Assuring the Influenza Vaccine Supply

by

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Abstract

Influenza disease epidemics occur seasonally in the United States and cause significant morbidity and mortality among certain high-risk groups. Influenza vaccines have been shown to decrease mortality and morbidity from influenza infection and are a safe and effective means of influenza prevention. Despite the availability of vaccine many high-risk groups are not vaccinated annually as is recommended by public health and medical experts. Lack of predictable, widespread vaccine uptake contributes to production and market issues affecting a consistently adequate and timely influenza vaccine supply. Problems with vaccine production in general are exacerbated by unique qualities of influenza vaccine production. Added to these problems is the urgent need to prepare for an impending influenza pandemic. Addressing these issues will involve public education and promotion of influenza vaccine, research and development of new vaccine technology and government intervention to assure a safe and adequate influenza vaccine supply.
Influenza Disease

Influenza is a contagious, viral respiratory infection characterized by fever, dry cough, sore throat, extreme fatigue, headache, nasal congestion and body aches (Centers for Disease Control and Prevention [CDC], 2005). Duration of the illness is most commonly 2-7 days however cough and malaise can continue for two weeks or more. Person to person spread occurs primarily via large respiratory droplets. Incubation period is short, from 1-3 days. The period of communicability for adults is probably 3-5 days from onset of symptoms and up to 7 days from clinical onset for children (Heymann, 2004, p. 283). Studies have shown that influenza viruses can live for 24 to 48 hours on nonporous environmental surfaces and less than 12 hours on porous surfaces. This indicates that transmission can occur when hands that touch contaminated surfaces subsequently come into contact with oral, ocular, or nasal mucosa. Fomite transmission appears to be rare (Bean, et. al., 1982).

Complications of influenza can include pneumonia, secondary bacterial infections, and exacerbation of underlying chronic heart or lung disease and death. An estimated average of 36,000 Americans die annually from influenza and 200,000 hospitalizations are attributed to this infection. (Thompson, et.al, 2003, 2004) In those aged greater than 65 years, influenza related deaths range from between 30 and 150 per 100,000 (World Health Organization [WHO], 2005). Groups more likely to suffer complications or severe disease are the elderly, very young children and those with chronic cardiac, pulmonary, renal, and metabolic disease and anemia or a compromised immune system (Heymann, 2004).
Treatment of influenza is largely palliative although there are antiviral medications that can be used successfully to mitigate symptoms and/or shorten the course of the illness by 1.5-2.5 days. Currently there are two classes of antiviral medication available for treatment of influenza. These are adamantanes or M2 ion channel inhibitors (i.e. amantadine and rimantadine) and neuraminidase inhibitors (i.e. oseltamivir and zanamivir). Adamantanes are effective only against influenza A. These drugs may be used for treatment or chemoprophylaxis for influenza A. The neuraminidase inhibitors are effective against both influenza A and B but are not approved in the U.S. for preventive treatment. The treatment for influenza infection must be initiated as soon as possible and within 48 hours after symptoms begin to be effective (Stiver, 2003). These medications are very useful in outbreak situations and for prophylaxis treatment for high-risk individuals. Recently one of the antiviral medications used to treat influenza, adamantane, was found to be ineffective because high levels of drug resistance had developed in the influenza A (H3N2) viruses. The CDC issued an alert to medical providers to use one of the other antiviral drugs (CDC, 2006). This development emphasizes the need for prevention of influenza and the focus on influenza vaccination as the foundation of a successful influenza prevention campaign (CDC, 2005).

An unstable virus. Two types of influenza virus cause epidemic human disease, influenza A and influenza B. Influenza A viruses cause large epidemics with high mortality. Influenza A is further classified into subtypes based on the surface antigens hemagglutinin (H) and neuraminidase (N). Influenza A (H1N3)
and (H3N2) viruses have been circulating worldwide since 1977. Both influenza A and B undergo genetic reassortment (antigenic drift), although influenza B viruses undergo these changes less rapidly than influenza A. These minor genetic changes that occur during viral replication produce virus variants that result in the need for seasonal changes in the influenza vaccine to match as closely as possible the circulating strains. (CDC, 2005).

Antigenic shift is a major genetic change in the virus, resulting in a new viral strain to which humans have little to no immunity. Proteins on the surface of the virus recombine as a result of mutation or exchange of genetic material between multiple influenza viruses. This dramatic mutation of influenza virus has historically caused flu pandemics. These flu pandemics have all been caused by influenza A viruses. Potential pandemic strains must have an antigenic makeup to which the population has no immunity, be able to replicate in humans, and efficiently transmit from human to human. New pandemic strains are most likely to be of subtypes not previously recognized in human populations. Currently, strains of H5 and H7 subtypes are of greatest concern (Centers for Infectious Disease Research and Policy, 2005).

The following table outlines differences between seasonal influenza and pandemic influenza.
## Assuring the Influenza Vaccine Supply

### Table 1

<table>
<thead>
<tr>
<th>Seasonal Influenza</th>
<th>Pandemic Influenza</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outbreaks follow predictable seasonal patterns; occurs annually, usually in winter, in temperate climates</td>
<td>Occurs rarely (three times in 20th century-last in 1968)</td>
</tr>
<tr>
<td>Usually some immunity built up from previous exposure</td>
<td>No previous exposure; little or no pre-existing immunity</td>
</tr>
<tr>
<td>Healthy adults usually not at risk for serious complications; the very young, the elderly and those with certain underlying health conditions at increased risk of serious complications</td>
<td>Healthy people may be at increased risk for serious complications</td>
</tr>
<tr>
<td>Health systems can usually meet public and patient needs</td>
<td>Health systems may be overwhelmed</td>
</tr>
<tr>
<td>Vaccine developed based on known flu strains and available for annual flu season</td>
<td>Vaccine probably would not be available in the early stages of a pandemic</td>
</tr>
<tr>
<td>Adequate supplies of antivirals are usually available</td>
<td>Effective antivirals may be in limited supply</td>
</tr>
<tr>
<td>Average U.S. deaths approximately 36,000/yr</td>
<td>Number of deaths could be quite high (e.g., U.S. 1918 death toll approximately 500,000)</td>
</tr>
<tr>
<td>Symptoms: fever, cough, runny nose, muscle pain. Deaths often caused by complications, such as pneumonia.</td>
<td>Symptoms may be more severe and complications more frequent</td>
</tr>
<tr>
<td>Generally causes modest impact on society (e.g., some school closing, encouragement of people who are sick to stay home)</td>
<td>May cause major impact on society (e.g. widespread restrictions on travel, closings of schools and businesses, cancellation of large public gatherings)</td>
</tr>
<tr>
<td>Manageable impact on domestic and world economy</td>
<td>Potential for severe impact on domestic and world economy</td>
</tr>
</tbody>
</table>

Note. From CDC website, [http://www.pandemicflu.gov/season or pandemic.html](http://www.pandemicflu.gov/season-or-pandemic.html) 
Retrieved March 5, 2006.

*Disease surveillance.* Unlike many communicable diseases, physicians and laboratories are not required to report individual cases of influenza to the health authorities. Surveillance for influenza in the U.S. is accomplished through
a system that includes World Health Organization (WHO) and National Respiratory and Enteric Virus Surveillance System (NREVSS) laboratories, a network of approximately 1500 sentinel sites that report influenza-like illness (ILI) patient visits, the percentage of U.S. deaths attributable to pneumonia and influenza (P&I) reported through the 122 Cities Mortality Reporting System and estimated levels of influenza reported to the Centers for Disease Control and Prevention (CDC) by state and territorial epidemiologists. The U.S. Influenza Sentinel Providers Surveillance Network includes physicians, hospitals, university health centers and public health agencies. These participants report ILI data to CDC each week and collect representative samples for virus strain identification. The case definition of ILI for these surveillance purposes is a fever of 100 degrees F or higher and cough or sore throat. Significant outbreaks of influenza, as well as reports of severe illness and death are also reported to the CDC by local health officials. (CDC, 2003,2005). This system of disease reporting allows the CDC and local and state health officials to monitor influenza activity in the nation.

*Economic burden of disease.* Total economic costs associated with influenza disease are difficult to calculate for various reasons. In many cases influenza infection is not confirmed in persons seen at a medical practice or admitted to the hospital. A diagnosis is made based on clinical symptoms and is not always confirmed by laboratory testing. The laboratory tests are often costly and are most often used for surveillance and in outbreak situations (Blitz, Cram, Monto, Fendrick, 2002). Many individuals who lose work or school days to
influenza infection may not been seen at a medical provider because of lack of health care coverage or if symptoms are relatively mild. However, it is estimated that approximately 62 million people restrict their work or school activities or seek medical care for influenza-like illness every year (AHA, 2004). Studies have been done to assess the burden to families of influenza disease in children. Prinicipi and Esposito (2004) reviewed studies that concluded that prevention of influenza in otherwise healthy school-aged children would have significant effects on the families. Results would include fewer missed workdays for adults and fewer hospitalizations and medical visits for the children and their household contacts. Because school-aged children are considered an important source of community-wide transmission of influenza, some experts have recommended mass vaccination of school-aged children to reduce the impact of influenza in the community (White, Lavoie, Nettleman, 1999; Halloran& Longini 2006).

A 2001 study of the economic burden of influenza-like illness (ILI) in long-term-care facilities in Virginia demonstrated the substantial cost associated with ILI. In the four facilities studied for the 1998-99 influenza season the mean costs for each case was between $968 and $1341, not including the cost of prophylaxis for asymptomatic resident contacts (Carroll et.al, 2001).

The most common complication of influenza is pneumonia. Since influenza may be confused with other respiratory infections and may not be laboratory confirmed in many cases, the mortality associated with influenza is often calculated in terms of excess deaths from pneumonia (WHO, 2005). A study by the Connecticut Department of Public Health estimated the economic
cost of influenza and pneumonia in their state in 1998 to be 170 million dollars in hospital admissions alone. The cost of influenza epidemics in the United States is estimated to be 12 billion annually (Bower, 2000).

Influenza vaccine

Influenza vaccines have been available for more than sixty years (WHO, 2002). Inactivated influenza vaccine is composed of antigens matching the two currently circulating wild influenza A viruses and an influenza B virus. Thus the vaccine is labeled a trivalent vaccine, protecting against three viral strains. Surveillance is used in the tropical regions of the world to determine which viruses are circulating and are likely to cause epidemic disease in the world’s temperate zones. The antigens are made non-infectious or “killed” in order to promote immunogenic protection without producing disease. There are three types of killed influenza virus vaccines: whole virus, split and subunit virus vaccines. Most industrialized countries use the split or subunit virus because it causes fewer vaccine reactions (WHO, 2005).

A live, attenuated influenza vaccine (LAIV) was approved for use in the United States in June 2003. The vaccine is currently approved for use in healthy, non-pregnant individuals aged 5-49 years. This vaccine, FluMist™, produced by Medimune, Inc. of Maryland, is administered intranasally. The efficacy of the vaccine was studied and found not to be significantly different from the inactivated influenza vaccine. Benefits of the LAIV are the vaccine’s potential to induce a broad mucosal and systemic immune response and administration by nasal spray rather than intramuscular injection. Drawbacks include storage
limitations (must be kept frozen prior to administration) and higher cost than the injectable vaccine (CDC, 2003). Obviously, the most important disadvantage to this vaccine is that it cannot be used to vaccinate high-risk individuals.

Vaccine efficacy. No vaccine is 100% effective in all individuals. Various factors influence the efficacy of the influenza vaccine. Most important is the accuracy of the match between the viral antigens contained in the vaccine and the particular pathogen to which the person is exposed. Factors contributing to the effectiveness of the vaccine include age and health status of the vaccinee and the accuracy of the diagnosis. In approximately 70-90% of healthy adults the trivalent vaccine will prevent laboratory confirmed illness (WHO, 2005). It is expected that those with compromised immune systems will experience less efficacy with vaccination. The Advisory Committee on Immunization Practices estimated only a 30-40% efficacy rate in the frail elderly (CDC, 1997). Trivalent influenza vaccines (TIVs) have been shown to be highly effective in children greater than 6 years old but demonstrate poor efficacy in children less than 2 years. There is no licensed influenza vaccine for infants less than 6 months old. Children less than 36 months old receive one-half the adult dose of vaccine and children aged less than nine years should receive two doses of vaccine administered one month apart. TIV can be administered at the same time as other recommended childhood vaccines.

Vaccine administration recommendations. The Advisory Committee on Immunization Practices (ACIP) is a group of experts selected by the Secretary of the U.S. Department of Health and Human Services to provide advice and
guidance on the most effective means to prevent vaccine-preventable diseases. This information is formalized via written recommendations for the administration dosage, schedule, and vaccine contraindications for pediatric and adult populations (CDC, NIP, n.d.). As data is gathered regarding morbidity and mortality attributed to influenza or ILI, new groups may be added to those recommended for influenza immunization. These guidelines are designed to provide vaccine coverage for groups at high risk for serious complications from influenza infection. This determination is based on influenza associated hospitalization rates and mortality. Included in the priority groups currently are contacts to high-risk persons including health-care workers and household contacts of children less than 6 months old (CDC, 2005).

Vaccine manufacturing. The manufacturing process for the influenza vaccine is a very complex process and is different than that of many other vaccines. As noted previously, the influenza vaccine changes or has the potential to change every year in order to match the strains of circulating influenza viruses. The vaccine cannot be stored but excess doses must be destroyed or disposed of after the end of the vaccination season.

Cultivation and development of the vaccine is very labor intensive and time consuming. Production time from start to delivery is approximately ten months (CDC, 2004). The virus is cultivated and grown in fertilized chicken eggs. The high-yield donor virus is in inoculated into the eggs and incubated for several days. One dose of vaccine is produced from one or two eggs (GSK, 2005).
The vaccine must be designed, developed, tested and ready for delivery in a short period of time. The influenza vaccine must be delivered to providers by October in order to be used to vaccinate high-risk individuals. In the United States influenza season runs from November to March. The time between vaccination and development of antibodies is approximately two weeks.

*Market factors.* Vaccine manufacturing is not as profitable as other pharmaceutical products. Medications are used far more frequently than vaccines and vaccine prices are strongly influenced by the federal government. The federal government, at a significantly lower price than private purchasers pay, purchases fifty-two percent of the childhood vaccines used in the U.S. This combination of factors has contributed to the abandonment of vaccine manufacture by many pharmaceutical companies (Cohen, 2002).

Influenza vaccine production is largely based on the previous year’s demand. This number can be variable and related to actual or perceived influenza activity, media reporting of deaths from influenza, etc. Few pharmaceutical countries in the United States produce influenza vaccine. Vaccines produced in other countries must be approved and licensed by the FDA for use in this country.

**Influenza Vaccine Delivery and Distribution**

Problems with influenza vaccine delivery and distribution were evident in the 2000 and the 2001 influenza vaccination season. In 2000 problems with vaccine manufacturing, including difficulty with one manufacturer growing one of the viral strains and two manufacturer’s regulatory problems with the Food and
Drug Administration (FDA) combined to create a significant delay in vaccine delivery. The decision in 2000 by one pharmaceutical company to permanently discontinue the manufacture of influenza vaccine along with continued regulatory problems with two pharmaceutical companies led to another less severe delay in delivery of influenza vaccine in 2001. While many in the public perceived these delays as shortages, they were not true shortages as the number of doses of influenza vaccine manufactured closely approximated the expected number. However many providers did not receive vaccine delivery during peak times of high demand. A major concern of many physicians and other community members was the uneven distribution pattern that allowed grocery store chains and other non-medical organizations to receive vaccine before hospitals, nursing homes and physicians offices (Fukuda, O'Mara & Singleton, 2002). One study in Tennessee surveyed elderly residents and found that the vaccine delay resulted in changes in the location where the flu shot was obtained but did not change vaccination rates in the patient sample (Santibanez, Nowalk, Zimmerman, Bruehlman, 2003).

A true influenza vaccine shortage emerged in October 2004 though it may not have been as extreme as widely reported. The U.S. pharmaceutical manufacturer, Chiron, announced that they would not be delivering the approximately 45 million expected doses of the influenza vaccine, Fluvirin. The Medicines and Healthcare products Regulatory Agency (MHRA) of the U.K. had suspended the manufacturing license for Fluvirin at the facility in Liverpool, U.K. Earlier in the fall of the year the company reported that in the final release
inspection they found bacterial contamination in a few lots of vaccine. This would mean a delay in vaccine delivery. The company completed internal investigations and submitted to reviews by the MHRA and expressed confidence that the problems were limited to the lots identified in August of 2004. However, on October 5, 2005 Chiron received a letter stating their manufacturing license had been suspended for three months for failure to follow Good Manufacturing Practice regulations in their operations ( Congressional Quarterly, 2004).

The media reported that this loss of vaccine cut the nation's flu vaccine supply in half. While this was technically true, when Chiron projected almost 50 million doses would be supplied to the U.S. this was more flu vaccine than had ever been available in this country before (Brookes). The average number of doses of influenza vaccine used in previous recent years ranged from between 70-80 million (Fukuda, 2002). With the doses supplied by the other licensed flu vaccine manufacturer, Aventis Pasteur, this created a supply for the U.S. market of almost 100 million doses. It is unclear if that many doses had been ordered or sold (Brookes). One study indicated that, based on immunization rates reported for high-priority groups in the 2002-2003 season, about 43 million doses would be enough to immunize the high-risk population in the U.S. in 2004 (Treanor, 2004). A report by the United States Government Accounting Office stated that for the 2002-2003 influenza season there were 95 million doses of vaccine produced. Of these, about 83 million doses were used (GAO, 2004). Ironically, just prior to the announcement that one of the two suppliers of flu vaccine in the U.S. would not be releasing their vaccine supply, federal and state officials had
made announcements expanding the recommendations for influenza vaccination. In the wake of the projected shortage these recommendations had to be restricted and vaccination limited to the priority groups defined by the CDC and ACIP (CDC, 2004).

The following is the list of priority groups for vaccination with inactivated influenza vaccine as determined by the CDC and ACIP for the 2004-2005 influenza season.

- all children aged 6–23 months;
- adults aged ≥65 years;
- persons aged 2–64 years with underlying chronic medical conditions;
- all women who will be pregnant during the influenza season;
- residents of nursing homes and long-term care facilities;
- children aged 6 months–18 years on chronic aspirin therapy;
- health-care workers involved in direct patient care; and
- out-of-home caregivers and household contacts of children aged <6 months (CDC, 2005).

The live attenuated intranasal vaccine was promoted for those eligible to receive it. The recommendation included health care workers with direct patient contact. Because it is a live virus vaccine, there is the potential of virus shedding by the vaccinee. The CDC and ACIP determined that only health care workers with direct patient contact with severely immunosuppressed patients should not receive the FluMist if they were otherwise eligible (CDC, 2003).
Affected populations. It was well documented in the media that the loss of the Chiron flu vaccine created severe problems in access for the most vulnerable populations, specifically elderly adults. Dramatic reports emerged of elderly patients waiting in lines for hours to be immunized. One elderly woman in California reportedly died after she fainted and fell during a four-hour wait for a flu shot (Boehm, 2004).

The Harvard School of Public Health conducted a national survey to determine the experiences with obtaining influenza vaccination among persons in high priority groups during this shortage. Table two shows the results of the survey, that approximately 63\% of those 65 and 46\% of chronically ill adults who attempted to get a flu shot were successful. Sixty-seven percent of the children aged 6-23 months who tried to obtain influenza vaccination received the vaccine.

Table 2

<table>
<thead>
<tr>
<th>Priority Group</th>
<th>%</th>
<th>(95%CI*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persons aged ≥ 65 years (n=242)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did not try to get vaccine</td>
<td>51</td>
<td>(42-59)</td>
</tr>
<tr>
<td>Tried to get vaccine</td>
<td>49</td>
<td>(41-56)</td>
</tr>
<tr>
<td>Could not get the vaccine</td>
<td>37</td>
<td>(28-46)</td>
</tr>
<tr>
<td>Received the vaccine</td>
<td>63</td>
<td>(54-72)</td>
</tr>
<tr>
<td>Persons with chronic illness (n=306)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did not try to get vaccine</td>
<td>63</td>
<td>(56-70)</td>
</tr>
<tr>
<td>Tried to get vaccine</td>
<td>37</td>
<td>(29-44)</td>
</tr>
<tr>
<td>Could not get the vaccine</td>
<td>54</td>
<td>(45-69)</td>
</tr>
<tr>
<td>Received the vaccine</td>
<td>46</td>
<td>(37-55)</td>
</tr>
<tr>
<td>Children aged 6-23 months (n=249)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did not try to get vaccine</td>
<td>50</td>
<td>(39-59)</td>
</tr>
<tr>
<td>Tried to get vaccine</td>
<td>50</td>
<td>(39-59)</td>
</tr>
<tr>
<td>Could not get the vaccine</td>
<td>24</td>
<td>(16-32)</td>
</tr>
<tr>
<td>Received the vaccine</td>
<td>76</td>
<td>(68-84)</td>
</tr>
</tbody>
</table>
The influenza vaccine shortage affected physicians as they were forced to make decisions about who would or would not receive a flu vaccination. While the CDC had defined priority groups for vaccination controlling administration of private vaccine supplies was virtually impossible. Access to vaccine varied widely with reports of some low-risk individuals getting immunized with no questions asked to elderly persons waiting in line for up to nine hours ("Flu vaccine ", 2004).


Figure 1. Physician responses when patients disagree with public health guidelines in an emergency.
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Their conclusions state that while the medical provider may not be able to comply with the patient’s request if it is contrary to public health guidelines the physician’s responsibility remains as the patient’s advocate, to address and acknowledge their needs and concerns (Lo & Katz, 2005).

Hospitals and long-term care facilities faced similar ethical decisions during the vaccine shortage. Some hospitals confronted issues of defining “direct healthcare workers” and explaining to some staff why they were not chosen to receive vaccine (Healthcare Benchmarks, 2004).

Despite the confusion, inconvenience and very serious consequences of the vaccine shortage crisis, it appears that in most cases the majority of high-risk groups who wanted the vaccine were immunized (CDC, 2004). This can in large part be attributed to the public health response from the federal level to state and local health districts. The CDC coordinated distribution of available vaccine after the October 5th Chiron announcement (NAACHO, 2005). In most cases the state and local health departments became the “brokers” for the distribution of vaccine supplies to the most vulnerable citizens utilizing the secure Web-based database developed by the CDC and Aventis Pasteur. This information allowed states to determine vaccine distribution in the private sector and identify gaps and excess supplies (Congressional Quarterly, 2004).

Public health agencies were challenged during this particular vaccination season. In many states public health agencies used disaster preparedness
plans to coordinate vaccine administration and secure doses of influenza vaccine for high-priority individuals (Bashir and Ransom, 2005). The public health infrastructure in many areas was burdened as workers were pulled from their usual jobs to respond to the flu vaccine shortage crisis.

Tables 3 and 4 show some of the results of a web-based survey conducted by the National Association of County and City Health Officials to assess the response of their members to the flu vaccine crisis and the impact on the routine public health activities.

Table 3

<table>
<thead>
<tr>
<th>Action</th>
<th>% of LPHAs Responding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Held late-season influenza clinics</td>
<td>60</td>
</tr>
<tr>
<td>Exercised and implemented preparedness plans, including conducting mass vaccination clinics</td>
<td>76</td>
</tr>
<tr>
<td>Rescheduled previously planned clinics</td>
<td>9</td>
</tr>
<tr>
<td>Cancelled clinics</td>
<td>39</td>
</tr>
<tr>
<td>Redistributed vaccine to local partners</td>
<td>38</td>
</tr>
<tr>
<td>Formed flu coalitions/community partnerships</td>
<td>94</td>
</tr>
<tr>
<td>Implemented priority schemes, including lotteries</td>
<td>19</td>
</tr>
<tr>
<td>Other</td>
<td>11</td>
</tr>
</tbody>
</table>

Table 4

<table>
<thead>
<tr>
<th>Action</th>
<th>% of LPHAs Responding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Communicable disease investigations, including surveillance</td>
<td>33</td>
</tr>
<tr>
<td>HIV/STD/TB testing, screening and services</td>
<td>9</td>
</tr>
<tr>
<td>Inspections</td>
<td>6</td>
</tr>
<tr>
<td>Family planning/WIC/nursing outreach services</td>
<td>24</td>
</tr>
<tr>
<td>Administrative activities</td>
<td>30</td>
</tr>
<tr>
<td>Trainings</td>
<td>22</td>
</tr>
</tbody>
</table>

Responses to vaccine shortage. Unfortunately, there were some unsavory reactions to the flu vaccine shortage crisis. There were reports of price gouging, theft of vaccine and other drastic responses ("Flu vaccine", 2004). Many U.S. citizens traveled to Canada to obtain a flu shot (Brookes).

The U.S. Department of Health and Human Services did purchase vaccine that was not licensed for use in this country. Glaxo SmithKline provided 1.5 million doses of Fluvarix, which was approved for use in Germany (GAO, 2005). For legal purposes the vaccine must be administered as an investigational drug and the recipient was required to sign a waiver before the vaccine could be administered. In addition to the relatively late arrival of the vaccine, in December 2004, reluctance by many citizens to sign the waiver and some citizens' concerns about safety meant that none of these doses were used (Desroches, et al, 2005, GAO, 2005).

Prior to the eventual reallocation of sufficient flu vaccine to immunize the high-risk population, the dose-sparing strategies of using ½ of the adult dose and intradermal versus intramuscular injection were considered. These strategies had been studied previously and were found to have some validity (Treanor, et al., 2002, Kenney, et al., 2004).

In lieu of being vaccinated, persons not eligible for either the live virus intranasal vaccine or the inactivated vaccine were advised to use common-sense influenza prevention measures. Respiratory hygiene was stressed, as well as
frequent hand washing and staying home when ill (CDC, 2004, Healthcare
Benchmarks, 2004).

Local public health agencies as well as private providers grappled with
distributing the limited vaccine to the priority groups (Brookes, 2005,). At the
time, the CDC was not willing to further prioritize vaccine delivery within the
defined groups. The problem did prompt the CDC to create an ethics committee
to debate such questions of rationing of vaccine during times of extreme
shortages or limited supply.

In August 2005 the CDC and ACIP provided tiered recommendations for
use by state and local health officials in the event of another vaccine shortage.
The guidelines state that the groups in tier 1A should be vaccinated before
anyone in an extreme shortfall of vaccine. During less dramatic vaccine
shortages all groups in tier 1 should be considered equivalent and should be
vaccinated first, followed by groups 2 and 3.

Table 1 Priority Groups for Vaccination with Inactivated Influenza Vaccine

<table>
<thead>
<tr>
<th>Tier</th>
<th>Priority Group</th>
</tr>
</thead>
</table>
| 1 A  | • Persons aged ≥ 65 years with comorbid conditions  
|      | • Residents of long-term-care facilities         |
| 1 B  | • Persons aged 2-64 years with comorbid conditions  
|      | • Persons aged ≥ 65 years without comorbid conditions  
|      | • Children aged 6-23 months                      
|      | • Pregnant women                                 |
| 1 C  | • Health-care personnel                          
|      | • Household contacts and out-of-home caregivers of children |
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2

<table>
<thead>
<tr>
<th>aged &lt; 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
</tr>
<tr>
<td>- Household contacts of children and adults at increased risk of influenza-related complications</td>
</tr>
<tr>
<td>- Healthy persons aged 50-64 years</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>- Person aged 2-49 without high-risk conditions</td>
</tr>
</tbody>
</table>

Note. From MMWR Vol. 54 No. 30

Discussion

*Increasing influenza vaccine uptake.* One of the goals of Healthy People 2010 is to increase the influenza immunization rate among high-risk populations, up to 90% of those over age 65 and up to 60% for other high-risk individuals (CDC, 2000). Data collected from national surveys indicate that vaccine uptake, even in times of sufficient supply and especially among those at highest risk is woefully inadequate. The following tables illustrate the deficits in immunizing these high priority groups in the two previous influenza vaccination seasons.

Table 5

<table>
<thead>
<tr>
<th>Selected Group</th>
<th>Percentage Coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages 18-49, High-risk</td>
<td>24.2</td>
</tr>
<tr>
<td>Ages 50-64, High-risk</td>
<td>46.3</td>
</tr>
<tr>
<td>Ages 50-64, Total</td>
<td>36.8</td>
</tr>
<tr>
<td>Ages 65 and older</td>
<td>65.5</td>
</tr>
<tr>
<td>Pregnant Women</td>
<td>12.8</td>
</tr>
<tr>
<td>Health Care Workers</td>
<td>40.1</td>
</tr>
<tr>
<td>Household Contacts</td>
<td>18.9</td>
</tr>
</tbody>
</table>

From the 2003 National Health Interview Survey, coverage level data for selected groups targeted for influenza vaccine (CDC, 2005).
Table 6

<table>
<thead>
<tr>
<th>Selected Group</th>
<th>Percentage Coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages 18-64, High-risk</td>
<td>25.5</td>
</tr>
<tr>
<td>Ages 65 and older</td>
<td>62.7</td>
</tr>
<tr>
<td>Ages 6-23 Months</td>
<td>48.4</td>
</tr>
<tr>
<td>Ages 2-17, High-risk</td>
<td>34.8</td>
</tr>
<tr>
<td>Health Care Workers</td>
<td>35.7</td>
</tr>
</tbody>
</table>

From the Behavioral Risk Factor Surveillance System (BRFSS), selected data collected during the 2004-05 influenza season (CDC, 2005).

Health care workers. CDC has recommended influenza vaccination for healthcare workers (HCWs) with direct patient contact since 1984 and for all HCWs since 1993 (Talbot, et al, 2005). Despite this it is estimated that only 36-40% of HCWs receive flu vaccine each year (CDC 2005). Vaccination of health care workers key in controlling influenza spread to high-risk individuals.

Surveys of unvaccinated HCWs show that reasons for not receiving the vaccine reflect those cited by members of the general public. The reasons include, 1) procrastinated/forgot; 2) inconvenience; 3) concerns about adverse effects; 4) belief that the vaccine is ineffective; 5) fear of needles; and 6) belief that influenza is not a serious disease (Toy, Janosky & Laird, 2005; Roush, 2005; Zimmerman, et al).

The Immunization Action Coalition, a non-profit organization, creates and distributes educational material for health professionals and the public that promote the safe and effective delivery of immunization services. Their stated
goal is to increase immunization rates and prevent disease. The following are steps outlined for health care institutions to establish an influenza vaccination program for their staff. The steps to include:

- Persuade top management to commit to an annual employee vaccination program.
- Make the vaccination program convenient for all employees.
- Offer vaccines free of charge to all staff—full-time, part-time, and volunteers.
- Develop campaigns to educate employees.
- Educate health care workers to be advocates for influenza vaccination.

(Immunization Action Coalition, 2004).

**Vaccination of children.** The CDC has recommended annual influenza immunization for high-risk children 6 months of age or older for almost 40 years (Rickert, Santoli, Shefer, Myrick, Yusuf, 2006). Although in the past the flu vaccine has not been recommended for healthy children, today vaccination of children 6-23 months of age is strongly recommended by the Advisory Committee on Immunization Practices.

However, vaccination of high-risk children remains unacceptably low. Research has shown that medical provider recommendation is a strong motivator for receiving influenza vaccination (Mayo & Cobler, 2004). One study researched reasons that physician adherence to national recommendations to administer influenza vaccine to high-risk children remains low. Their findings suggest a combination of factors including lack of coordination of care among specialist and
generalists and a need for more organizational capacity for identifying and recalling high-risk patients (Rickert, Santoli, Shefer, Myrick, Yusuf, 2006).

Of course parents are the target of educational interventions and recommendations related to immunization of children. Because children already are required to have numerous vaccines some parents avoid the influenza vaccine. A Denver study of five pediatric practices showed a substantial positive change in parental attitudes about influenza vaccination during the 2003-2004 flu season. This was attributed to an intensively publicized influenza outbreak and concurrent physician recommendation for vaccination (Daley, et al, 2006).

Public education. Unfortunately the public underestimates flu as an illness. Experts agree that education is necessary to achieve broader public understanding of the morbidity and mortality of influenza and the safety and efficacy of the flu vaccine (Zimmerman, et al, 2003). Education about all forms of influenza protection, including the nasal spray vaccine is necessary (DesRoches, Blendon & Benson, 2005). Some have suggested direct to consumer advertising to those aged 65 years and older would be a cost-effective method of promoting influenza immunization in this age group (Patel, et al, 2006).

Assuring the vaccine supply. Concerns about the influenza vaccine supply have been an issue for several years. Shortages of other vaccines recently have heightened the fear of influenza vaccine shortfalls (Cohen, 2002). The influenza supply is even more precarious for reasons noted previously: 1) the varying demand for vaccine; 2) inability to stockpile vaccine beyond one influenza
season; 3) complexity of influenza vaccine development and 4) the dearth of manufacturers supplying flu vaccine.

In 1993 the Institute of Medicine (IOM) proposed the development of a National Vaccine Authority that involves the creation of a government-owned, contractor operated national vaccine facility (IOM, 2001). This authority would control production and distribution of all vaccines and monitor supply and demand. This plan is widely opposed by the pharmaceutical industry (Cohen, 2002).

There has been legislation introduced to address the problems of influenza vaccine supply. The Flu Protection Act introduced by Congressman Rahm Emanuel of Illinois in 2004 establishes funds for a influenza vaccine public awareness campaign and provides tax incentives for companies to improve their production capacities. The measure also calls for funds for the creation of more vaccine companies with more rapid production capability, requires planning by the CDC for any future influenza vaccine shortages and calls for more accurate estimates of needed vaccine each year through greater cooperation between manufacturers and the federal government (US House of Representatives, 2005).

Senators Hillary Clinton of New York and Pat Roberts of Kansas introduced the Vaccine Security Act in 2005. Components of the bill include:

- Market guarantees:
  - Health and Human Services would set annual targets for influenza vaccine production
The Secretary authorized to stockpile and buyback vaccine and purchase antivirals.

Companies wishing to participate in buyback program must supply information allowing CDC to track distribution of vaccine.

Manufacturers must give 12 months notice to the Secretary before deliberately discontinuing influenza vaccine production.

Regulatory assistance to manufacturers.

- Increased research into vaccine development alternatives:
  - Additional financing for NIH research into alternatives such as cell-based culture and permanent influenza vaccine.
  - Establishment of county by county electronic vaccine tracking system.
  - Development of medical personnel registry to help during emergencies including influenza vaccine shortages.
  - Increased outreach and education on influenza vaccine.

- Pandemic vaccine liability:
  - Liability protections for products specifically design for pandemic flu (U.S. Senate, 2005).

Senator Richard Burr of North Carolina introduced the Pandemic Vaccine and Drug Development Act of 2005 to the U.S. Senate. One of the components of this bill is the creation of the Biomedical Advanced Research and Development Agency (BARDA). This legislation would support research and development in the vaccine industry among other measures (Kling, 2005).
None of the above mentioned legislation has been passed yet. All the proposals are designed to strengthen and organize the nation’s influenza vaccine supply and distribution process. The increasing reports of Avian influenza and the prediction of an impending influenza pandemic have benefited the goal of overhauling this country’s interpandemic flu vaccine infrastructure. As part of the National Pandemic Influenza Preparedness and Response Plan, the U. S. Department of Health and Human Services has awarded a $75 million grant to Sanofi Pasteur to develop cell-based rather than egg-based influenza vaccine technology. The plan also calls for a U.S. based manufacturing facility for the cell-based influenza vaccine (Kling).

The cell-based technology has several advantages over the egg-based production of flu vaccine. This process avoids risks associated with the egg-based technology: potential impurities in eggs that may cause sterility problems and allergies to egg albumin. The step of adapting the virus to grow in eggs is avoided. The procurement of millions of eggs and long timeline from inoculation to delivery is unnecessary. Virus grown in mammalian cell culture is identical to the original clinical isolates. Growth of viruses in eggs result in antigenic variants that are distinct from the original virus. The cell culture vaccine more accurately matches the wild circulating virus (Glaxo SmithKline [GSK], n.d.). Another considerable advantage of the cell-based technology is the ability to ramp up production fairly quickly in times of need. The cell cultures can be frozen for future use.
Assuring the Influenza Vaccine Supply

Research and public health recommendations. Obviously research into the development of new influenza vaccine is important and is already underway. While the egg-based technology is well established, cost-effective and proven to produce effective vaccine, there are disadvantages (GSK). The goal of eliminating these issues fosters further research and development. Until these new methods are developed and established, strategies to assure an adequate influenza vaccine supply must be addressed as well as contingency plans for another vaccine shortage.

Halloran and Longini (2004) suggest research is needed to determine whether increased influenza vaccine coverage in schoolchildren would reduce overall influenza attack and death rates in the community as a whole. This kind of data could guide vaccine rationing in times of shortfall and also inform public education and marketing techniques for influenza prevention.

Mayo and Cobler (2004) identify the need for a comprehensive study to compare motivators, barriers and decision making of vaccinated versus unvaccinated patients. Again, this would be useful information for designing promotional programs as well as helping clinicians educate clients and their colleagues.

Decisions will have to be made on the best method to assure an adequate yearly supply of influenza vaccine. Should the government provide the industry with tax incentives or subsidies in order to avoid the shortages that have occurred? Some of the proposals presented by legislators and others prefer that the government begin to manufacture and distribute the vaccine to avoid the
market forces that have contributed to the departure of influenza vaccine manufacturers from the market. Perhaps there should be a compromise as in Canada, which has two sources of influenza vaccine, the government supplied at no cost to high-risk persons and privately supplied vaccine for pay for all others (Boehm). At the least, there must be both public and private investment in manufacturing surge capacity and partnerships to more efficiently and effectively serve the public. A report by the United States Government Accountability Office (GAO) on the vaccine shortage of 2004-2005 concluded that, “planning, timely action, and communication are key to an effective response” (GAO, 2005, p.23).

Lessons learned from the influenza vaccine crisis will enable public health agencies from the local to the federal level to develop communication and emergency response plans to deal with a similar situation in the future.

**Conclusions.** Achieving the goal of high levels of influenza vaccine coverage will backfire if there is not a consistently adequate, timely, and accurately distributed supply of influenza vaccine. Conversely, increased demand for influenza vaccine will enable vaccine manufacturers to profit from vaccine manufacturing and provide incentive for continued private and public investment in the industry. In addition, advances in influenza vaccine technology and production are an integral component of planning for an impending influenza pandemic response.
References


Center for Infectious Disease Research and Policy, University of Minnesota. *Pandemic Influenza*. Retrieved February 22, 2006 from cidrap.umn.edu/cidrap/content/influenza/panflu/biofacts/panflu.html


