INTRODUCTION

During the past decade, substantial increases in the production 
and distribution of influenza vaccine have been critical for 
improving vaccination coverage among groups specifically tar-
geted for vaccination, as well as among healthy persons in the 
U.S.\textsuperscript{1} The increases have been critical because annual vaccina-
tion is the cornerstone of efforts to reduce the health burden 
from influenza, a respiratory infection resulting in an average of 
approximately 20,000 deaths and 114,000 hospitalizations per 
year in the U.S.\textsuperscript{2,3,4}

The vaccine used in the U.S. contains three inactivated 
(killed) influenza virus strains, antigenically similar to contem-
porary circulating virus strains. Three manufacturers (Aventis 
Pasteur, Evans Vaccines, Ltd., and Wyeth Lederle Laboratories) 
currently distribute influenza vaccine in the U.S. Vaccine from 
Aventis and Wyeth is approved for use in persons six months of 
age and older, whereas vaccine from Evans is approved for use 
in persons four years and older, because efficacy data for use in 
younger children have not been submitted to the Food and 
Drug Administration (FDA).

In most years, vaccine typically has been available to practi-
tioners and other vaccine providers by October and November, 
the optimal months for vaccination against influenza in the U.S. 
In 2000 and 2001, however, the availability of influenza vaccine 
was significantly lower during those months than in previous 
years, which left many clinicians and patients unable to find vac-
cine and led to the cancellation of many vaccination cam-
paigns.\textsuperscript{5,6} Ironically, in both years, increasing supplies of 
vaccine became available in December, but the waning levels of 
demand resulted in substantial surpluses of unused vaccine.

The difficulties and complications associated with the pro-
duction and distribution of influenza vaccine make it unique 
among current vaccines. Two of the primary reasons for this sit-
uation are the need to update influenza vaccines annually, so the 
vaccine strains remain antigenically similar to the viruses in cir-
culation, and the need to complete all manufacturing, regulato-
ry, and distribution steps within very short time frames, so that 
sufficient vaccine supplies are available to providers in time for 
winter influenza epidemics. In this article, we briefly review the 
recent influenza vaccine distribution delays, key points about 
the influenza vaccine production and distribution processes, and 
steps that should be considered to strengthen the influenza vac-
cine supply system.

BACKGROUND

The 2000 and 2001 Vaccine Delays

The magnitude of the 2000 and 2001 vaccine distribution 
delays is best illustrated by comparing the volume of vaccine 
delivered by manufacturers by the end of October in those 
years with the amount of vaccine delivered by the same time 
point in 1999 (Figure 1). In 1999, four manufacturers distribut-
ed a combined total of approximately 75.8 million doses of vac-

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Cumulative Monthly Influenza Vaccine Distribution, U.S., for 1999, 2000, and 2001\textsuperscript{1,2}}
\end{figure}

\textsuperscript{1} Data presented in this figure were supplied by the current three 
influenza vaccine manufacturers to Centers for Disease Control and 
Prevention (CDC).

\textsuperscript{2} These data represent aggregate monthly distribution of influenza 
Delayed Distribution of Influenza Vaccine

cine (99% of the year’s total) by the end of October. By contrast, in 2000 and 2001, three manufacturers distributed a combined total of approximately 26.6 million (38% of the year’s total) and 43 million (55% of the year’s total) doses of vaccine, respectively, by the end of October. The volume of vaccine delivered by the end of October is an important benchmark because October and early November, traditionally, have been the months of peak influenza vaccine demand in the U.S.7

The basis for the delays differed somewhat by year. In 2000, some manufacturers experienced difficulties growing and processing the influenza A (H3N2) vaccine strain. Such difficulties are not unusual, especially early in the production and processing of new vaccine strains. Different manufacturers employ different manufacturing techniques, which can affect how well a specific influenza virus strain grows or processes for a particular manufacturer. As a result, some manufacturers might experience difficulties growing or processing a particular strain in a certain year, while other manufacturers do not experience similar difficulties. In any case, manufacturers commonly “tweak” or make minor adjustments (within a range of established and validated parameters) to their vaccine production processes to optimize the yield of vaccine strains.

In 2000, however, two of the four manufacturers also experienced regulatory issues related to the FDA’s current Good Manufacturing Practices (GMP). The combination of growth and processing problems related to one strain and unrelated current GMP issues resulted in an unprecedented distribution delay of approximately six weeks.

During the summer of 2000, responses to the delay were complicated by continued uncertainty over the potential magnitude of the delay and the question of whether a significant absolute shortage would occur. Uncertainties about these issues made it difficult, in turn, to widely communicate precise information about the delays. One of the steps taken by Centers for Disease Control and Prevention (CDC) in the late summer, as insurance against the possibility of a significant shortage, was to contract with Aventis Pasteur for the production of an additional nine million vaccine doses, beyond the company’s planned production. These doses first became available to providers in early December, but by that month, the national demand for vaccine had waned substantially; eventually 7.5 million of these vaccine doses remained unused.

Also in 2000, Parkdale Pharmaceuticals, Inc. decided to permanently stop production of influenza vaccine, leaving Aventis Pasteur, Evans Vaccines, Ltd., and Wyeth Lederle Laboratories as the remaining companies selling influenza vaccine in the U.S. The time needed by these manufacturers to expand their vaccine production and to make up for the loss of Parkdale Pharmaceuticals, as well as continued current GMP issues experienced by one of the three manufacturers, led to a second, albeit less severe, influenza vaccine distribution delay in 2001.

A major consequence of the 2000 delay, and to a lesser extent the 2001 delay, was a situation in which some providers received limited or no supplies of vaccine while other providers were able to procure full allotments during periods of high vaccine demand. In some instances, vaccine was delivered to community- or work-site-based clinics and large store chains before delivery of vaccine to physician offices, hospitals, and nursing homes. The prices of vaccine to some providers also increased. A group of physicians surveyed by the General Accounting Office indicated that the average price paid by them for vaccine ordered in June was $2.90 (range: $1.90–$6.35), which rose to an average of $6.98 (range: $2.50–$12.80) per dose in October and November.7 The uneven distribution of vaccine, coupled with price increases and increasing provider concerns about inadequate reimbursement for influenza vaccination activities, provoked strong reactions and expressions of concern by many physicians and others.

The uneven distribution patterns largely reflected the differing rates at which companies were able to produce and distribute vaccine to secondary distributors or to end-users of vaccine, as well as the free market nature of the influenza vaccine distribution system. This distribution situation stands in contrast to that for pediatric vaccines, for which the federal government has a substantial role. For example, CDC establishes contracts for the purchase of substantial amounts of vaccine on behalf of state and territorial health departments through the Vaccines for Children Program. No governmental or single private entity has a similar central coordinating role in the distribution of influenza vaccine to providers.

Recent Patterns in Influenza Vaccine Production and Distribution

Among the current manufacturers, Aventis Pasteur and Wyeth Lederle produce influenza vaccine in manufacturing plants located in the U.S. while Evans Vaccines produces influenza vaccine in the United Kingdom, but distributes a percentage of their production in the U.S. In most years, more doses of influenza vaccine are produced by manufacturers, and are released by the FDA, than are distributed. For example, in 1999, 2000, and 2001, respectively, the manufacturers produced combined totals of approximately 77.2 million, 77.9 million, and 87.7 million doses of influenza vaccine while distributing, in those same years, an estimated 76.7 million, 70.4 million, and 77.7 million doses.
Vaccination coverage levels have also increased to about 46% in the 1999–2000 season among persons 50–64 years of age with high-risk medical conditions and to about 28% among persons 18–49 years of age with high-risk medical conditions (Table 1). Nonetheless, vaccination coverage levels in these groups remain far below the target level of 60% set by the 2000 and 2010 Healthy People objectives. Among adults aged 18 to 49 without identified high-risk conditions, the use of influenza vaccine is also low, but it has increased substantially from 12.5% in the 1996–1997 influenza season to 17.3% in the 1999–2000 season.

In the 1999–2000 influenza season, approximately one-half of all administered influenza vaccine doses went to groups of persons at high risk for complications from influenza, i.e., those over 65 years of age and younger persons with a high-risk medical condition, while another one-fourth was administered to other target groups, i.e., those 50 to 64 years of age or those under 50 who were in close contact with high-risk persons. The remaining vaccine was utilized by healthy persons under 50 years of age (Table 1).

### Expanding Recommendations for Influenza Vaccine Use

An important consideration related to increasing influenza vaccine use is the recent expansion of groups targeted for influenza vaccination by the Advisory Committee on Immunization Practices (ACIP), an advisory group to CDC. The ACIP has a central role in developing U.S. vaccination policy and has long targeted influenza vaccination efforts toward groups at elevated risk for developing severe complications from influenza infection, as well as persons in close contact with the “high-risk” groups. The “high-risk” groups include persons over 65 years of age, as well as younger persons with one or more medical conditions (including a chronic pulmonary or cardiac condition, diabetes, an immunosuppressive state or condition and the second or third trimester of pregnancy). The “close contact” group includes health care workers and family members. In 2000, the ACIP also began recommending influenza vaccination of all persons 50 to 64 years of age, primarily to increase vaccination levels among persons in this age group with high-risk medical conditions.

The combined number of people for whom influenza vaccination is currently recommended is approximately 152 million people, including 75 million in the high-risk category and 77 million in the other targeted groups (Table 1). In 2002, ACIP also began encouraging annual influenza vaccination for all children six through 23 months of age and their close contacts. The number of persons for whom influenza vaccination is recommended or encouraged is much greater than the current levels of vaccine demand. Nonetheless, the continued efforts of ACIP and other groups to expand influenza vaccine usage, coupled with important demographic trends such as the rapidly growing numbers of elderly persons, suggest that the demand for influenza vaccine could increase substantially in the future.
Delayed Distribution of Influenza Vaccine

### Table 1 Estimated Vaccine Use Among Persons at High Risk for Complications From Influenza, Other Target Groups, and Other Persons, 1999–2000 Influenza Season, U.S.

<table>
<thead>
<tr>
<th>Group</th>
<th>Population (millions)¹</th>
<th>Percent Vaccinated²</th>
<th>Vaccine Doses Used³ (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High Risk</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65+ yrs</td>
<td>74.9</td>
<td>47.3%</td>
<td>35.4</td>
</tr>
<tr>
<td>Chronic Illness⁴</td>
<td>35</td>
<td>68.1%</td>
<td>23.8</td>
</tr>
<tr>
<td>50-64 yrs</td>
<td>12.3</td>
<td>45.5%</td>
<td>5.6</td>
</tr>
<tr>
<td>18-49 yrs</td>
<td>18</td>
<td>27.5%</td>
<td>5</td>
</tr>
<tr>
<td>6 mo. to 17 yrs</td>
<td>7.6</td>
<td>10%</td>
<td>0.8</td>
</tr>
<tr>
<td>Pregnant Women⁶</td>
<td>2</td>
<td>10%</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Other (Healthy) Target Groups</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health Care Workers &lt;65 yrs⁷</td>
<td>7</td>
<td>42.3%</td>
<td>3</td>
</tr>
<tr>
<td>Other persons 50-64 yrs</td>
<td>27.6</td>
<td>32.9%</td>
<td>9.1</td>
</tr>
<tr>
<td>Household Contacts &lt;50 yrs</td>
<td>42</td>
<td>18%</td>
<td>7.6</td>
</tr>
<tr>
<td>Of those at high risk⁸</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Non-target persons &lt;50 yrs</strong></td>
<td>127.9</td>
<td>13%</td>
<td>16.6</td>
</tr>
<tr>
<td>Total, persons aged &gt;5 mo.</td>
<td>279.4</td>
<td>25.7%</td>
<td>71.7</td>
</tr>
</tbody>
</table>

1. Based on 2000 population estimates (Census Summary File 1, Matrices P13 and PCT12, U.S. Census Bureau).
2. Except where noted, estimated using persons interviewed during January through March 2000 for the National Health Interview Survey (NHIS) and responding to questions about receipt of influenza vaccine during the prior 12 months (preliminary public use data from the 2000 NHIS, National Center for Health Statistics).
3. Estimated population times estimated proportion vaccinated.
4. Estimated number of persons at high risk for influenza complications because of chronic illness based on age-specific population from 2000 census and estimated proportion of persons (or parents for persons aged <18 years) reporting selected medical conditions for the 2000 NHIS (provisional data) (29.3% for persons aged 50-64 and 13.6% for persons aged 18-49). For persons aged 18-49, reported medical conditions included having one or more of the following conditions: ever having been told by a physician that they have diabetes, emphysema, coronary artery disease, angina, heart attack, or other heart conditions; being diagnosed with cancer in the past 12 months (excluding non-melanoma skin cancer) or ever being told by a physician that they had lymphoma, leukemia, or blood cancer; being told by a physician in the past 12 months that they have chronic bronchitis or weak or failing kidneys; or reporting an asthma attack or episode in the past 12 months. For children aged <18 years, high-risk conditions included ever having been told by a physician of having diabetes, cystic fibrosis, sickle cell anemia, congenital heart disease, other heart disease, and/or asthma. Estimate for children was based on average of estimates using either asthma ever diagnosed, or asthma episode or attack in the prior 12 months (7.4%–14.2%).
6. Estimate of women who would be past first trimester of pregnancy based on four million births in the U.S. multiplied by 7/12, the proportion of births during the first year for which the mother would be past the first trimester for a month during three- or four-month influenza season, assuming nine-month average pregnancies and equal distribution of births per month, with adjustment to exclude women with chronic illnesses (12%–14%). Vaccine coverage based on NHIS estimates of women reporting that they were pregnant at the time of the interview.
7. Based on self-reported occupation from the 2000 NHIS.
8. Estimates of healthy household contacts based on multiplying the estimated number of high-risk persons by the average number of household contacts (from the NHIS), stratified by age groups. Adjustments were made to account for multiple numbers of persons per household likely to be at high risk. A mid-range estimate is presented in this table. Vaccine coverage assumed to be 18% for household contacts <50, based on 2000 NHIS vaccination coverage estimates for persons living with someone aged 65 or older, or a high-risk child.
9. Assumes 5% coverage among children aged <18 years who are not high-risk and do not live in a household with someone at high risk, and uses an estimate of 17.3% coverage for adults aged 18–49 not in vaccine target groups.

### CRITICAL COMPONENTS OF THE INFLUENZA VACCINE PROCESS

The public and private sectors both play extensive and critical roles in the influenza vaccine process. Primary responsibilities of the public sector include monitoring changes among circulating influenza viruses, annually updating the vaccine strains, monitoring the vaccine’s effectiveness and coverage rates, and developing recommendations to guide vaccine use. Primary responsibilities of the private sector include the production, distribution, and administration of the vaccine. Both sectors share the responsibility for ensuring the safety and potency of the vaccine. The manufacturers conduct quality-control checks at all stages of the production process while the FDA conducts safety and potency checks on monovalent and trivalent vaccine lots before they are released. In addition, the FDA conducts inspections of plants to ensure that each manufacturer is adhering to current GMP standards. Although complicated, and to a certain extent "fragile," the current system has worked remarkably well for several decades and has been able to provide increasing doses of vaccine for the U.S. since the 1980s. Some of the key steps of the process are briefly reviewed.

#### Global Surveillance

The ability of vaccine to provide protection against influenza depends on a close antigenic match between the strains contained in the vaccine and the circulating viruses. In practice, changes in antigenicity among circulating viruses occur frequently because influenza A and B viruses both undergo antigenic “drift,” a process in which genetic mutations among
influenza viruses result in the production of antigenic variants. Eventually, some of the variants begin to circulate widely and replace older strains. Because antibodies to older strains or to previous vaccinations might not provide protection to one of the newer antigenic strains, the emergence of new strains must be monitored closely so that the vaccine strains can be updated as needed. Typically, each of the vaccine strains is updated about every one to three years.

The monitoring of influenza viruses is accomplished through a global surveillance system maintained by the World Health Organization (WHO). In the U.S., approximately 120 laboratories associated with state health departments, universities, and large hospitals and other laboratories associated with the Department of Defense provide surveillance data and isolates of currently circulating viruses. Approximately 110 laboratories in 83 other countries also participate in the WHO system and provide information and isolates from their countries to reference centers located in Atlanta, London, Melbourne, and Tokyo. As one of the four global reference centers, the Influenza Branch of CDC coordinates national influenza surveillance and helps to facilitate international surveillance efforts. Isolates sent to CDC by U.S. laboratories and by some international laboratories are characterized for their antigenic and molecular features. All of the surveillance and strain characterization information is made available to the vaccine strain-selection process.

### Annual Strain-Selection Process

The process of selecting strains for U.S. influenza vaccine is a broadly collaborative effort involving several public health agencies and representatives from a broad range of private sector groups. Each year, three strains are selected at two public meetings, usually held in January and March, of the Vaccine and Related Biological Products Advisory Committee (VRBPAC), an advisory group to the FDA. At the VRBPAC meetings, national and international surveillance data on viruses and related disease activity and other relevant information, such as the ability of antibodies induced by current vaccines to cover newer viruses, are reviewed. Typically, selection of the strains by VRBPAC begins at the January meeting and is completed at the March meeting. The FDA has the final responsibility for selecting the influenza strains that will be used in influenza vaccines sold in the U.S. In the period between the two FDA meetings, the WHO convenes a separate meeting to recommend influenza vaccine strains for the Northern Hemisphere (another WHO meeting is held in September to recommend strains for Southern Hemisphere influenza vaccines). Although the WHO recommendations are not binding, most countries usually adhere to them. In the future, the timing of the FDA and WHO meetings might be changed so that the WHO meeting precedes a consolidated FDA meeting.

The selection of vaccine strains at the January meeting is complicated by the need to balance two critical considerations. On the one hand, selecting as many vaccine strains as possible in January is highly desirable from a manufacturing point of view. The early selection of strains provides the maximum amount of time possible to produce vaccine and provides the maximum cushion if unforeseen and unpredictable difficulties arise while growing or processing the strains. However, the “correct” selection of vaccine strains that are expected to predominate in the following winter is absolutely essential for an effective vaccine and their selection depends on the availability of an adequate amount of surveillance and strain characterization information from the current influenza season and the preceding summer. Sometimes, a less than desirable amount of information on circulating viruses is available in January if, for example, the influenza season has started late, or activity levels have been low and few viruses have been isolated, or because the flow of surveillance information or isolates has been impeded for other reasons.

In some years, the emergence of a new and significantly important virus strain (e.g., the emergence of the influenza A (H3N2) virus Sydney strain in 1997) can occur after the vaccine strain selection process has been completed. The practical solution has been to select at least one strain at the
January VRBPAC meeting, so that manufacturers can begin producing some of the vaccine strains, with the remaining strains selected in March.

The VRBPAC (and WHO) recommendations also usually are worded to allow the regulatory authorities and the manufacturers an important degree of latitude in selecting the actual strains to be used in the vaccine by indicating that a virus “like” the recommended strain can be used in the vaccine. This means that a virus that is antigenically similar to the recommended vaccine strain can be used in the vaccine. This approach is important because it allows the manufacturers to identify and use virus strains with manufacturing properties suitable for that manufacturer. One drawback is that the use of different vaccine strains by different companies in some years can lead to considerable confusion among providers and the general public.

Manufacturing Considerations
Many of the influenza vaccine production steps used by the manufacturers are considered proprietary, but in general, the manufacturing steps include the growth of vaccine strains in embryonated eggs, the production of monovalent concentrates, the formulation of trivalent vaccine, the processes to ensure the inactivation, sterility, safety, and potency of the vaccine, the updating of the product inserts, and the filling, packaging and distribution of the vaccine. The FDA (and the manufacturers) must test and review several test results to ensure that the vaccine meets specifications before the FDA can release vaccine for distribution.

A few key points related to the vaccine production process are worth emphasizing. First, the manufacture of influenza vaccine involves inherent uncertainties each year because one or more of the vaccine strains usually change every year, and the intrinsic growth and processing properties of viruses can vary. Moreover, even after preliminary testing for growth and processing characteristics, the way in which different viruses will respond to the specific production methods employed by a manufacturer is not fully known until full scale manufacturing has started. Second, the time pressures to complete key steps are relentless. The manufacturing process has evolved into a year-round activity in which preparations for the following year must begin almost immediately after cessation of vaccine production for the immediate year. Starting one step often depends upon the completion or near-completing of preceding steps, making the timing of each step critical. For example, the ordering of the embryonated eggs must occur a year or more in advance, limiting the ability of manufacturers to respond quickly to unforeseen shortfalls or delays in the production of vaccine by other manufacturers.

In practice, the intense time pressures have affected the manufacturing process in several ways. For example, the identification of strains that might potentially be used in the vaccine, as well as characterization of their growth and processing properties, now begins well in advance of the actual selection of the vaccine strains by VRBPAC. Candidate vaccine viruses are provided to the manufacturers as early as possible so the manufacturers can study their growth and processing properties of specific viruses. Other laboratories also help to develop suitable candidate “high growth” influenza A viruses, which are essential for producing influenza A viruses in the amounts needed to meet current levels of vaccine demand. Another example is the common practice whereby manufacturers begin growing and processing a virus strain at risk to themselves, before the first strain selection meeting, to attempt to maximize vaccine supplies.

The Regulatory Process
The FDA and the manufacturers work together to ensure the potency and safety of the influenza vaccine sold in the U.S. For example, FDA staff prepare and provide the reagents used by the manufacturers (and the FDA) to test the potency of vaccine lots. Monovalent bulk lots of vaccine are tested both by the manufacturers and by the FDA. After the monovalent lots have been released by the FDA, the companies blend them to make trivalent vaccine, which then is submitted to the FDA again for further testing and final release. The FDA also inspects the vaccine manufacturers to ensure that their production processes and plants are in compliance with current GMPs. If these standards are not met, and if substantial amounts of time are needed to correct the problems, then disruptions and delays can occur in the production schedule of the vaccine. Steps taken by manufacturers to upgrade facilities or to enhance production capacity can also affect production.

The Distribution System
The system for distributing influenza vaccine from manufacturers to vaccine recipients is complex and not centralized. Individual manufacturers employ different vaccine distribution strategies, and deliver varying amounts of vaccine to the market on different schedules. Some manufacturers distribute vaccine solely through secondary distributors, who sell vaccine to other distributors or to providers. Other companies will sell vaccine directly to end-users. The system as a whole involves hundreds of primary, secondary, and tertiary distribution companies, pharmacies, and many tens of thousands of providers.

Most vaccine distribution and administration is accomplished within the private sector with relatively small amounts of vaccine purchased and distributed by the federal government or local state health departments. For example, between 1999 and 2001, CDC purchased an average of 1.8 million doses of vaccine each year, on behalf of many state health departments. Other states purchase vaccine directly from manufacturers or large distributors. In addition, the Department of Defense purchases influenza vaccine to immunize its forces.

DISCUSSION AND POSSIBLE NEXT STEPS
Several points related to the recent influenza vaccine delays and the influenza vaccine process are worth emphasizing. First, the overall process has worked well for decades despite its many
Delayed Distribution of Influenza Vaccine

complexities and “fragilities.” Although the recent delays highlight the need to take certain actions to strengthen the system, such major disruptions have been exceptional and the potential benefits of any fundamental changes should be considered carefully against the potential drawbacks.

Second, disruptions to the influenza vaccine supply can never be fully anticipated. The information needed to select the new vaccine virus(es) each year depends in part on when influenza activity starts relative to the strain selection meetings and upon a vast voluntary network of surveillance laboratories that in many areas is poorly supported. In addition, the development and production of influenza vaccine involves the processing of new biologic agents each year. In some years, important growth and processing issues occur that cannot be fully predicted until production begins. Similarly, the emergence of regulatory issues, such as those related to current GMP, cannot always be anticipated.

Third, a fundamental concern is the decline in the number of manufacturers producing influenza vaccine for the U.S. Although the remaining three influenza vaccine manufacturers have increased their production capacity substantially and plan further expansion, the small number of remaining manufacturers is of major concern because it leaves the U.S. with a minimal safety net if unanticipated problems affect the production capabilities of any of the remaining manufacturers. This situation will become worse if any of the remaining companies decide to stop selling inactivated influenza vaccine. The small number of manufacturers and the lack of new companies entering the field is directly related to the economics of influenza vaccine manufacture and the profitability of this product. From the perspective of individual recipients and providers, increases in the price of vaccination can be alarming, especially if the levels of reimbursement lag behind vaccination prices. Nonetheless, the long-term viability of the influenza vaccine supply process in the U.S. depends on the attractiveness of influenza vaccine as a product for manufacturers and their perception that its production will provide adequate levels of profit.

Fourth, despite the perception by many that there was a “shortage” of vaccines in 2000 and 2001, the overall pattern was more of a shifting mismatch during the fall and winter months between the levels of demand and supply for influenza vaccine. One of the striking aspects about both of the 2000 influenza seasons was that several millions of doses of vaccine remained unused at the end of each season. The demand for vaccine decreased substantially by December, even though influenza activity had not yet peaked in either season; consequently, many people for whom vaccine was recommended remained unvaccinated.

Although the optimal timeframe for influenza vaccine administration is October through the end of November, the continued vaccination of unvaccinated persons after November is highly desirable, especially for improving the protection of groups at high risk for complications from influenza. Traditionally, many vaccine providers, including physicians, stop administering vaccine after mid-November because they believe it is no longer indicated or it is too late. However, 15 out of the 25 influenza seasons between 1976 and 2001 peaked in February or later, indicating that continued vaccination clearly has the potential to benefit substantial numbers of people. The continuation of vaccination activities after November would also help to ensure that available influenza vaccine supplies are not wasted. Implementing this approach will require extensive educational efforts over years to change the vaccination behaviors of many vaccine providers and recipients; nonetheless, this critical change is needed.

The recent delays also demonstrated that the current system encounters difficulties in responding rapidly to unanticipated vaccine supply disruptions. For example, with the exception of the small amounts of vaccine purchased by the federal government and some state governments, the existing system for purchasing, distributing, and administering influenza vaccine is a private-sector enterprise involving a complicated and noncentralized network in which manufacturers sell and distribute vaccine to large and small distributors and to providers directly. Both the distributors and providers comprise large numbers of heterogeneous enterprises. Providers, for example, range from small solo physician office practices to large vaccination campaigns conducted at work sites or at commercial enterprises, such as grocery or pharmacy store chains. During years in which the supply of vaccine is adequate, this system has worked well. However, this system was very difficult to coordinate under the rapidly changing conditions of the recent vaccine delays.

Although a more centralized distribution system could, theoretically, respond more rapidly to meet urgent supply shortfalls, an overly centralized system would also run the risk of being unnecessarily cumbersome and bureaucratic during years of normal vaccine supply. An intermediate approach would be to strengthen the federal government’s role in adult immunization activities, similar to the magnitude of its role in pediatric vaccination efforts. This approach could retain the benefits of the current distribution system, while providing the foundation for a more coordinated response if future influenza vaccine supply disruptions occur. It could also allow for more focused efforts to attain national vaccination coverage objectives.

The timely distribution of accurate and helpful information is always critical, during both urgent and normal conditions. However, the recent delays also highlight the fact that such information is often simply not available in a timely manner. For example, during the 2000 vaccine delay, rapidly changing conditions during the summer made it significantly more difficult for CDC, the FDA, and others to predict the eventual degree of the delay or to know whether a substantial shortage would occur. The 2000 delay also highlighted the importance and difficulty of reaching certain groups, especially individual physicians and other private vaccine providers.

These issues are complicated and will be difficult to address. Nonetheless, the population of the U.S. is aging and the overall
number of people at high risk for complications from influenza is increasing. In addition, the demand for influenza vaccine has increased, both among groups targeted for vaccination and among healthy people not specifically targeted for vaccination. Given this situation, the myriad problems raised by the 2000 and 2001 influenza vaccine delays, and the possibility of future delays or shortages, it is clear that these issues must be addressed if the U.S. is to sustain adequate influenza vaccination efforts in the future. Moreover, it is sobering to realize that the more severe 2000 delay took place within the context of one of the mildest influenza seasons recorded in several years. The consequences of a similar delay in a more typical influenza season could have been much graver.

Since the delays, several groups have taken a number of steps to address some of these issues. For example, an investigation of the 2000 delay was conducted by the General Accounting Office, the investigative arm of the U.S. Congress. The report noted that the Department of Health and Human Services undertook several steps in response to the 2000 vaccine delay, but concluded that similar disruptions could be repeated in the future and that additional steps were needed. These include the completion of a national influenza pandemic plan and more meetings between public health officials, vaccine manufacturers, distributors, physicians, and others to develop guidelines.

The ACIP developed new recommendations on the timing of vaccination so that vaccine doses available early in the season would go first to persons in high-risk groups and to health care workers. In recognition of the recent vaccine delays, and continued uncertainty about future seasons, the ACIP recommendations for 2002 continue to recommend the scheduling of influenza vaccination so that vaccination of certain groups (i.e., high-risk groups, close contacts of high-risk groups, health care workers, and children requiring two doses of vaccine) can begin in October and the vaccination of others can begin in November. CDC provided specific guidance to state and local health departments and co-hosted two meetings with the American Medical Association. As recommended by the General Accounting Office report, these meetings brought together a wide range of public and private sector representatives to identify both problems raised by the recent delays and practical solutions, including those related to the Medicare payment for the influenza vaccine and its administration. A third meeting is scheduled for May 2002. In 2000 to 2001, the National Institutes of Health conducted a study on the immunogenicity of a half dose of influenza vaccine in healthy adults as a possible option for stretching the vaccine supply. The manufacturers have worked extensively to increase their production capacities. Some have also begun to alter their vaccine distribution practices so that all vaccine orders are at least partially filled early in the season, rather than have some orders completely filled and other orders completely unfilled. Many providers have begun to schedule their vaccination efforts to reflect the ACIP recommendations. Several organizations, such as CDC and the FDA, have substantially stepped up their efforts to communicate information about vaccine supplies.

The steps taken to date are encouraging and will continue, along with others, into 2002 and beyond. The discussions between public and private sector groups have led to a better understanding and greater degree of cooperation. Nonetheless, increasing the number of vaccine manufacturers, changing the behavior of vaccine providers and vaccine recipients so that vaccination efforts continue into December and the beginning of the following year, and strengthening the presence of the federal government in adult immunization activities are all essential steps that have yet to be accomplished. Additional information regarding influenza vaccine can be obtained at www.cdc.gov/nip/flu.

REFERENCES


