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Mass Vaccination for Annual and Pandemic Influenza

B. Schwartz (✉) · P. Wortley

Immunization Services Division, National Immunization Program, Centers for Disease Control and Prevention, 1600 Clifton Road NE, Atlanta, GA 30333, USA
bxs1@cdc.gov

Abstract Influenza virus causes annual epidemics and occasional pandemics. Frequent mutations in circulating influenza strains ("antigenic drift") result in the need for annual vaccination. More than two-thirds of persons in the U.S. are recommended for annual vaccination. Because influenza vaccine is available seasonally, mass vaccination strategies are well suited to its delivery. Although doctors offices are the most frequent setting for influenza vaccination overall, workplaces, clinics, and community sites (retail stores and pharmacies) also are common vaccination settings. Influenza vaccination also is delivered in mass vaccination clinics to health care workers and military personnel. Universal influenza vaccination, which has been recommended as a strategy to improve prevention by increasing vaccination coverage and providing indirect protection of adults by decreasing infection and transmission among children, would require expanded use of mass vaccination, for example in schools, as well as in the community. Influenza pandemics occur when a new influenza A subtype is introduced into the population ("antigenic shift"). Most or all of the population is susceptible to the pandemic virus and two doses of vaccine may be needed for protection. U.S. pandemic preparedness and response plans indicate that the entire population should be vaccinated beginning with defined priority groups including those who provide essential services including healthcare and those at highest risk of severe illness and death. Pandemic influenza vaccination will occur primarily through the public

sector in mass clinic settings. Vaccination program planning must consider issues including coordination, staffing, clinic location and lay-out, security, record keeping, and communications. Exercising vaccination clinics is important for preparedness and can be done in the context of annual influenza vaccination.

1 Influenza Disease and Vaccine

Influenza is an acute viral infection characterized by fever, cough, myalgia, and malaise. Complications include pneumonia – either from the viral infection or a secondary bacterial pathogen – otitis media, myositis, myocarditis, and encephalitis. Illness generally is mild and self-limiting but occasionally, severe or complicated disease results in hospitalization and death. In temperate climates, influenza causes annual epidemics, typically during winter months. Attack rates of infection are highest in children who often are the source of transmission within families and communities. In community outbreaks, as many as 40% of children may become infected compared with 10%–20% of adults. By contrast, the burden of severe influenza is concentrated among the elderly; in the US, about 90% of deaths and half of influenza hospitalizations occur among those aged 65 years or more. High high-risk groups also include persons with chronic underlying illnesses, children less than 2 years old, and pregnant women. Recent US estimates suggest that about 36,000 persons die each year from influenza (Thompson et al. 2003), more than for all other vaccine preventable diseases combined, and about 200,000 are hospitalized (Thompson et al. 2004).

Protection against influenza following infection or vaccination is mediated by antibody to hemagglutinin and neuraminidase antigens. These glycoproteins change antigenically through mutation ('antigenic drift') resulting in the continual formation of new viruses. Antibodies induced by prior infection or vaccination may partially protect against infection with a drifted strain. Rarely, reassortment of genetic material between two influenza viruses occurs, resulting in a strain with markedly different HA and/or NA antigens ('antigenic shift'). Antigenic shift among influenza A viruses can result in global epidemics, or pandemics, with circulation of a new virus subtype to which there is little or no prior immunity. The 1918 influenza pandemic, in which an H1N1 strain was introduced into a largely immunologically naive population caused over 500,000 US deaths and, according to some estimates more than 50 million deaths globally. Other twentieth century pandemics, occurring in 1957 (H2N2) and 1968 (H3N2), caused about one-tenth of the number of deaths. Although the timing and severity of influenza pandemics are unpredictable, most experts agree that they are inevitable. Recent transmission of H5N1 influenza viruses from domestic poultry to humans in the context of widespread avian infection in Asia, and other recent instances of animal to human transmission of novel influenza strains, highlight the ongoing pandemic threat (World Health Organization 2005).

Influenza vaccine protects against disease by inducing antibody primarily to the HA protein. Current influenza vaccines are trivalent, targeting two influenza A (H1N1 and H3N2) and one influenza B strain. Because circulating influenza strains may change with each influenza season, vaccination is needed annually. About 50 countries worldwide have influenza vaccination recommendations. In the US vaccination is recommended by the Advisory Committee on Immunization Practices (ACIP) for those who are at high risk for severe illness and their contacts (Table 1), which includes almost two-thirds of the entire population (CDC 2004a). Annual vaccination coverage, however, falls far short of that recommended; only about 83 million doses of influenza vaccine were distributed during the 2003–2004 season for the 186 million persons in the target population. The substantial ongoing mor-

Table 1 Groups targeted for annual influenza vaccination in the US. Recommendations are from the Advisory Committee on Immunization Practices, 2004

Persons at increased risk for influenza complications

- Children 6–23 months old
- Adults 65 years old or older
- Adults and children who have chronic disorders of the cardiovascular or pulmonary systems, including asthma, or who required regular medical follow-up or were hospitalized during the preceding year because of chronic metabolic disease, including diabetes mellitus, renal dysfunction, hemoglobinopathy, or immunosuppression, including that caused by medication or human immunodeficiency virus (HIV) infection
- Women who will be pregnant during the influenza season
- Residents of nursing homes and other chronic-care facilities that house persons of any age who have chronic medical conditions
- Children and adolescents who are receiving long-term aspirin therapy and may be at risk for Reye syndrome after influenza infection

Other recommended groups

- Persons aged 50–64 years
- Health care workers
- Care givers and household contacts of persons in high-risk groups for whom vaccination is recommended, and for infants aged 0–5 months for whom influenza vaccines have not been licensed

bidity and mortality from influenza and the difficulty achieving high rates of vaccination coverage in the elderly and high-risk groups has led to consideration of expanded vaccination recommendations. Universal influenza vaccination may enhance prevention by stimulating increased vaccine uptake by groups currently recommended to be vaccinated, and by decreasing transmission of infection and indirectly protecting vulnerable populations through vaccination of children. Ontario, Canada, adopted a universal vaccination recommendation in 2000, resulting in a significant increase in coverage; disease impacts have not yet been assessed.

2 Mass Vaccination for Annual Influenza Epidemics

Influenza vaccine is particularly well suited for delivery by mass vaccination strategies. Annual vaccine for the Northern Hemisphere becomes available in late-summer or early-fall and must be administered before disease becomes widespread. By contrast with routine vaccination of infants where age-defined medical care visits provide an opportunity for immunization, influenza vaccine is delivered seasonally and most vaccine is administered to adults who seldom make routine medical care visits. Even among children, influenza vaccination visits at medical practices may create a substantial burden. Researchers analyzed a large administrative database to assess the number of additional provider visits that would be required to fully implement a recommendation for vaccination of 6–23-month-old children. If vaccination occurred during a 3-month window and only well child care visits were used for vaccination, 39% of children would require one additional visit and 35% would require two additional visits to be fully immunized (Szilagyi et al. 2003a). The same investigators also assessed the time required for influenza vaccination visits among children at four urban and three suburban practices. The median visit length was 14 min (urban, 22 min; suburban, 9 min) with the majority of that time spent waiting in an examination room (Szilagyi et al. 2003b). The investigators concluded that influenza vaccination of young children at provider's offices would place a substantial burden on busy pediatric practices and that office-based mass vaccination strategies such as vaccination clinics would increase efficiency. Vaccination clinics also may decrease costs which, in a setting of individual, provider-based influenza vaccination, may exceed reimbursement rates when all staff time costs and office overhead are considered. Both facility-based and 'drive-through' vaccination clinics have been implemented as part of a strategy to efficiently increase vaccination rates in children and adults. Other components required for an effective approach include standing orders for vaccination, use of reminder systems, and careful planning of logistics (National Foundation for Infectious Diseases 2003).

Mass influenza vaccination among adults also has been implemented in a variety of settings. Data on where persons were vaccinated against influenza during the previous year were collected in the Center for Disease Control and Prevention's 1999 Behavioral Risk Factor Surveillance System (Table 2) (CDC, unpublished data). Workplaces were the second most common site for influenza vaccination (17.8% of vaccinations), and were the most common site among persons 18–49 years old. Other community vaccination sites in nonhealth care settings contributed an additional 12.4% of influenza vaccinations. Receipt of influenza vaccination in community settings was more common among persons who were younger, healthy, employed, white, college-educated, and who had not had a recent routine check-up. While Black and Hispanic adults were less likely to receive their influenza vaccine at workplaces or other community sites, it is unclear whether this was related to the acceptability of community-based vaccination or access to the locations where vaccine was offered. Influenza vaccination at sites other than provider offices, in addition to decreasing the burden on office-based providers, may offer greater convenience and decreased costs both to the vaccinee and the health care system. Given the importance of influenza vaccination in settings other than physicians' offices, guidelines have been established defining quality standards for immunization in nontraditional settings to assure that the immunizations delivered are safe and effective (Table 3) (CDC 2000).

Table 2 Sites where adults received influenza vaccine, 1998–1999. Data are from the US Behavioral Risk Factor Surveillance System, 1999

Setting	Percent of age group			Total
	18–49 years	50–64 years	≥65 years	
Doctors office. HMO	32.5%	44.6%	62.8%	47.0%
Hospital/emergency department	8.1%	6.7%	5.9%	6.9%
Health department	6.4%	6.8%	6.4%	6.5%
Other clinic/health center	9.0%	9.2%	9.0%	9.1%
Workplace	33.2%	20.1%	1.4%	17.8%
Store	4.5%	6.5%	4.8%	5.1%
Senior/recreational/community center	1.4%	2.7%	6.8%	3.8%
Other nontraditional setting sure	4.7%	3.3%	2.5%	3.5%
Not sure	0.3%	0.2%	0.4%	0.3%

Table 3 Quality standards for adult immunization programs in nontraditional settings based on a report of the US National Vaccine Advisory Committee (MMWR, 2000)

1. Information and education for vaccinees

   Provide information on benefits and risks of vaccination and on the importance of having a medical home and receiving other preventive services
2. Vaccine storage and handling

   Adhere to recommendations in package inserts, especially regarding storage temperature, and maintain records for documentation
3. Immunization history

   Screen before vaccination for immunizations received, health history, allergies, and adverse events following previous vaccinations
4. Contraindications

   As part of the history, assess whether any contraindication exists to vaccination
5. Record-keeping

   Record vaccination information (vaccinees name and age, pre-existing health conditions, vaccination date, vaccine type, dose, site and route of administration, name of the vaccine provider, manufacturer, lot number, and the date the next dose is due). Copies should be given to the vaccinee and their primary-care provider or local health department if no provider is identified
6. Vaccine administration

   Providers who administer vaccine must have the legal authority to do so and must administer vaccine according to information in the package insert
7. Adverse events

   Vaccinators must be trained to recognize and manage adverse reactions. If adverse events occur, they should be reported to the Vaccine Adverse Event Reporting System

Influenza vaccination of residents and staff of nursing homes and other long-term care facilities has been documented to decrease influenza disease and mortality. In a 1991 Canadian survey of nursing homes, the reported mean vaccination coverage at 1,270 responding facilities was 78.5%. Factors associated with higher vaccination coverage among residents included vaccine being offered to all residents, obtaining consent for vaccination at admission rather than annually, automatically vaccinating incompetent residents whose guardians could not be contacted, having a single nonphysician staff member organize the program, and having more program components covered by written policies. Higher coverage among staff was associated with promoting vaccination and holding vaccination clinics in the facility (McArthur et al. 1999).

Occupation-based strategies are an effective approach to vaccinate health care workers, who are recommended for annual vaccination to decrease transmission of infection to patients. Surveillance at one academic medical center found that nosocomial cases accounted for 32% of all influenza among hospitalized patients during the 1987–1988 influenza season when only 4% of health care workers were vaccinated. Following implementation of a program to vaccinate hospital staff, coverage among health care workers increased to 67% for the 1999–2000 season; that year no nosocomial influenza cases were identified. Logistic regression analysis showed a statistically significant inverse association between the rate of health care worker vaccination and the rate of nosocomial influenza among patients (Salgado et al. 2004). Hospital vaccination clinics have succeeded in increasing coverage rates among health care providers by reducing financial barriers and facilitating access (D'Heilly and Nichol 2004). Mobile cart programs, bringing vaccination directly to patient care units (Sartor et al. 2004), represents one innovative and successful strategy.

Vaccination clinics at workplaces outside the health care system also have been implemented to prevent influenza disease-associated absenteeism among employees. A placebo-controlled trial in Minnesota in 1994–1995 showed that vaccination of healthy working adults 18–64 years old resulted in 25% fewer episodes of upper respiratory illness (URI), 43% fewer days of URI-associated sick leave, 44% fewer physician office visits for URI, and a cost savings estimated at almost $47 per person vaccinated (Nichol et al. 1995). However, a similar controlled trial over two influenza seasons (1997–1998 and 1998–1999) at a US manufacturing company found substantially less impact on health outcomes and worker absenteeism, and calculated net societal costs that exceeded benefits (Bridges et al. 2000). Differences between the two studies may relate to rates of influenza disease and vaccine efficacy in the different influenza seasons or differences in leave-taking behaviors; workplace vaccination may be cost-effective in some years or some industrial settings and not in others.

Mass vaccination of military personnel also has been implemented to decrease health impacts and time lost to influenza illness. Crowded living conditions and increased exposure from deployment to areas where outbreaks may be occurring contribute to high rates of respiratory infections in military settings (Gray et al. 1999). Annual influenza vaccination of US military personnel was implemented in the 1950s. This program has been successful in decreasing infections and preventing epidemics. Disease outbreaks, however, may occur when the strains in the vaccine do not match those that are circulating. In 1996, 42% of crew members on a US navy ship developed influenza despite 95% having been appropriately immunized; the H3N2 virus isolated from patients was antigenically distinct from the strain included in the vaccine (Earhart et al. 2001). Military personnel also have been at high risk when antigenic shifts occur. Service personnel experienced substantial mortality and morbidity in the 1918 pandemic; a military unit that traveled to Asia experienced the initial outbreak among Americans in the 1968 pandemic; and a large cluster of cases in 1976 at Fort Dix, New Jersey, led to the swine influenza vaccination program.

Retail stores provide another venue for annual mass vaccination. In many states, pharmacists are allowed to provide immunizations. By dispensing prescription medications, pharmacists are able to identify persons with high-risk conditions and can offer influenza vaccination to this target population. A survey of persons vaccinated by pharmacists in 17 cities found that 84% visited the pharmacy intending to be vaccinated, while 10% went to the pharmacy to receive a prescription medication and 7% to purchase other merchandise. A majority of vaccinees cited convenience as the primary reason for seeking vaccination at a pharmacy compared with other locations (Grabenstein et al. 2001). By contrast with pharmacies where vaccinations are administered throughout the influenza vaccination season, immunization at grocery stores usually is provided by contracted nurses in campaigns lasting 1 or 2 days.

Although mass influenza vaccination clinics in health care and community settings and in institutions increase access to vaccination, access alone is not sufficient to achieve high vaccination coverage. The most important factor associated with receipt of any vaccination is the recommendation of a health care provider, which can easily be made in the context of office visits but not at the time of mass vaccination in a community or workplace setting. Therefore, other mechanisms must be used to motivate and educate potential vaccine recipients, and to overcome barriers to influenza vaccination such as fear of side effects, perception that influenza is a mild disease and that immunization is not important, and cost. Factors associated with a successful occupational program were assessed in a survey of occupational health nurses employed by health care and nonhealth care companies. Successful workplace vaccination programs (those vaccinating more than 50% of employees) were significantly more likely to be implemented by a health care company, to have the costs of vaccination covered by the employer, to have management encouragement of vaccination, and to be implemented by a company having more experience with workplace vaccination (D'Heilly and Nichol 2004).

The features that contribute to a successful community-wide vaccination program are illustrated by a program implemented collaboratively between a hospital system and the health department in a mid-sized US city (Parry et al. 2004). Public awareness was fostered through a variety of media events. A consent form and vaccination cards were developed and an electronic database created to track vaccinations, facilitate roster billing to Medicare for elderly vaccinees, and generate patient recall reminders. Several clinic sites were established, contracts were established with area corporations, and health department staff visited long-term care facilities for the elderly to provide on-site vaccinations. Cost of vaccination was low and health department and hospital employees received free vaccine. The first year following implementation, this program increased the number of influenza vaccinations administered by 70% and at the end of the third program year, by 150%. Emergency department visits for all respiratory diagnoses decreased by 34% and for chronic obstructive lung disease by 46% compared with other areas of the county without this program (Parry et al. 2004).

3
Mass Vaccination for Pandemic Influenza

Several critical factors distinguish vaccination for annual influenza epidemics and for an influenza pandemic. The entire population may be susceptible to a pandemic strain, leading to universal vaccination recommendations. Two vaccine doses may be required to induce an acceptable antibody response to a subtype that has not circulated previously among people. And groups at high risk for severe illness may differ from annual risk groups. During the 1918 pandemic, the age-specific mortality curve was 'W' shaped, with a high risk of death in young adults along with those at the extremes of age.

In the face of increased pandemic vaccine needs, it is likely that vaccine initially will be unavailable as at least 4 months are needed to develop and obtain regulatory approval for the new product. Once production begins, supply in countries with domestic producers will be limited based on manufacturing capacity; in countries without domestic production, vaccine likely will be unavailable as countries will retain what they produce for their own population. Six manufacturers produced influenza vaccine in the US at the time of the 1957 Asian influenza pandemic, this number decreased to four by the 1976 swine influenza program, and currently a single manufacturer produces influenza vaccine from a completely US-based supply chain. Based on current estimates of production capacity from that manufacturer and assuming that 15 μg of antigen will be required per dose and a two-dose vaccination schedule, it is likely that less than half of the US population could be fully vaccinated during the first year of pandemic vaccine production.

Delayed vaccine availability and limited supply will require that pandemic vaccine be targeted to defined priority groups, which would differ from those for annual vaccination. Priority groups likely will include health care workers, persons critical to the pandemic response, public safety workers such as police and fire fighters, and other essential community service providers, in addition to those at high risk for severe disease. The need to effectively target vaccine to priority groups, many of which will be defined by occupation, and to eventually vaccinate the entire population make mass vaccination strategies critical during a pandemic.

Influenza vaccine was used during the 1957 and 1968 pandemics as well as during the swine influenza scare in 1976. In 1957, disease caused by the pandemic strain first occurred in China in February. A vaccine reference strain was delivered to manufacturers in May and the first doses of monovalent vaccine were available in September, over a month after the initial US outbreak in Louisiana. At the peak of the US pandemic in mid-October, fewer than half of the approximately 60 million doses eventually produced had been delivered. Health care workers, essential public servants, and persons at high risk were recommended as priority groups. While manufacturers, at the urging of the Public Health Service, voluntarily distributed vaccine equitably between states, no attempt was made by the public health care sector to control vaccine distribution or enforce vaccination priorities. Consequently, virtually all vaccine doses were delivered by the private sector without regard to the recommendations (US Public Health Service, unpublished data).

The emergence of a new influenza strain in 1968, resulting in the Hong Kong influenza pandemic, occurred relatively late in the year. The ACIP issued influenza vaccination recommendations in late-June for a polyvalent vaccine incorporating older influenza A and B strains (CDC 1968a). In July, an influenza outbreak caused by the new strain was recognized in Hong Kong and in August, US military personnel were infected following a trip to Asia. A new monovalent vaccine, containing the Hong Kong strain was prepared but supply was limited. Therefore, ACIP limited recommendations to adults and children with 'chronic debilitating diseases' and those in older age groups (CDC 1968a). Limited supply of monovalent vaccine before the occurrence of disease outbreaks decreased implementation of a mass vaccination response to the pandemic. However, a landmark study was done to evaluate the impact of mass vaccination of school children on the course of the influenza outbreak in a Michigan community (Monto et al. 1969). In the intervention community, school-based vaccination was implemented with coverage of almost 92% among elementary school children and 75% among high-school students. School absenteeism and rates of respiratory illness were compared for this community and a nearby control community. School absenteeism peaked at about 14% in the control community but never exceeded 8% in the community with the school-based program. Compared with the control community, rates of respiratory illness were substantially lower among the children who had been immunized and also among unvaccinated children attending the same schools. Rates of respiratory illness also were less among young adults in the intervention community, documenting indirect protection (herd immunity) associated with vaccination of children (Monto et al. 1969).

The swine influenza episode in 1976 generally is remembered as a debacle because of vaccine-associated cases of Guillain–Barré syndrome (GBS) and the absence of swine influenza disease. The swine influenza vaccination program also was the first public sector mass vaccination campaign for a pandemic influenza threat. Following identification of H1N1 'swine influenza' disease and person-to-person spread of infection among military personnel at Fort Dix, New Jersey, it was decided to mount a campaign with the goal of vaccinating all Americans. Federal funding was appropriated for vaccine purchase and manufacturers made about 150 million monovalent vaccine doses. State-based mass vaccinations began in October, about 8 months after manufacturing activities began. Within the first 10 days of the program, over one million people had been vaccinated, almost exclusively by mass public sector campaigns. Program intensiveness and vaccination coverage varied greatly between and within states. By the time the program was halted in mid-December following detection of the link with GBS, over 40 million persons had been immunized (Neustadt and Feinberg 1978).

Lessons learned from these pandemic vaccination experiences, along with those from vaccination for annual influenza, have laid the foundation for vaccination strategies for the next pandemic. In 2004, the US released a national pandemic influenza preparedness and response plan to provide guidance to all levels of government and to the health care system regarding critical activities to undertake before and during a pandemic (US Department of Health and Human Services 2005). As in 1957, the plan recommends focusing initially available pandemic vaccine supply to designated priority groups, while similar to 1976 is the recommendation that the entire US population be vaccinated as supply becomes available. Recognizing the difficulty targeting vaccine in 1957 given a private sector program, greater public sector involvement, as in 1976, is proposed.

The goals of a pandemic response include reducing influenza-associated morbidity and mortality, and decreasing societal disruption and economic loss. Vaccination is likely to be the most important intervention to achieve these goals. Global influenza surveillance systems have been strengthened to provide earlier warning of the spread of a new influenza subtype among people, increasing the window for vaccine development, production, and administration before pandemic disease is widespread. Nevertheless, with limited influenza vaccine production capacity and the potential rapid spread of disease globally, vaccine shortages appear inevitable. Optimally achieving pandemic response goals, therefore, requires that available vaccine be effectively targeted to defined priority groups.

A critical strategy to reduce pandemic health impacts – among persons with influenza as well as those with other life-threatening diseases that require care during a pandemic – is to preserve the quality of medical care, particularly in hospitals. Vaccinating hospital personnel would reduce absenteeism due to illness or fear of acquiring disease in the workplace. Because of limited vaccine availability and the need to vaccinate multiple priority groups, targeting vaccination to those hospital personnel who are most essential to quality patient care during a 6–8-week community pandemic outbreak would improve efficiency. Protecting outpatient primary care providers also would be important as delivery of health care in the community will be needed to keep hospitals from becoming overwhelmed.

Maintaining public safety and other essential community services also is important to achieving pandemic response goals. The specific occupational groups to include in this category are not clear and may differ between regions or communities. Limited vaccine supply may dictate a more restricted definition than would be optimal. A critical benchmark to guide decision-making on priority groups may be the question: could the service be adequately maintained despite the loss of one-third of employees who would likely become ill during the outbreak period?

Protecting persons at high-risk for severe or fatal influenza is the focus of annual influenza recommendations and also will be a priority during a pandemic. Based on current ACIP recommendations, almost 30% of the US population is included in this category. Risk groups in a pandemic, however, could differ from those for annual disease. For example, if an H2 strain were to cause the next pandemic, some elderly persons may have partial immunity because of prior exposure to this subtype. Most 2004 human cases and deaths from H5N1 avian influenza in Asia have occurred in children and young adults although it is unclear whether this reflects increased risk of severe illness or more frequent exposure to the poultry vector. An assumption that risk groups will be similar to those for annual disease can be used for pandemic planning but actual vaccination recommendations and programs will need to be based on the epidemiology of the pandemic. A strategy of indirectly protecting persons at high risk by vaccinating children, who are most likely to transmit infection, could be considered (Monto et al. 1969). However, this approach would be a radical departure from past and current practices and would not likely be adopted in the absence of strong supportive data from mathematical models and community trials.

Mass vaccination campaigns coordinated by public health personnel would be most efficient and effective in delivering vaccine to priority groups in a pandemic. Evaluations of adherence by office-based clinicians to special recommendations during shortages of influenza and other vaccines have shown doses frequently being administered to persons not in recommended groups (Broder et al 2005; CDC 2004b). The risks and consequences of misallocation would be exacerbated in a pandemic when risk of severe disease is high and vaccine supply limited. Public sector control of vaccine supply and administration in occupational and community clinic settings would optimize targeting and enhance meeting response goals early in a pandemic. As vaccine supply increases and key priority groups are protected, strategies for vaccine delivery may evolve toward the primarily private sector program used in annual influenza outbreaks, possibly with a greater public sector role to ensure equity in access to vaccine among all racial and ethnic groups.

The national pandemic influenza preparedness and response plan outlines goals for pandemic vaccination and offers guidance regarding priority groups, but planning and implementing specific public sector vaccination activities will be a responsibility of the state and local health departments. State pandemic plans define preparedness activities that will be undertaken during the interpandemic period and response activities that will be implemented during the pandemic (Table 4). State functions include receiving vaccine and storing it securely, distributing vaccine to local health departments, administering it to state level personnel in priority groups, monitoring vaccine coverage and adverse events, and coordinating communications and education. Local leadership will be needed as plans must be tailored to the specific needs of communities, partnerships must be developed with local health agencies and others, and vaccination programs must be implemented.

Mass vaccination for a pandemic will be similar to programs for other public health emergencies. The major components of a mass vaccination plan are summarized with specific reference to issues relevant to an influenza pandemic.

3.1 Coordination

Mass vaccination programs require coordinating large numbers of people and multiple agencies. Incident command provides a standardized structure that is appropriate for a range of public health emergency response programs and can be included in an all-hazards plan. Characteristics of an incident command structure include pre-defied roles and responsibilities for all staff, a clear and uniform chain of command, scalability to meet different levels of program needs, and integration into a community's emergency operations system. Because all communities will be affected by a pandemic, defining the command structure at national, state, and local levels and the interactions between these will be important.

Table 4 Pandemic influenza vaccination preparedness activities to be implemented by State Health Departments

- Improve vaccine delivery during the interpandemic period for recommended groups
- Define vaccination priority groups specifically within the guidance provided from the national level
- Develop and translate educational materials for the public, including CDC's Vaccine Information Statement, which is required by law to be given to all vaccinees
- Develop standing orders allowing influenza vaccination without an individual order by a physician
- Identify health care workers who can assist in a mass vaccination program during a pandemic
- Define the legal basis for licensed and nonlicensed health care personnel providing vaccinations
- Identify whether state statutes provide for mandatory vaccination in specific settings during a pandemic
- Develop a mass vaccination plan and clinic flow-charts
- Develop a mechanism for local health departments (LHDs) to order vaccine from the State
- Develop plans for secure vaccine storage and secure delivery to LHDs
- Develop a registry to track vaccination and provide reminders if a two-dose schedule is needed
- Develop a system to monitor vaccine adverse events in collaboration with CDC and national adverse event surveillance systems
- Review vaccination plans developed by LHDs and assure their adequacy
- Conduct tabletop and field exercises of vaccine preparedness and vaccination

3.2 Staffing

The first step in determining staffing is to define the size of the population to be vaccinated and the strategies needed to reach those populations. Uncertainties regarding priority groups and vaccine supply complicate the planning process. Neighboring jurisdictions would benefit from joint planning activities as persons who live in one state may be vaccinated in a neighboring state where they are employed. Because many vaccinations are likely to be provided in health care and other occupational settings, staff and other human resources already may be on-site. After determining the number of persons to be served, rough calculations can be made to determine the number of staff needed to vaccinate a given population in a given time period. At least two software programs exist to help determine staffing needs (Hupert and Cuomo 2003; CDC 2004c). Although increasing the number of clinics enhances convenience to the public, the number of clinics must be balanced against available staffing as economies of scale are greatest for large clinics.

Identifying sufficient staffing is one of the greatest challenges of mass vaccination. While vaccination early in a pandemic likely will be coordinated by the public sector, staffing needs far exceed what health departments alone can provide, particularly since public health staff likely will have additional pandemic response tasks and may be impacted by pandemic disease. Thus, public health must partner with the private sector to staff mass vaccination clinics. Establishing agreements during the interpandemic period with health care agencies that provide mass vaccination annually in workplaces and other community sites is one potential strategy. Volunteers also may be used in some mass vaccination clinic roles. It may be necessary to relax scopes of work so that persons not normally licensed to vaccinate can legally perform this function in emergency circumstances. Issues of liability protection for vaccinators and other clinic staff may need to be addressed.

Given the uncertainty of when a pandemic will occur and who specifically would staff a vaccination program, training is likely not possible before the event except for persons who will be responsible for training others. Training plans need to be developed in such a way that a relatively small number of persons can train others on a 'just in time' basis.

3.3
Location of Clinics

Clinic location will depend on the target groups for vaccination, characteristics of the community, and human and physical resources available. In an exercise conducted in San Francisco, many neighborhood clinics were held, an ideal approach for a densely populated area where people could walk to clinics and important given limited parking space. In other settings, where the population is more dispersed, availability of adequate parking may be crucial. The need to assure equity in access between racial, ethnic, and socioeconomic groups requires an understanding of issues and needs specific to different subgroups within a community. Clinics located in occupational settings may be optimal for vaccination of some priority groups. Potential locations for community clinics include schools, churches, or auditoriums.

3.4
Clinic Lay-Out

The clinic must be laid out with a number of sequential stations, including for example eligibility screening, registration, medical screening, and vaccination areas. Clinics should have a separate area for special needs patients (e.g., advanced age, infirm) who may not be able to walk through the clinic stations. Ideally, all vaccination clinics in a jurisdiction will share the same floor plan making it easier for staff to move between clinics. Translation services will be important in some communities. Buildings where clinics are to be held need to have separate entry and exit doors to allow for unidirectional flow, functional and accessible restrooms, adequate space for all clinic functions, and separate areas for vaccine preparation and staff breaks.

3.5 Security and Crowd Control

The importance of security for mass vaccination clinics and the number of persons needed for this purpose should not be underestimated. Security staff will be needed for crowd control, traffic movement and personnel safety. In a setting where vaccination priorities are strictly enforced, security personnel may need to help turn away those not in the designated groups. Limiting the number of controlled entry and exit portals will facilitate clinic security.

3.6 Communication and Public Education

The scale of a mass vaccination campaign in a pandemic and the anxiety inherent to a health emergency when a key preventive intervention must be rationed call for clear and consistent communication with the public. The public must be informed of the need to target vaccine supplies, the rationale and the approach to defining priority groups, and the eventual availability of vaccine for everyone. In addition, people must be informed of the procedures to be used in the vaccination campaign before it begins. This includes informing them where and when they need to present for vaccination, the expected processes, and the importance of follow-up if a two-dose vaccination schedule is required. Information must be disseminated through the appropriate channels to reach all the target populations and must be disseminated in multiple languages as needed.

3.7 Exercises

Clinic drills offer an opportunity to test a clinic lay-out, identify and remedy bottleneck areas, and optimize staffing. Exercises are important not only to determine how well the plan will function, but also to help develop partnerships with other agencies and between the public and private sectors. By contrast with other emergency preparedness vaccination programs where opportunities to realistically test vaccination plans are not available, with influenza such opportunities occur annually. Thus, exercises to vaccinate hospital-based heath care workers can help achieve annual influenza prevention goals while also enhancing pandemic preparedness.

Monitoring and evaluation of pandemic influenza vaccination programs are an important shared responsibility of national, state, and local public health personnel. Systems must be developed or existing immunization registries adapted to capture pandemic vaccination data. The ability to use such systems to automatically generate reminders for a second dose, if needed, would be of benefit. Analysis of coverage data at community level should be done periodically during the pandemic to determine whether persons are completing their vaccination schedule, to assess whether vaccine is being effectively targeted to priority groups, and to determine whether disparities in coverage exist between segments of the population among the target populations.

Careful monitoring for adverse events is important for any vaccination program but particularly for pandemic influenza vaccination given the occurrence of GBS associated with swine influenza vaccination in 1976. During a pandemic, national adverse event surveillance may be augmented by state-based systems to stimulate reporting and analyze and investigate signals of potentially vaccine-linked adverse events. The ability to distinguish between coincidental and vaccine-associated events is a particular challenge. Within the first 2 weeks after implementing the swine influenza vaccination program in October 1976, three elderly persons in Pittsburgh died of cardiac disease within a day after vaccination. The local coroner would not rule out vaccination as a contributing factor, the media disseminated the story widely, and several states suspended their vaccination programs. Subsequent analysis of data on cardiac mortality showed that in the context of a mass vaccination campaign, three deaths shortly after vaccination could be expected to occur. The furor subsided, the President demonstrated confidence in the program by being vaccinated, and vaccinations resumed (Neustadt and Feinberg 1978). This episode illustrates, however, the potential for mass vaccination activities to be derailed by vaccine safety concerns and the importance of communication and education before the campaign about the occurrence of coincidental health events, and the value of having calculated, in advance, the expected frequencies of common health events.

4
The Future of Mass Vaccination for Annual and Pandemic Influenza

The significant annual health impacts of influenza, the difficulty achieving high coverage rates among older adults and those at high-risk for severe disease, and lower vaccine efficacy in these populations, have led to consideration of expanded vaccination recommendations. Children experience the highest rates of influenza and transmit infection to household contacts (Neuzil et al. 2002; Principi et al. 2004). Community-based studies have shown that vaccinating children against influenza also decreases influenza disease among adults (Monto et al. 1969; Glezen 2004). A longitudinal study of excess pneumonia and influenza mortality in Japan suggests that rates dropped between 1962 and 1987 when the influenza vaccination program was targeted at school children but increased once the program was discontinued in favor of vaccinating the elderly and those at high risk (Richert et al. 2001). Results from mathematical models also predict greater vaccination program impacts when vaccine is targeted to children (Weycker et al. 2005), with adults indirectly protected because of decreased exposure to influenza as transmission within the community is decreased.

Major challenges exist to implementing a childhood influenza vaccination strategy, potentially under a universal vaccination recommendation. Influenza vaccine supply delays and shortages have occurred in the US during recent years and influenza vaccine manufacturing capacity falls short of that needed to support implementation of expanded recommendations. Developing feasible strategies to reach children and achieve high vaccination coverage, and acceptability of annual vaccination to children, their parents, and medical care providers are additional challenges. Vaccination campaigns in schools would be an ideal approach to achieve access to the large majority of children. In the Michigan community-based study, 86% of all school children were vaccinated: 92% of those in elementary school and 75% of high-school students. Under Ontario, Canada's universal vaccination recommendation, coverage among children tended to be greater in health districts that held school-based clinics compared with those that did not (S. Tamblyn, personal communication). Mass vaccination in schools would be facilitated by use of more acceptable vaccine delivery methods than injection. Intranasal administration of live-attenuated influenza vaccine, licensed in the US for use in healthy persons 5–49 years old, offers an alternate approach. This vaccine also may offer greater cross-protection against drifted influenza variants leading to better effectiveness than inactivated vaccine when the match between the circulating and vaccine strain is less close or in a second year after vaccination the previous season (Gaglani et al. 2004).

If a universal influenza vaccination recommendation were made, in addition to school-based vaccination, implementation would require additional community-based strategies, including expansion of clinics at health departments, workplaces, retail locations, and community centers. Easier vaccine delivery methods also would be of value for adult vaccination; self-administration of the intranasal vaccine has been proposed but would require licensure. Achieving success in vaccinating adults also requires strengthening the public-sector adult immunization infrastructure, which has been a critical factor in the pediatric vaccination program. Key elements of proposals to strengthen adult immunization are enhancing capabilities at state health departments and increasing the public sector role in vaccination financing for adults, possibly through federal financing of vaccines for low income and uninsured adults who do not qualify for current entitlement programs. Some state health departments have conducted mass vaccination exercises for pandemic preparedness which may mimic their role if universal influenza vaccination were recommended annually.

Vaccination for pandemic influenza is constrained primarily by the limited vaccine supply that would be available. If manufacturing capacity were expanded or if innovations in vaccine formulation or delivery were studied and licensed before the next pandemic, approaches to pandemic vaccination also may change. Major expansions in production capacity are unlikely because manufacturers calibrate capacity to annual vaccine demand; in addition, building new facilities requires several years. A more promising solution is licensure of 'antigen-sparing' approaches which would expand the number of doses produced by decreasing the amount of vaccine antigen required in each dose. Adding an aluminum adjuvant to influenza vaccine (Hehme et al. 2002) and administering vaccine intradermally (Belshe et al. 2004; Kenney et al. 2004) have been shown to enhance immune response to vaccination for some circulating as well as novel influenza strains and may make possible lower antigen dose formulations; further investigation of these strategies is needed. An intervention that substantially expands pandemic vaccine availability may decrease the need for strict adherence to vaccination only of priority groups. Efficient mass vaccination programs would be more critical if more doses were available to be administered. Intradermal vaccination would pose special challenges due to the difficulty administering intradermal vaccination with needle and syringe. New intradermal or transcutaneous vaccine delivery methods are being developed to overcome this obstacle (Glenn et al. 2003).

The optimal long-term solution to pandemic and annual vaccination is the development of a new influenza vaccine that induces an immune response to an antigen that is present in all influenza subtypes and does not change. This will prove challenging as natural influenza infection one year does not protect against infection with another strain the following year. However, the availability of various strategies to enhance immune responses beyond what occurs in nature may make this goal possible. A common-epitope influenza vaccine would likely obviate the need for annual vaccination and would mean that persons vaccinated previously would be immune or partially immune to the pandemic strain, depending on the level and duration of protection afforded by vaccination. It also would mean that vaccine could be stockpiled and the risk of shortages eliminated. Although this is a long-term goal that may not be achieved by the time of the next pandemic, the nature of the influenza virus and inevitability of annual epidemics and periodic pandemics, makes it a goal worth pursuing vigorously.

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