

Universal Influenza Vaccination: The Time to Act Is Now

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*“There is a time in the life of every problem when it is big enough to see and small enough to solve.
For flu preparedness, that time is now.”*

—Michael Leavitt, U.S. Secretary of Health and Human Services, at the World Health Assembly’s Ministerial Meeting on Avian Influenza, May 16, 2005, Geneva, Switzerland¹

Annual influenza epidemics create a significant public health burden each year in the United States. That influenza continues to pose a public health threat despite being largely preventable through vaccination is indicative of continuing weaknesses in the U.S.’s public health system. Moreover, the burden of annual influenza epidemics and the fragility and instability of the capacity to respond to them underscore the U.S.’s ongoing vulnerability to pandemic influenza and highlights gaps in bioterrorism preparedness and response efforts. This article examines the burden of annual influenza epidemics in the U.S., efforts to combat that burden with vaccination, shortcomings of influenza vaccination efforts, and how those shortcomings exemplify weaknesses in pandemic influenza and bioterrorism preparedness efforts. We make the case for establishing an annual universal influenza vaccination program to assure access to influenza vaccination to anyone who can safely receive vaccination and desires it. Such a program could greatly reduce the annual burden of influenza while advancing and maintaining U.S. pandemic influenza and bioterrorism preparedness and response efforts.

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Medical and public health professionals, government officials and agencies, and nongovernmental organizations have long called for increasing influenza vaccine usage in the U.S. and around the world.^{2–17} Reasons for

doing so include reducing influenza-associated morbidity and mortality, reducing the economic burden of influenza, preparing for pandemic influenza, and fostering bioterrorism preparedness.

This article examines the burden of annual influenza epidemics in the United States, efforts to combat that burden with vaccination, shortcomings of U.S. influenza vaccination efforts, and how those shortcomings exemplify weaknesses in pandemic influenza and bioterrorism preparedness efforts. The article makes the case for establishing an annual universal influenza vaccination program to assure access to influenza vaccination to anyone who can safely receive vaccination and desires it.

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INFLUENZA: A SIGNIFICANT BURDEN

Influenza epidemics occur every year in the United States. They occur because changes in the proteins on the surface of circulating influenza virus strains—a process known as antigenic *drift*—allow them to evade host immunity and cause disease despite previous influenza infection and/or vaccination.^{18–20}

The overall societal burden of annual influenza epidemics is difficult to quantify and, as a result, not fully understood.^{21–23} It is a combination of influenza's burden on the public's health and the healthcare system and the concomitant economic burden.

Influenza's Burden on the Public's Health

- It is estimated that 5–20% of the U.S. population suffers influenza infection each year—roughly 15–60 million infections annually based on current U.S. Census data.^{20,24,25}
- Children have the highest rates infection—in some epidemics exceeding 40% in preschool children and 30% in school-age children.^{26–28}
- People ≥ 65 years old and people of any age with certain underlying medical conditions (e.g., chronic health problems, immunosuppression) tend to suffer the most serious illness with higher risks for hospitalization and death.^{15,27}
- People ≥ 65 years old experience the highest influenza-associated mortality.^{15,19,21}
- It is estimated that 36,000 deaths/year occur due to influenza (approximately 1 out of every 10,000 Americans).^{29,30} This estimate may be conservative; some suggest that annual influenza-associated mortality may be as high as 70,000–90,000 deaths/year.^{16,31}
- Influenza-related mortality is increasing in the U.S., due in part to the aging population.³⁰ (See Appendix 1.)

Influenza's Burden on the Healthcare System

- It is estimated that there are more than 200,000 influenza-associated respiratory and circulatory hospitalizations/year in the U.S.^{15,32} Influenza-associated hospitalizations appear to be increasing in the U.S., due in part to the aging population.³²
- Annual influenza epidemics increase outpatient visits and create a great demand on hospital emergency departments, frequently causing them to close temporarily.^{26,33–36} (See Appendix 2.)

Influenza's Economic Burden

- The economic burden associated with influenza in the U.S. is estimated at more than \$12 billion/year.²

- Most of the economic burden is manifested in indirect costs, which are the costs associated with losses in productivity and school or work absenteeism, estimated at \$10–15 billion/year.³⁷ (See Appendix 3.)

REDUCING THE BURDEN: VACCINATION

Vaccination is the principal method for reducing the burden of influenza.¹⁵ Each year a new vaccine must be developed, produced, and distributed because antigenic drift enables circulating influenza virus strains to evade host immunity built up by previous influenza infection and/or vaccination.^{19,38} Vaccine effectiveness varies from year to year and is determined primarily by the age and immune status of vaccine recipients in combination with the degree of antigenic similarity between circulating influenza virus strains and those that comprise the vaccine.¹⁵ When the vaccine and the circulating influenza strains are antigenically similar, influenza vaccination is 70–90% effective in preventing influenza illness in healthy adults under 65 years of age.¹⁵ Influenza vaccination is also effective in preventing influenza illness in children and in adults 65 years old or older—although it tends to be less effective than among adults under 65 years old.^{3,15,39–45}

In addition to preventing infection, influenza vaccination also can reduce disease severity and decrease the occurrence of influenza-associated illnesses.¹⁵ For example, influenza vaccination has been found to reduce the incidence of myocardial infarction, stroke, primary cardiac arrest,^{13,46–49} acute otitis media in children,^{50–52} and asthma exacerbations during influenza season.⁵³ Influenza vaccination also reduces influenza-associated deaths.^{15,54} While the full extent to which influenza vaccination reduces influenza-associated mortality is unclear,* meta-analyses of influenza vaccination among the

*There is considerable debate on the extent to which influenza vaccination prevents influenza-associated mortality among the elderly.^{55–60} Recent analyses have indicated that previous studies, which found influenza vaccination to significantly reduce the risk of hospitalization and death among the elderly, may overestimate the benefits of influenza vaccination due to biases in the previous studies.^{61–63} The issue is far from resolved, and further research is needed to better understand the utility of influenza vaccination among the elderly before any changes in vaccination policy should be considered. Some argue that the new findings support increasing influenza vaccination efforts among groups who transmit influenza virus within communities (e.g., schoolchildren) to reduce the overall incidence of influenza and its concomitant morbidity and mortality as well as furthering research into better influenza vaccines for the elderly.^{55,60}

elderly have found that vaccination can reduce the risk of death by about half.^{41,44,45}

Influenza vaccination also has been found to reduce influenza's burden on the healthcare system (e.g., hospitalizations, outpatient visits) and reduce influenza-associated work and school absenteeism and lost productivity.^{15,54,64–78} Numerous analyses have found that influenza vaccination is a cost-effective or cost-saving strategy[†] for reducing the burden associated with influenza among the elderly,^{15,40,69–72,78–80} and many analyses have shown that expanding vaccination efforts to include healthy working adults and children also can be cost-effective or cost-saving.^{15,40,73–75,81–88}

CURRENT INFLUENZA VACCINATION EFFORTS

The Advisory Committee on Immunization Practices (ACIP)⁸⁹ makes yearly recommendations to the U.S. Department of Health and Human Services (HHS) for the use of influenza vaccine. ACIP recommendations help determine which vaccines will be included in the schedule of vaccines recommended for routine administration to the pediatric and adult populations and, as such, heavily influence the national standards for immunization.⁹⁰ ACIP's influenza recommendations include: (a) target groups for whom influenza vaccine is recommended because they are most vulnerable to a severe influenza infection (e.g., children 6–23 months, adults ≥ 65 years) or are likely to transmit influenza infection to highly vulnerable groups (e.g., healthcare workers); and (b) less vulnerable, nontarget groups for whom vaccine is encouraged contingent on a sufficient vaccine supply (e.g., people who provide essential community services, any person ≥ 6 months old “who wishes to reduce the likelihood of becoming ill with influenza”).¹⁵

[†]Cost-effectiveness analyses compare the costs of a healthcare intervention to a desired health outcome of that intervention (e.g., dollars spent/lives saved) to help determine the most efficient way to allocate healthcare resources. The cost-effectiveness of a particular healthcare intervention is dependent on the economic variables (e.g., direct, indirect, intangible costs) and the health outcome(s) (e.g., lives saved, illnesses prevented) used in the analysis and the perspective from which the analysis is undertaken (e.g., individual, employer, insurer, government). In general, healthcare interventions tend to cost money, not save it. Whether such interventions are deemed cost-effective (i.e., economical in terms of health benefits gained versus money spent) and, therefore, worth pursuing is largely a value judgment as there is no consensus for determining cost-effectiveness. However, an intervention that is found to be cost-saving (i.e., results in a net economic saving) would surely be considered cost-effective, at least from an economic perspective.

The number of people in target priority groups for whom ACIP recommends influenza vaccination each year is approximately 190 million, nearly two-thirds of the U.S. population.⁹¹ However, in recent years the number of people targeted for influenza vaccination by ACIP has far exceeded vaccine production levels, and vaccination efforts have fallen considerably short of fulfilling ACIP recommendations (Table 1).^{92–95}

There is no single explanation for the low level of influenza vaccination usage in the United States. It is not simply that the vaccine supply is inadequate to meet demand. In fact, since the late 1990s, influenza vaccine production has tended to exceed distribution, which has, in turn, tended to exceed usage.^{93–95} Even during the highly publicized vaccine shortage for the 2004–05 influenza season and the initial high demand for vaccination, in some areas vaccine was unused, prompting ACIP to expand its interim recommendations on two occasions.^{96,97} Despite expanded vaccination efforts, as many as 5 million doses of vaccine were never used.^{98–100} Thus, while size of the vaccine supply plays an important role in determining vaccine usage—especially in terms of timing and availability—the situation is far more dynamic. Contributory factors to the low level of influenza vaccine usage in the U.S. include: mistrust of the vaccine (e.g., belief that it can cause the flu), fear of vaccination (e.g., pain, side effects), belief that the vaccine will not prevent infection, forgetting to be vaccinated, previous side effects from vaccination (real or perceived), inconvenience of getting vaccinated, being unaware that influenza vaccination is recommended, cost, lack of health insurance coverage, lack of primary medical care, primary healthcare provider not recommending or recommending against vaccination, low health-risk from influenza (i.e., not in a high-risk target group for vaccination), and lack of available vaccine (real or perceived).^{101–112}

CURRENT INFLUENZA VACCINE PRODUCTION CAPABILITY

In the U.S. influenza vaccine production is a private sector enterprise driven largely by market forces wherein manufacturers attempt to produce enough vaccine to meet expected demand and generate an optimal return on their investment.^{113,114} This system has fostered an influenza vaccine production capacity of roughly 80–100 million doses/year, 50–60 million doses of which can be produced domestically.^{93,94,115,116}

The high costs associated with producing vaccines (e.g., costs from research and development, clinical trials, achieving and maintaining regulatory approval, manufacturing) in combination with uncertain demand and low profits have resulted in a reduction in the number of

TABLE 1. INFLUENZA VACCINATION COVERAGE RATES AMONG SELECTED TARGET PRIORITY GROUPS

<i>Target Priority Group^a</i>	<i>Estimated % Vaccinated 2003–04</i>	<i>Estimated % Vaccinated 2004–05</i>
People aged 50–64 years	36.8 ^b	40.6 ^{b,c}
People aged ≥65 years	65.5 ^b –67.7 ^d	62.7 ^d –68.7 ^b
People aged 18–64 years with high-risk medical conditions	34.2 ^b –43.1 ^d	25.5 ^d
Children aged 2–17 years with high-risk medical conditions	41.7 ^d	34.8 ^d
Children aged 6–23 months	NA ^e	48.4 ^d
Healthcare workers with patient contact	40.1 ^b –49.0 ^d	35.7 ^d

^aAs recommended by the Advisory Committee on Immunization Practices.

^bNational Health Interview Survey.^{15,188,189}

^cThis group was not included in the priority groups initially targeted for vaccination by ACIP in its interim 2004–05 influenza vaccination recommendations because of the vaccine shortage but was later added in updated interim recommendations.¹⁹¹

^dBehavioral Risk Factor Surveillance System.^{188,190,191}

^eVaccination of this group was not recommended by ACIP until the 2004–05 influenza season.¹⁹⁰

influenza manufacturers for the U.S. market.^{114,117,118} For the 2005–06 influenza season, four manufacturers are expected to produce approximately 71–97 million doses of vaccine for the U.S. market, although most of the vaccine (~60 million doses) will be produced by one manufacturer.^{119,120} One consequence of this dearth of manufacturers is a fragile production capacity that is unable to handle an unexpected production problem or unanticipated surge in demand. For example, the U.S.'s influenza vaccine shortage in the 2004–05 season was the result of contamination problems with one of the three manufacturers who were expected to produce vaccine for the U.S. market that season, cutting the amount of available vaccine nearly in half.^{92,114}

ANNUAL INFLUENZA EPIDEMICS: INDICATIVE OF LARGER PROBLEMS

The burden of annual influenza epidemics and the fragility and instability of the capacity to respond to them underscore the U.S.'s ongoing inability to adequately respond to an influenza pandemic. There have been three influenza pandemics in the past 87 years, and, while it is uncertain when the next one will occur, another pandemic is widely viewed as inevitable.^{121,122} The ongoing avian influenza outbreak in Asia has raised great concern that the next influenza pandemic may be close at hand.^{123,124}

Influenza pandemics result when a major change occurs in the proteins on the surface of an influenza virus strain—a process known as antigenic *shift*—which results in a new influenza strain for which there is little or no existing immunity.¹⁸ Influenza pandemics are marked by high attack rates and increased mortality.¹⁹ One analysis estimates that, in the U.S. alone, the next pandemic could result in 20–47 million illnesses, 18–42 million outpatient visits, 314,000–734,000 hospitalizations, and 89,000–207,000 deaths.¹²⁵ Another analysis estimates that an influenza pandemic in the U.S. could result in from 786,000 to 4.7 million hospitalizations and 180,000 to 1 million deaths.¹²⁶

The current U.S. influenza vaccine production, procurement, and delivery system is insufficient to supply enough vaccine for the entire U.S. population quickly in the event of a pandemic.^{17,94,115} It is estimated that the U.S.'s domestic influenza vaccine production capacity of ~60 million doses would be able to produce enough pandemic vaccine to vaccinate only 30–90 million people.¹¹⁵ Results from an ongoing clinical trial of a candidate pandemic vaccine suggest that those estimates may be optimistic (see Appendix 4).¹²⁷ And it is unlikely that the U.S. would be able to import pandemic vaccine from one of the few countries with a production capacity until those countries meet their own needs.¹¹⁵ It also is unlikely that the current U.S. influenza vaccine procurement and delivery system—a noncentralized, largely private-sector undertaking—could adequately handle the

demand for vaccine that a pandemic would create, given that the current system has had great difficulty managing vaccine shortages in nonpandemic years.^{93,94}

The federal government has recently taken major steps to foster pandemic preparedness, including releasing the *National Strategy for Pandemic Influenza*, the *HHS Pandemic Influenza Plan*, and checklists for state and local health departments, businesses, community organizations, and families and individuals to aid pandemic preparedness efforts; implementing a federal-state influenza-pandemic planning process; and appropriating approximately \$3.8 billion for pandemic preparedness activities for FY06. The *HHS Pandemic Influenza Plan*, intended to serve as a “blueprint for all HHS pandemic influenza preparedness planning and response activities,” is not specific on issues such as pandemic vaccine production, purchase, and distribution.^{128–130} Part 3 of the plan, HHS Agencies’ Operational Plans, is “currently under development” and will “elaborate on coordination, command and control, logistics, and planning, as well as financial and administration considerations.”¹²⁸ Until HHS’s operational plans are released, states—which bear most of the responsibility for pandemic preparedness and response—will find it difficult to fully integrate their plans with the federal plan and to effectively operationalize their pandemic response plans. In addition, not all states have a pandemic response plan, existing state response plans remain inadequately tested, federal performance measures for evaluating the quality of state plans do not yet exist, and many weaknesses remain in response scenarios.^{131,132} For example, the resources and infrastructure necessary to vaccinate the U.S. population are not in place.^{133–136}

The U.S.’s ongoing vulnerability to annual influenza epidemics and pandemics also highlights weaknesses in public health emergency preparedness and response efforts. One weakness is the inability to vaccinate large numbers of people after a biological attack.^{137–139} For example, the ability to vaccinate entire communities within “a short period of time (e.g., within 5–10 days)”¹⁴⁰ after a confirmed case of smallpox is a critical component of smallpox preparedness planning, yet few communities are fully prepared to do this.^{131,141–144} While response plans exist on paper, few communities have successfully identified a sufficient number of healthcare workers to staff their planned smallpox vaccination clinics, vaccinated and trained those healthcare workers, or adequately exercised their vaccination plans.^{132,141,142,144} A 2005 survey found that “[o]nly seven states and two cities” are “recognized by the U.S. Centers for Disease Control and Prevention as [being] adequately prepared to administer and distribute vaccines and antidotes [from the Strategic National Stockpile] in the event of an emergency.”¹³²

POLICY RECOMMENDATION: UNIVERSAL INFLUENZA VACCINATION

The U.S. should establish an annual, federally funded, locally run universal influenza vaccination program to ensure that anyone who wishes to be vaccinated, and can safely be vaccinated, has access to vaccination. There are three overarching reasons for establishing such a program. First, the burden of annual influenza epidemics justifies substantially increasing the production and use of influenza vaccine in the U.S. Second, the threat of pandemic influenza significantly bolsters the urgency of such efforts. Indeed, the *HHS Pandemic Influenza Plan* states: “The success of the pandemic influenza vaccination program will be determined in large part by the strength of state and local vaccination programs during the Interpandemic Period.”¹²⁸ Third, the threat of bioterrorism warrants continued and increased investment in improving the U.S.’s capability to quickly vaccinate substantial portions of its population.

As broadly conceived here, the federal government would purchase all of the influenza vaccine for the nation each year, distribute the vaccine to states, and provide support (fiscal, logistical, etc.) for administration. Such a program will have five main benefits:

1. Reduce the annual burden of influenza epidemics;
2. Develop and maintain the infrastructure and expertise necessary to implement universal vaccination;
3. Develop and maintain the influenza vaccine production, procurement, and delivery systems necessary to respond to annual influenza epidemics and pandemics;
4. Reduce the potential for panic and maximize compliance with universal vaccination recommendations; and
5. Reduce the bioterrorism threat.

1. Reduce the Burden of Annual Influenza Epidemics

A universal influenza vaccination program would target the entire U.S. population for vaccination instead of focusing efforts on high-risk target groups and, as such, could substantially increase influenza vaccine coverage, thereby significantly reducing the incidence of influenza.¹⁴⁵ For example, preschool- and school-aged children—who are not currently designated as a target group for whom influenza vaccination is recommended by ACIP—experience the highest influenza infection rates and are one of the main avenues through which influenza enters households and spreads through communities.^{146,147} Expanding vaccination efforts to include these children could minimize this route of spread, potentially resulting in a dramatic reduction in the overall incidence

of influenza.^{148,149} One study estimated that vaccination of 85% of school-aged children against influenza reduced the communitywide influenza attack rate by as much as 67% relative to neighboring communities where minimal vaccination occurred.^{150,151} Another study found that vaccination of 20–25% of children reduced the incidence of medically attended acute respiratory disease in adults 35 years of age and older by 8–18% during influenza season.¹⁵² Mathematical modeling studies also suggest that vaccinating children against influenza can prevent communitywide epidemics.^{151,153–155} One study estimates that vaccinating 20% of children could result in a 46% reduction in the total number of annual influenza cases populationwide in the U.S. and that increasing vaccination levels to 80% among children could reduce the total number of influenza cases by 91%.¹⁵⁴

Reducing the incidence of influenza would reduce its concomitant morbidity and mortality. An analysis of a universal influenza vaccination program of children in Japan estimated that the program prevented 37,000–49,000 deaths per year from all causes.¹⁵⁶ Another study estimates that universal influenza vaccination could potentially save 91,000 lives per year in the U.S. from cardiovascular disease alone.¹³ In addition to lessening human suffering, reducing influenza-associated morbidity and mortality would also reduce influenza's burden on the healthcare system by decreasing associated doctor visits and hospitalizations and duration of hospital stays. Moreover, reducing influenza-associated morbidity and mortality would decrease the substantial economic costs associated with influenza epidemics, including reducing the economic burden of influenza on Medicare, which can be expected to increase with the aging U.S. population. One study estimated that the average cost of influenza-associated hospitalizations to Medicare from 1990–96 was \$372.3 million per year.¹⁵⁷

2. Develop and Maintain the Infrastructure and Expertise Necessary to Implement Universal Vaccination

A universal influenza vaccination program would greatly enhance the U.S.'s ability to rapidly vaccinate large numbers of people in the event of an influenza pandemic or bioterrorist attack by creating the plans and infrastructure necessary to implement universal vaccination and exercising universal vaccination annually.^{91,145,158} Specifically, vaccination sites and providers would be identified, personnel would be accustomed to working together, and the public would become familiar with the process of universal vaccination. Additionally, potential problems with the successful implementation of vaccination plans would be identified and strategies developed to address them. For example, specific groups unable or unlikely to comply with universal vaccination recommendations (e.g., el-

derly in nursing homes, the homeless, some racial/ethnic groups) would be identified, and plans to ensure their participation in future vaccination programs could be designed, tested, and implemented.

3. Develop and Maintain the Influenza Vaccine Production, Procurement, and Delivery Systems Necessary to Respond to Annual Influenza Epidemics and Pandemics

In the vaccination program proposed here, the federal government would purchase all of the influenza vaccine for the U.S. each year and distribute the vaccine to the states for use. Such a program would require the creation of a centralized procurement and delivery system designed to handle the demands of annual influenza epidemics and pandemics. A centralized system would be better suited to manage annual influenza epidemics and pandemics than the current, noncentralized, largely private sector procurement and delivery system, which has struggled to handle vaccine shortages in nonpandemic years. The potential benefits of a centralized procurement and delivery system to pandemic response or to a vaccine scarcity in nonpandemic years include: providing federal, state, and local governments the maximum ability to effectively and equitably target scarce vaccine resources; preventing the potential for price gouging by removing open market competition for vaccine; removing the burden of vaccine rationing decisions from vaccine manufacturers; and providing a system to effectively monitor and manage vaccine distribution.¹⁵⁹

A universal influenza vaccine program would create a large, predictable influenza vaccine market because the federal government would set the market size each year by purchasing all of the influenza vaccine for the U.S. Such a program, if funded adequately and maintained for the long term, could foster the development of sufficient vaccine production technologies and capacity to produce enough vaccine to vaccinate every U.S. citizen. This topic raises two separate, yet related, issues: (a) current vaccine production technology/formulations, and (b) new production technologies/formulations.

Influenza vaccine production is currently based on relatively old production technologies in which influenza virus seed strains used to produce vaccine are created using a technique called genetic reassortment, and vaccine is produced in egg-based production systems.¹¹⁵ At present, pandemic influenza vaccine production—if required—also will be based on these technologies.¹¹⁵ As noted above, the current U.S. domestic influenza vaccine production capacity of ~60 million doses is insufficient to meet the demand in nonpandemic years and will not be sufficient to respond to a pandemic.¹¹⁵ At a minimum, domestic production ca-

capacity would need to be increased to 200 million doses/year to provide a pandemic influenza vaccine production capacity sufficient to vaccinate the entire country based on current production technologies and vaccine formulations (see Appendix 4).¹¹⁵ Expanding U.S. production capacity to this extent is unlikely under the current open-market-based system, where uncertain demand drives production capacity. If the federal government removes this uncertainty by setting the market each year through a universal purchase, the market should stabilize and then can be expanded by increasing the amount of vaccine purchased each year in accordance with policy objectives.

While expanding current influenza vaccine production capacity is necessary to improve the U.S.'s ability to respond to annual influenza epidemics and prepare for pandemics, it is also necessary to develop and employ new influenza vaccine production technologies because current technologies are outdated and not well suited to respond to a pandemic. Egg-based influenza vaccine manufacture requires significant preplanning to produce a large supply of embryonated chicken eggs; vaccine seed strains are difficult to produce using genetic reassortment; at least 6 months is required to produce vaccine from the time that a pandemic strain is identified; and supplies of vaccine would be inadequate owing to the limits of the production technique and the current level of production capacity.^{115,122,133,160}

To foster better influenza pandemic preparedness, new technologies to produce influenza vaccine must be developed and applied. HHS is funding research into new production techniques and formulations for influenza vaccine (e.g., cell culture-based vaccines, antigen-sparing vaccines). Given the uncertainty of the annual market for influenza vaccine, these efforts alone are not likely to motivate large vaccine manufacturers to sufficiently invest in research and development for new influenza vaccine production technologies, nor to create new vaccine production capacity based on these technologies. Yet it is essential to bring the large vaccine manufacturers into this effort to take advantage of their expertise and resources. Creating a large and consistent demand for influenza vaccine by implementing a universal vaccination program as described here would likely attract additional vaccine manufacturers into the influenza market and spur more investment into research and development for better vaccines, more efficient vaccine production methods, and increased production capacity.

4. Reduce the Potential for Panic and Maximize Compliance to Universal Vaccination Recommendations

An annual universal influenza vaccination program would help prepare the public for a bioterrorist attack or

influenza pandemic by providing familiarity with the general procedure of universal vaccination (e.g., where to go, who will be providing vaccination, what the process is like). This experience should enhance the public's confidence in the government's ability to provide universal vaccination, thereby decreasing the potential for panic. In addition, making the public a partner in the development of vaccination policies and plans—by creating avenues through which input and feedback on policies and plans can be provided and implementation issues addressed—should help build the public's trust and foster public commitment to the program's success.^{161,162} These factors increase the likelihood that the public will comply with requests from health authorities and/or elected officials in the event of an attack or outbreak, helping to minimize the potential death and suffering that could result.¹⁶³

5. Reduce the Bioterrorism Threat

A universal influenza vaccination program could reduce the risk of a bioterrorist attack with the influenza virus because the U.S.'s enhanced ability to effectively respond to such an attack would diminish the anticipated rewards (e.g., mass casualties, panic) that a potential bioterrorist might expect from an attack. Moreover, it may also serve as a deterrent against attacks with other biological agents for which vaccines have been developed and stockpiled (e.g., smallpox), because it shows potential bioterrorists that the U.S. can quickly and effectively respond to an attack.¹⁶⁴ A universal influenza vaccination program also might have deterrent effects that extend to biological agents for which other prophylactic countermeasures are available (e.g., anthrax), because much of the infrastructure and planning necessary to implement universal vaccination is also applicable to the mass distribution of other countermeasures.¹⁶⁵

IMPLEMENTATION ISSUES

Implementing an annual universal influenza vaccination program in the U.S. will be a major undertaking. Challenges such as creating the infrastructure; building and testing vaccine procurement, production, and delivery systems; and sorting out liability issues will require time, funding, and commitment and will require the close collaboration of the various stakeholders. Only the federal government has the financial resources and the convening power and authority to bring the stakeholders together and undertake such a program on a national scale. A few implementation issues are discussed briefly below.

Costs

Implementation of a universal influenza vaccination program as envisioned here will require significant finan-

cial input. However, it is difficult to project how much it would cost as it depends on various factors, including the amount of vaccine purchased each year and at what price and the costs of implementing the program (e.g., vaccine distribution and administration costs, advertising and education campaigns, etc.).

The federal government currently pays from \$9.71/dose for inactivated influenza vaccine to \$12.02/dose for pediatric, preservative-free inactivated influenza vaccine to \$17.24/dose for the live, attenuated influenza vaccine (approximately \$1–2 off the private sector cost for each of these vaccines; see Table 2).¹⁶⁶ As a “back-of-the-envelope” calculation, assume that the initial goal of the program is to achieve an influenza vaccine coverage of 200 million vaccinations per year and that the vaccine purchase includes: 10 million doses (5%) of pediatric vaccine; 90 million doses (45%) of live, attenuated vaccine; and 100 million doses (50%) of inactivated vaccine. Using the current federal government price for influenza vaccine, this comes to roughly \$2.6 billion/year (~\$13/dose). The same calculation using the private sector cost for vaccine comes to approximately \$3.0 billion/year (~\$15/dose). While this calculation is crude, it gives a sense of the potential order of magnitude of the costs for vaccine purchase. And it does not include implementation costs (e.g., distribution, administration), which are uncertain but also are likely to be substantial.

The above estimate for the cost of vaccine purchase may be high, as the federal government likely will be able to take advantage of economies of scale to negotiate a lower price for vaccine. However, there is an inherent tension in negotiating a low price for vaccine if the government is going to be the sole purchaser. If the government were to use its purchasing power to negotiate too low a price for vaccine, it could have the unintended consequence of precipitating market exit for influenza vaccine manufacturers and could also reduce investment in research and development for better influenza vaccines, because vaccine manufacturers generally use profits gained from product sales in the U.S. market to invest in

research and development.⁹⁰ It also might be difficult to determine a fair price for influenza vaccine if the federal government purchases all influenza vaccine, because there will be no open-market competition to determine what price the consumer will accept.⁹⁰ Open-market competition is not the only means to determine an adequate price for a vaccine, and it has been suggested that calculating a vaccine price based on the value of the social benefit provided by the vaccine could be a better way to arrive at a fair price for government vaccine purchases that would provide an adequate incentive for research and development.^{90,167,168}

While a universal influenza immunization program will likely be expensive, it also will provide immediate and offsetting economic benefits by reducing the burden of annual influenza epidemics. As noted above, many studies suggest that expanding influenza vaccination efforts to include healthy adults and children can be cost-effective. Whether a universal influenza vaccination program would be cost-effective would depend largely on the efficacy of the vaccine each year and how the program is implemented (e.g., when, where, and by whom vaccine is provided).

In addition to the immediate economic benefits of a universal influenza immunization program, the cost of the program is further justified by the benefits that accrue to pandemic influenza and bioterrorism preparedness (e.g., ability to successfully and quickly implement universal vaccination), which have an associated economic benefit. A 1997 analysis estimated that the potential economic impact of a bioterrorist attack on the U.S. with anthrax, tularemia, or brucellosis (noncontagious diseases) could be on the order of \$477.7 million to \$26.2 billion per 100,000 persons exposed at a minimum.¹⁶⁹ The report also found that the “rapid implementation of a post-attack prophylaxis program” is essential to minimizing economic losses, and delays in implementing prophylaxis programs result in “markedly reduced savings.”¹⁶⁹ A 1999 analysis estimated that, without “large-scale vaccination,” the next influenza pandemic could cost the

TABLE 2. CDC PRICE LIST FOR INFLUENZA VACCINE^a

<i>Vaccine</i>	<i>CDC Cost/Dose</i>	<i>Private Sector Cost/Dose</i>
Inactivated influenza vaccine	\$9.71	\$10.70
Pediatric, preservative-free inactivated influenza vaccine	\$12.02	\$13.00
Live, attenuated influenza vaccine	\$17.24	\$18.95–\$19.95

^aCDC Vaccine Price List; prices last reviewed/updated: December 22, 2005; contract end date: February 28, 2006.¹⁶⁶

U.S. \$71.3–166.5 billion in 1995\$—roughly \$88–206 billion in 2006\$.^{125,170} Notably, neither of these analyses included the potential economic impact that could be expected from disruptions to commerce and society, which also would be quite large. The 2003 SARS epidemic, for example, is estimated to have cost Asian economies approximately \$11–18 billion (with the most severe impact in the travel and tourism industries), and the direct costs to the U.S. Postal Service from the 2001 anthrax attacks are estimated at ~\$3 billion.^{171,172}

ACIP Recommendation

A recommendation for universal influenza vaccination from ACIP is likely necessary to implement a universal vaccination program. ACIP began considering such a move in 2004.^{91,145} However, a universal influenza vaccination recommendation from ACIP is not sufficient to create a universal vaccination program. For example, a universal recommendation will not institute a universal purchase program at the federal level and will not increase federal funding for implementation support. Moreover, expanding to a universal recommendation absent a clear mandate at the executive level and without a program to foster and maintain adequate vaccine production capacity and assure universal access to vaccine would be problematic under the U.S. vaccine system as it is currently structured (see Appendix 5).¹¹²

New Legislation

The universal influenza vaccination program envisioned here will require authorizing legislation, as the current U.S. vaccine system is not appropriately structured to easily incorporate a universal influenza vaccination program. Congress could enact entirely new legislation or, for example, amend Section 317 of the Public Health Service Act, which provides discretionary grants to states for vaccine purchase and infrastructure support.^{90,173,174} New authorizing legislation would have to be drafted carefully and include the addition of new funding in order to avoid undermining current vaccination programs.

A universal influenza immunization program also will require the creation of adequate liability protection for participants in the program (e.g., vaccine manufacturers, providers). As seen with the U.S.'s National Smallpox Vaccination Program, it is essential to work through the liability issues for participants in a national vaccination program prior to implementation.¹⁷⁵ Because a universal influenza vaccination program is justifiable for national security as well as for public health reasons, it is reasonable that the federal government should provide some form of liability protection to participants.

On July 1, 2005, the Secretary of HHS added influenza vaccines used for annual influenza epidemics (i.e., triva-

lent vaccines; see Appendix 4) to the list of vaccines covered under the National Vaccine Injury Compensation Program (VICP).¹⁷⁶ Under VICP, the federal government provides no-fault compensation to injured vaccinees or their families for specified adverse events resulting from vaccination with covered vaccines.^{177,178} If the petitioner is found ineligible for compensation under VICP or is dissatisfied with the award, the petitioner can sue in civil court.^{175,177} VICP affords liability protection to vaccine manufacturers and providers because, by law, vaccine injury claims involving VICP-covered vaccines must first be filed with VICP before civil litigation can be pursued, and, if a petitioner accepts an award under VICP, a subsequent claim cannot be brought.¹⁷⁸

Whether VICP would offer appropriate liability protection for a universal vaccination program needs to be studied. Current influenza vaccines have a very good safety profile,^{15,179,180} and there have been few lawsuits related to influenza vaccine.¹⁸¹ Thus, the liability exposure for the universal immunization program during *interpandemic* years using current influenza vaccine formulations may be low, and VICP may be a reasonable liability solution from the federal government's perspective. But vaccine manufacturers and providers may not prefer this solution, as the scope of the coverage remains unclear. HHS has not yet specified the adverse events related to influenza vaccination that will be covered under VICP,¹⁸² and VICP offers only limited liability protection because a petitioner can still sue.^{175,178} The public also may not consider VICP to be an adequate solution owing to reported shortcomings of VICP (e.g., VICP is highly adversarial, proving causation is extremely difficult, limitations on attorneys' fees and expenses make experienced attorneys unwilling to represent claimants).¹⁷⁵ Pending legislation introduced in the 109th Congress to improve VICP may address some of these issues associated with VICP if passed.¹⁸³

Pandemic influenza vaccines are not covered under VICP, and VICP likely would not provide the level of liability protection that vaccine manufacturers and providers would desire in the event of a pandemic, given that there will probably be increased liability exposure because there will be minimal time for safety testing for pandemic vaccine and vaccine formulations with poorer safety profiles than interpandemic vaccines may be required.¹⁸⁴ On December 30, 2005, President Bush signed the Public Readiness and Emergency Preparedness Act into law as part of the Department of Defense Appropriations Act, 2006 (Public Law No: 109-148), which can be used to provide liability protection for participants in the universal immunization program in the event of a pandemic.¹⁸⁵ The new law provides liability protection to "covered persons" (e.g., manufacturers, distributors, administrators) for the administration of a "covered countermeasure" (e.g., drugs or biologic products used to "di-

agnose, mitigate, prevent, treat, or cure a pandemic or epidemic”) upon the issuance of a declaration by the Secretary of HHS determining that a public health emergency exists or threatens which requires the administration of countermeasures identified by the Secretary.¹⁸⁵ Under the law, covered persons are “immune from suit and liability under Federal and State law” except when a plaintiff proves “willful misconduct” by a covered person resulting in “death or serious physical injury.”¹⁸⁵ The Public Readiness and Emergency Preparedness Act also provides for the creation of a compensation program for “covered injuries” resulting from the administration or use of a countermeasure identified in the Secretary’s declaration.¹⁸⁵

The extent of liability protection that could be applied to pandemic influenza vaccine under the Public Readiness and Emergency Preparedness Act is much greater than the protection offered under VICP for seasonal influenza vaccines. While it is reasonable to offer greater liability protection for pandemic vaccines in order to foster participation in pandemic preparedness and response efforts by vaccine manufacturers and providers, some have raised concerns that the liability protection offered in the Public Readiness and Emergency Preparedness Act is too broad and the compensation plan is insufficient, which may hinder public participation in preparedness and response efforts.^{186,187} Concern also has been raised that the law gives the Secretary of HHS broad power to declare a public health emergency and determine which countermeasures will receive liability protection, and the Secretary’s decisions are not reviewable by courts.^{186,187} The law also could be read to allow the Secretary of HHS to declare a public health emergency and provide liability protections under this law for inter-pandemic influenza epidemics. However, it has been reported that the law is only intended to be used in rare circumstances (e.g., influenza pandemic or bioterrorist attack).¹⁸⁶ Whether this type of liability and compensation scheme is best suited for fostering pandemic preparedness and response needs to be studied.

A PATH FORWARD

The federal government should convene and fund a working group of stakeholders (e.g., vaccine manufacturers, state and local health department personnel, physicians, community leaders) to oversee the design and implementation of federally funded pilot studies to offer influenza vaccination to the entire population of selected localities (e.g., rural, urban). These studies would provide a better understanding of potential implementation issues (e.g., logistics, infrastructure and workforce needs, costs, public participation) that may arise in establishing a national universal influenza vaccination program as

discussed in this article. The pilot studies also would help develop and test the systems necessary to implement such a program (e.g., vaccine production, procurement and delivery systems, liability coverage, education campaigns). Should these pilot studies demonstrate that a universal vaccination program is feasible and effective, the federal government should establish a national universal influenza program.

In sum, a universal influenza immunization program could greatly reduce the annual burden of influenza. Add to that potential benefit the impact that such a program could have on pandemic influenza and bioterrorism preparedness and response, and it becomes clear that the time to act is now.

ACKNOWLEDGMENTS

The authors would like to thank Tom Inglesby, Jackie Fox, and the journal’s reviewers for their thoughtful comments on the manuscript.

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Appendix 1. Influenza's Burden on the Public's Health

The morbidity and mortality associated with influenza epidemics in the United States are difficult to quantify and, as a result, not fully understood.^{21–23} The influenza surveillance system in the U.S. is designed to “provide a national picture of influenza activity.”¹⁹² The U.S. influenza surveillance system is useful in identifying trends in influenza activity (e.g., increasing or decreasing activity, predominant types of influenza strains circulating) “but cannot be used to ascertain how many people have become ill with influenza during the influenza season.”¹⁹² Influenza cases are not required to be reported nationally in the U.S., and data on the incidence of influenza cases—one of the seven surveillance components of the U.S. influenza surveillance system—are collected by the World Health Organization in collaboration with the Centers for Disease Control and Prevention (CDC) through active surveillance of laboratory confirmed cases.^{24,192} Surveillance based on laboratory confirmation of cases invariably underestimates the incidence of influenza, because influenza infection in healthy people

usually resolves within a few days and a diagnosis, when made, is usually based on clinical presentation, not laboratory testing.¹⁹ Furthermore, influenza infection also can occur in conjunction with other pathogens, making diagnosis difficult.¹⁹³

Because of the shortcomings in ascertaining the incidence of influenza infection, influenza-associated mortality is the major determinant used to estimate the burden of influenza.¹⁹⁴ Influenza mortality data—another component of the influenza surveillance system—also are inadequately ascertained. As noted above, laboratory confirmation of a presumptive diagnosis of influenza infection is not the norm, and, therefore, hospital records and death certificates from which mortality data are derived frequently do not specify influenza as the cause of death.^{30,194} Moreover, mortality associated with influenza often results from secondary complications (e.g., bacterial pneumonia, congestive heart failure) that often occur after the influenza virus is no longer detectable.^{30,194}

Secondary bacterial pneumonia is considered the most common complication resulting from influenza infection, and deaths associated with pneumonia and influenza (P&I) are typically used to estimate the mortality associated with influenza and include “all deaths for which pneumonia is listed as a primary or underlying cause, or for which influenza is listed on the death certificate.”¹⁹ From 1999 through 2003, P&I was the seventh leading cause of death in the U.S., resulting in approximately 64,000 deaths/year.^{195–199} People ≥ 65 years old experience the highest influenza-associated death rates and account for more than 90% of P&I deaths.^{19,21} The P&I measure is valuable for monitoring yearly trends in influenza severity, but it is not a precise measure of influenza-associated mortality because it includes deaths from pneumonia that are unrelated to influenza and does not include deaths that result from other secondary complications of influenza.^{30,194}

To address the shortcomings of the P&I measure in assessing influenza-associated mortality, statistical models based on epidemiologic data (i.e., mortality data) have been developed to estimate influenza-associated mortality. While no consensus exists on the best method for estimating influenza-associated mortality,^{200–202} statistical modeling based on epidemiologic data gathered since the 1970s indicates that, on average, influenza-associated mortality is approximately 20,000–50,000 deaths/year, and the generally accepted estimate of influenza-associated mortality is 36,000 deaths/year.^{30,193,194,203} Because this estimate is based on imperfect cause-of-death surveillance data, it may be conservative, and some suggest that influenza-associated mortality may be as high as 70,000–90,000 deaths/year.^{16,31} Research also indicates that influenza-related

mortality is increasing in the U.S. due, in part, to the aging U.S. population.³⁰

Appendix 2. Influenza’s Burden on the Healthcare System

The increase in physician visits and hospitalizations during influenza season creates a substantial burden on the healthcare system. It has been estimated that 10–12 hospitalizations occur for each P&I death²⁰⁴—amounting to roughly 640,000–770,000 hospitalizations each year in the U.S. on average from 1999 through 2003. This number is misleading, however, because the P&I measure includes deaths from pneumonia that are not associated with influenza. One study, using statistical modeling of P&I hospitalizations, estimated an average of 114,000 hospitalizations per influenza season directly attributable to influenza—57% of which occurred among people under 65 years old.²⁰⁵ This study underestimates influenza’s total burden, because it looked only at hospitalizations due to P&I and did not assess the increase in hospitalizations that result from influenza-induced exacerbations of underlying chronic conditions. A more recent and broadly focused study estimated that there are more than 200,000 influenza-associated respiratory and circulatory hospitalizations per year in the U.S.³² This study, which analyzed data from 1979–2001, also found that the number of influenza-associated hospitalizations/year have “increased substantially” during the study period—due in part to the aging U.S. population—and that from 1991 through 2001, the average number of influenza-associated hospitalizations was almost 400,000 per year.^{32,55}

Annual influenza epidemics also increase outpatient visits and create a great demand on hospital emergency departments, frequently causing them to go on “diversion”—that is, temporarily diverting new patients elsewhere because of high patient volume.^{26,33–36}

Appendix 3. The Economic Burden of Influenza

Influenza epidemics generate a significant economic burden in the U.S., estimated to be more than \$12 billion per year.² The economic burden is calculated by adding the direct, indirect, and intangible costs incurred each year by influenza.³⁷ Direct costs are those attributable to the influenza virus, such as influenza-associated medical costs (e.g., physician/hospital fees, costs for laboratory tests, prescriptions) and costs associated with vaccination (e.g., costs of producing/administering vaccine, treating adverse events).^{37,79} Direct costs for influenza in the U.S. have been estimated at \$1–3 billion per year.³⁷ Indirect

costs, which account for the largest portion of the costs associated with influenza, refer to costs associated with losses in productivity and school or work absenteeism.³⁷ The Centers for Disease Control and Prevention estimates that in 1996, approximately 70 million workdays and 38 million schooldays were lost due to influenza in the U.S.²⁰⁶ Indirect costs have been estimated at \$10–15 billion per year.³⁷ Intangible costs are the most difficult to calculate and include costs associated with impaired performance and influenza's effects on quality of life (e.g., impaired ability to undertake leisure activities, pain and suffering, etc.).^{37,79,207}

Appendix 4. U.S. Pandemic Influenza Vaccine Production Capacity

Influenza vaccines produced and used to combat annual influenza epidemics are trivalent vaccines, which are composed of three different influenza virus subtypes—A/H3N2, A/H1N1, and B influenza.²⁰⁸ The specific virus strains representing each of these subtypes included in each year's vaccine are selected by the U.S. Food and Drug Administration (FDA) based on epidemiologic surveillance for the predominant circulating influenza virus strains.²⁰⁸ The closer the vaccine virus strains match the predominant influenza virus strains circulating among the populace each year, the more effectively the vaccine prevents disease.

Trivalent influenza vaccines are comprised of 15 μg of antigen from each of the three selected influenza virus subtypes (45 μg total antigen/dose). In the event of a pandemic, only the virus strain causing the pandemic would be included in the pandemic vaccine. Thus, for each dose of trivalent vaccine that can be produced at 45 μg antigen/dose using current production technologies and vaccine formulations, three doses of monovalent pandemic vaccine can be produced at 15 μg antigen/dose. Accordingly, the U.S.'s domestic influenza vaccine production capacity of ~ 60 million doses of trivalent vaccine can yield roughly 180 million doses of monovalent pandemic vaccine at 15 μg antigen/dose (assuming that the pandemic vaccine strain grows as well as intrapandemic vaccine strains grow in egg culture).¹¹⁵

In a pandemic, each person will likely require two doses of vaccine; thus, 180 million doses of monovalent vaccine would be enough to vaccinate 90 million people.¹¹⁵ Accordingly, it would require a domestic production capacity of ~ 200 million doses of trivalent vaccine per year to produce enough monovalent pandemic vaccine to vaccinate the entire U.S. population with two doses of vaccine at 15 μg antigen/dose.¹¹⁵ It is possible that a pandemic vaccine containing 15 μg antigen (i.e., standard dose) would be insufficient to provide protec-

tion and that a "high-dose" influenza vaccine (currently defined by FDA as containing 45 μg antigen/dose) would be required.¹¹⁵ If a "high-dose" vaccine were necessary, the U.S. domestic production capacity of ~ 60 million doses of trivalent vaccine at 45 μg antigen/dose would yield 60 million doses of monovalent pandemic vaccine at 45 μg antigen/dose—enough to vaccinate 30 million people with two doses of vaccine.¹¹⁵ To produce enough pandemic vaccine to vaccinate the entire U.S. population with two doses of vaccine at 45 μg antigen/dose would require an annual domestic trivalent influenza production capacity of 600 million doses.

Recent results from an ongoing clinical trial of a candidate vaccine against the H5N1 influenza virus strain, which has raised concern that the next influenza pandemic may be imminent, suggest that two doses of the candidate vaccine at 90 μg antigen/dose may be necessary to confer protection.¹²⁷ If this finding proves accurate, the U.S. domestic production capacity of ~ 60 million doses of trivalent vaccine at 45 μg antigen/dose would yield 30 million doses of monovalent pandemic vaccine at 90 μg antigen/dose—enough to vaccinate 15 million people with two doses of vaccine. To produce enough pandemic vaccine to vaccinate the entire U.S. population with two doses of vaccine at 90 μg antigen/dose, annual domestic trivalent influenza production capacity would have to be increased to 1.2 billion doses per year.

Increasing U.S. influenza vaccine production capacity using current technologies to two or four times the U.S. population in order to foster pandemic preparedness seems untenable given that there are new potential production technologies and vaccine formulations that may provide a better alternative to pandemic preparedness and eventually render old production technologies obsolete.¹¹⁷ For example, it is possible to improve vaccine production capacity by moving to cell culture-based production, which would be more scalable and have a shorter production time than egg-based production.^{117,160} In addition, it is possible to increase the potency of influenza vaccines by formulating them with adjuvant. An adjuvant is a substance that increases the immune response to the antigens contained in a vaccine. An adjuvanted influenza vaccine—called an *antigen-sparing* vaccine—would require less antigen to produce an effective immune response.¹¹⁵ Experimental, antigen-sparing influenza vaccine formulations containing 1.9 μg antigen/dose have been tested and proven immunogenic.²⁰⁹ Assuming such a formulation proves to be safe and efficacious, the U.S. domestic production capacity of ~ 60 million doses of trivalent vaccine at 45 μg antigen/dose would yield ~ 1.4 billion doses of monovalent, antigen-sparing pandemic vaccine at 1.9 μg antigen/dose—enough to vaccinate ~ 700 million people with two doses

of vaccine.¹¹⁵ Recent preliminary results from a clinical trial of an adjuvanted candidate H5N1 vaccine conducted in France found that the vaccine demonstrated a good immune response at two doses with 30 μg antigen/dose.²¹⁰

Appendix 5. The U.S. Vaccine System and ACIP Recommendations

The vaccine system in the United States is comprised of separate systems to provide adult and childhood vaccinations, both with private and public components.¹⁷³ It relies largely on private sector vaccine purchase and reimbursement of vaccine providers by individuals or third-party payers (e.g., Medicare, Medicaid, private insurance). Public sector immunization assistance is limited in scope to low-income, uninsured, and underinsured individuals (i.e., health insurance plan does not cover vaccination).²¹¹

The majority of recommended childhood vaccines are administered by the private sector (~61% in 2003)—primarily by individual providers (e.g., physicians) who are reimbursed by the individuals and/or third-party payers.^{173,174} While the private sector primarily administers childhood vaccines, the majority (~57% in 2002) of recommended childhood vaccines are actually purchased by the federal government and state and local governments.^{173,174} Most of the childhood vaccines purchased by the federal government are purchased under the Vaccines for Children Program (~41% in 2002), a federal entitlement program that provides vaccines to enrolled providers at no cost; the enrolled providers then administer them at a reduced rate to eligible children (i.e., children under 18 years of age and who are eligible for Medicaid, uninsured, Native American or Alaska Native, or underinsured).^{90,166,212} A smaller portion of the childhood vaccines purchased by the federal government (~11% in 2002) are purchased with discretionary grants provided under Section 317 of the Public Health Service Act (Immunization Grant Program), which has no eligibility restrictions, and an even smaller portion (~5% in 2002) are purchased under state and local programs (eligibility varies by locality).^{173,174,213} Vaccines purchased under these programs are provided for free at public health clinics or given to private physicians, who administer them for an administrative fee—the maximum fee they are permitted to charge by law as determined by the Centers for Medicare and Medicaid Services.^{174,214} Administrative fees are paid by individuals, reimbursed by third-party payers, or absorbed by providers.¹⁷⁴

Like childhood immunizations, the vast majority of adult immunizations are administered in the private sector by individual providers. Many adults also are immunized in nonmedical settings (e.g., work, grocery stores,

wholesale clubs).^{90,215} Unlike childhood immunizations, there is limited public assistance for adult immunizations. While discretionary grants under Section 317 are meant to “ensure that children, adolescents, and adults receive appropriate immunizations,”²¹³ grantees are not required to spend more than 2% of awards on adult immunization and minimal amounts of 317 grants are spent on the purchase of adult immunizations.^{173,216,217} The vast majority of adult immunizations are purchased by private sector providers who are reimbursed by the individuals and/or third-party payers upon vaccination.^{173,174}

ACIP recommendations heavily influence the accepted national standards for immunization in the U.S., essentially determining how vaccines will be used by health-care providers. Accordingly, ACIP plays a significant role in determining the size and stability of the vaccine market.⁹⁰ A universal influenza vaccination recommendation from ACIP would increase the use of influenza vaccine, helping to stabilize the market and increase vaccine supply.^{91,145} However, a universal recommendation under the current system could result in unintended consequences. ACIP decides which vaccines are included in the Vaccines for Children Program, and CDC negotiates annual federal contracts for the purchase of those vaccines at a reduced price.⁹⁰ State and local Vaccines for Children Program grantees then purchase those vaccines at the negotiated price using their award.⁹⁰ States also are allowed to purchase vaccines under the federally negotiated contracts for federally authorized state programs using Section 317 grant awards and/or their own funds.^{90,173} Thus, ACIP recommendations also play a significant role in determining both the size of the vaccine market and the portion of the market purchased by the public sector at a reduced rate. Consequently, ACIP recommendations directly influence U.S. prices for vaccines, which, in turn, directly affect industry involvement in the U.S. vaccine market.^{117,173}

Under the current system, a universal influenza vaccination recommendation from ACIP, if also included in the Vaccines for Children Program, could greatly expand the portion of influenza vaccine purchased by the public sector at a reduced rate. But it is unclear how much influenza vaccine would be purchased under the federal contract in response to a universal recommendation under the current system, whether the funds to purchase vaccine under the Vaccines for Children Program would be approved by the Office of Management and Budget (as required), and ultimately how this would affect the influenza vaccine market as it depends on how much of the market share is purchased by the government and at what price. If the government were to purchase a large share of the influenza vaccine market at too low a price, it could prompt manufacturers to forgo influenza vaccine production, prohibit new manufacturers from entering the mar-

ket, and reduce reinvestment by manufacturers into research and development for new influenza vaccines.⁹⁰ Conversely, a fair price and a sizable and consistent government purchase could have the opposite effect. It is unclear how this might play out under the current system, because the government purchases only a small portion of influenza vaccine each year at prices close to the wholesale price.^{166,217,218}

An ACIP recommendation for universal influenza vaccination also raises the issue of ensuring that those without means who are not currently provided for under the current system (e.g., uninsured and underinsured adults) have equitable access to vaccine.¹¹² Moreover, ACIP recommendations influence state assistance programs and insurance programs, and it is unclear how a universal recommendation would affect these components of the vaccine system—in particular, in regard to vaccine fi-

nancing.⁹⁰ For example, as of 2002, eight states had “universal purchase programs” wherein they purchase and distribute to providers all ACIP-recommended vaccines for all children.⁹⁰ These programs are funded using a combination of federal (Vaccines for Children Program, Section 317 grants) and state funding.⁹⁰ A universal recommendation for influenza vaccine by ACIP would increase the amount of influenza vaccine that these states would need to purchase. However, ACIP recommendations only directly influence funding for the Vaccines for Children Program; ACIP does not control Section 317 funding levels, which are appropriated by Congress each year, or state funding.⁹⁰ Whether these states would have sufficient funding to implement a universal purchase in response to a universal recommendation is uncertain. If sufficient funds are not available, states could be forced to exclude vaccines from these programs.