIATRICIANS' OFFICES. WE'D HAVE TO MAKE HOUSE CALLS WEARING MASKS, AND PEOPLE WOULD HAVE TO BE TAUGHT HOW TO PROVIDE INTRAVENOUS FLUIDS AT HOME. IT WOULD REQUIRE A DIFFERENT HEALTH SYSTEM THAN THE ONE WE ARE FAMILIAR WITH NOW. THE SICKEST CHILDREN WOULD BE IN THE HOSPITALS, AND THE OTHERS COULD STAY HOME AND BE SEEN THERE.”

-- KURT METZL, MD, FAAP, University of Missouri-Kansas City School of Medicine, Kansas City, Missouri.

Hospitals treating children infected with pandemic influenza also will face major challenges. Finding additional medical surge capacity, confronting potential health care workforce shortages due to illness or responsibilities for caring for sick family members, and anticipating disruptions in delivery of medical supplies and drugs are issues likely to confront all hospital administrators. However when it comes to pandemic planning with respect to children and adoles-

cents, hospital officials need to consider that children may be admitted and/or discharged without a supervising adult due to the parent or guardian's illness, death, or other care-giving issues, which in turn complicates consent for treatment.⁶³ Advance planning for the physical, emotional, and psychological needs of very sick children, who also may be experiencing bereavement due to the loss of a family member or friend, is vital.

PART VI: Diagnostics

Rapid diagnosis during a pandemic outbreak will be essential for complying with isolation recommendations and early treatment.

Currently available rapid flu tests cannot be used to identify a pandemic strain of flu. As of now, tests for possible pandemic strains would have to be sent to special laboratories and would take longer for results.

Pediatricians' 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, poly-

merase chain reaction (PCR), rapid antigen testing, or immunofluorescence, which are tests that are used to identify specific flu strains, such as H5N1 or other strains of avian flu.

Also, the accuracy of laboratory tests may vary by strain. It could take days, even weeks, between a throat or a nasal swab and a final reading. Moreover, only CDC and a few other international labs have the high-level biosafety facilities needed to perform specialized tests that reveal critical details about a virus's geographic origin and other features.

“RAPID DIAGNOSTICS TESTS EXIST FOR SEASONAL FLU. WE USE THEM A LOT. WE USE THEM TO CONFIRM FLU CASES. IF THERE WAS AVIAN FLU AROUND, IT WOULD BE VERY USEFUL TO HAVE A RAPID TEST.”

-- KURT METZL, MD, FAAP, University of Missouri-Kansas City School of Medicine, Kansas City, Missouri.

NEW DIAGNOSTIC TOOLS

Most public health experts agree that additional tools are needed that can rapidly diagnose pandemic flu strains at the point of care where patients are first seen and treated after they become ill. These would include physicians' offices, urban and rural clinics, and hospital emergency rooms, among other sites.

PCR technology

In February 2006, FDA licensed a new laboratory test that uses PCR technology -- a process that amplifies gene sequences -- and can detect H5 strains of flu, including H5N1, within 4 hours after arriving at a lab. Previous testing technology required at least 2 to 3 days. The test is called the Influenza A/H5 (Asian lineage) Virus Real-time RT-PCR Primer and Probe Set. If the presence of the H5 strain is identified, then further testing is conducted to identify the specific H5 subtype (for e.g., H5N1). The use of this test is limited to laboratories designated by the Laboratory Response Networks, with about 140 facilities in the United States.⁶⁴

New microchip test

The flu diagnostics field has been moving rapidly. Scientists from the University of Colorado at Boulder and CDC have developed an inexpensive "gene chip" test based on a single flu virus gene that could allow scientists to quickly identify flu viruses, including avian influenza H5N1. The researchers used the "MChip" to detect H5N1 in samples collected over a 3-year period from people and animals in geographically diverse locales. In tests on 24 H5N1 viral isolates, the chip provided complete information about virus type and subtype in 21 cases and gave no false positive results. The "MChip" could provide a significant advantage over available tests because it is based on a single gene segment that mutates less often than the flu genes typically used in diagnostic tests. As a result, the MChip may not need to be updated as frequently to keep up with the changing virus.⁶⁵

The MChip has several advantages over the FluChip, a flu diagnostic previously developed by the same research team and announced in August 2006. While the FluChip is based on 3 influenza genes -- hemagglutinin (HA), neuraminidase (NA) and matrix (M) -- the MChip is based on 1 gene segment. Unlike HA and NA, which mutate constantly and thus are technically difficult to use to develop gene chip diagnostic tests, the M gene segment mutates much less rapidly. The researchers believe that a test based on this relatively unchanging gene segment will continue to provide accurate results even as the HA and NA genes mutate over time. Another potential advantage is that the MChip would, for the first time, create a way to simultaneously screen large numbers of flu samples to learn both the type and subtype of virus present. Current real-time tests provide information about the type of virus (type A or B) in a sample, but additional tests must be run to determine the virus subtype (for example, H5N1 subtype).⁶⁶

This work -- and the FluChip research announced last summer -- are regarded as important incremental steps in diagnostics. The raw materials for the MChip cost less than 10 dollars, and discussions are under way to commercialize its manufacture.⁶⁷

“ CHILDREN AND YOUTH ARE PART OF A COMPLEX SOCIAL NETWORK THAT SUPPORTS THEM AS THEY GROW, LEARN AND DEVELOP. THE RAMIFICATIONS OF A PANDEMIC ARE SIGNIFICANT FOR THIS VULNERABLE POPULATION; HENCE APPROPRIATE PREPARATIONS FOR THE NEXT INFLUENZA PANDEMIC MUST ADDRESS THE PHYSICAL, PSYCHOLOGICAL AND SOCIOLOGICAL IMPACT THE DISEASE WILL HAVE ON CHILDREN, YOUTH AND THEIR CAREGIVERS.”

-- FROM "PANDEMIC INFLUENZA PLANNING FOR CHILDREN AND YOUTH: WHO'S LOOKING OUT FOR OUR KIDS?" HEALTHCARE MANAGEMENT FORUM/CANADIAN COLLEGE OF HEALTH SERVICE EXECUTIVES, SPRING 2007.

PART V: Policy Recommendations

It is critical that the health and welfare of children are considered in all aspects of pandemic influenza planning. This requires support and collaboration from multiple partners at the local, state, and federal levels. Although many of the pandemic flu issues relevant to adults are also relevant to children, there remain several issues unique to children and adolescents that require recognition and attention in the ongoing extensive efforts to explore our nation's readiness for influenza pandemic.

TFAH and AAP recommend that the following actions be taken to better protect the nation's children in the event of a severe influenza pandemic. These recommendations reflect the views of TFAH and AAP and do not necessarily reflect the views of those individuals interviewed for this paper or those who served as peer-reviewers.

- Primary care providers, such as pediatricians and pediatric medical and surgical subspecialists, should be included in pandemic planning at all levels of government.
- The U.S. Department of Health and Human Services should conduct additional studies on vaccine efficacy in young children, support the development of additional flu vaccine products, and conduct more studies of antiviral agents for infants.
- The U.S. Department of Health and Human Services should immediately convene an independent task force to study and make specific recommendations about the use of surgical masks, N95 respirators, and other personal protective equipment by children.
- HHS should conduct further studies on the feasibility of prolonged school and childcare center closures, including a more precise assessment of the long-term interruption of the school meals programs and how to mitigate the impact on students who rely on them.
- The federal government should ensure that the Strategic National Stockpile includes sufficient pediatric doses of antiviral medications to ensure treatment of 25 percent of the nation's children and adolescents, or about 18.4 million individuals. This will require additional procurement of the flavored liquid Tamiflu over the 100,000 treatment courses already purchased by the U.S. Department of Health and Human Services.
- HHS should provide guidelines to state and local health departments for evaluating hospital surge capacity (i.e., equipment, personnel, etc.) for children.

■ All schools should educate students in infection control. Children should receive grade-appropriate health education about communicable diseases and methods to interrupt disease spread (cover cough, wash hands, etc). This education should include discussion of actions that might take place during a severe epidemic, such as prolonged school closures. Materials are available through many federal and state agencies -- particularly public health agencies -- to enable educators to determine appropriate activities.

■ Educators and school administrators should be encouraged to get an annual influenza vaccination and should remind families that public health experts recommend annual flu vaccines for 1) all children with high risk conditions who are 6 months of age and older; 2) all healthy children ages 6 months through 59 months; 3) all household contacts and out-of-home caregivers of children with high risk conditions and of children

younger than 5 years if age; and 4) all health care professionals. CDC and state and local health official departments should encourage and support seasonal flu vaccination clinics in school settings to maximize flu vaccine coverage rates.

■ Educators and public health officials should consider the potential psychological ramifications on the student population before, during, and after a pandemic. Psychologists and grief counselors should be made available, by telephone if face-to-face encounters are not immediately possible, to help students cope with illness and loss of family, fellow students, and friends.

■ Educators and public health officials should plan for “influenza free” daycare centers (with availability of point-of-care rapid testing for symptomatic children) to allow working parents who are essential to maintaining a functioning society and economy, to continue to go to work.



APPENDIX A: Influenza Viruses: A Primer

There are 3 types of influenza viruses, classified as type A, B, or C, based upon their protein composition. Type A viruses widely circulate in many kinds of animals, including ducks, chickens, pigs, whales, and also in humans, and cause epidemics and pandemics. The type B virus widely circulates in humans, causing epidemics but not pandemics. Type C has been found in humans, pigs, and dogs and causes mild respiratory infections, but does not cause epidemics.⁷⁷

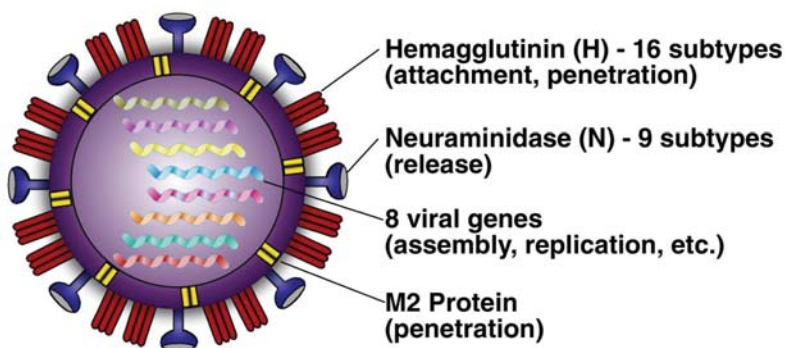
Type A influenza concerns public health officials the most. It was responsible for the 1918, 1957, and 1968 pandemics. Type A viruses are subdivided into groups based on two surface proteins on the virus, hemag-

glutinin, (HA), and neuraminidase (NA). Scientists have characterized 16 HA subtypes and nine NA subtypes.⁷⁸ These are often represented as H1 through H16 and N1 through N9.

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. This happens continuously, causing new strains of virus that are not recognized by the human immune system. This is why a new flu vaccine must be produced annually to protect against the year's most commonly occurring strains.

Type A influenza also undergoes infrequent and sudden extensive changes, called antigenic shift. Antigenic shift occurs when two different flu strains infect the same cell and exchange genetic material. The novel re-assortment of HA or NA proteins in a shifted virus creates a new influenza A subtype. Because people may have little or no immunity to such a new subtype, their appearance tends to coincide with pandemics.⁷⁹ 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.

Influenza A Virus



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

Avian Flu 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).⁸⁰

Global public health authorities are especially worried about a strain of avian flu known as H5N1. It is deadly to domestic fowl and several species of wild birds and can be passed from birds to humans. In recent years it has been circulating largely in Asia, and has proved especially dangerous to humans who become infected. The chief concern is that H5N1 could undergo mutations consistent with an antigenic shift that will make human-to-human transmission efficient and sustained, raising the likelihood of a pandemic.

APPENDIX B: Glossary of Terms and Acronyms

ACIP and NVAC: The Advisory Committee on Immunization Practices and the National Vaccine Advisory Committee, both advisory panels that study vaccines and make recommendations to the federal government regarding how and when to use them.

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 continuous small 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 large 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 influenza pandemics.

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: When used to describe a live vaccine, which 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. The Federal agency, based in Atlanta, responsible for investigating disease outbreaks, preventing and controlling infectious and chronic diseases, injuries, and workplace hazards. www.cdc.gov.

Epidemic: An epidemic is an outbreak of a 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.

Mask: A device used to cover the nose and mouth in order to prevent the transmission of microorganisms, such as bacteria and viruses.

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

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

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

NIOSH: The National Institute for Occupational Safety and Health (NIOSH) is the federal agency responsible for conducting research and making recommendations for the prevention of work-related injury and illness. NIOSH is part of the Centers for Disease Control and Prevention (CDC).

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: A disease epidemic that covers a wide global area.

Pediatric: Pertaining to children.

Polymerase: Any of many enzymes that catalyze the formation of DNA or RNA from precursor substances in the presence of pre-existing 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

Respirator: A device worn over the mouth or nose or both to protect the respiratory tract.

RNA: Ribonucleic acid. 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)

Social distancing: A term used to describe a public health intervention for isolation policies applied to specific groups, designed to reduce personal interaction and thereby disease transmission.

Stockpile: A supply stored for future use, usually carefully accrued and maintained. In the case of pandemic influenza, a national stockpile has been created to store vaccines and drugs.

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.

Vector: An entity that carries disease-causing microorganisms from one host to another. In this context, it is used to describe children who easily transmit infections because of their active social interactions.

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

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