Annual Universal Influenza Vaccination: Ready or Not?

Jon S. Abramson,1 Kathleen M. Neuzil,2 and Susan E. Tamblyn3

1Department of Pediatrics, Wake Forest University School of Medicine, Winston-Salem, North Carolina, 2Department of Medicine, University of Washington School of Medicine, VA Puget Sound Health Care System Seattle, Washington, and 3Department of Epidemiology and Biostatistics, Faculty of Medicine and Dentistry, University of Western Ontario, London, Canada

Influenza causes annual worldwide epidemics of respiratory disease. Currently, the United States and many other countries recommend influenza vaccination for persons who are at high risk for influenza-related complications. This commentary explores the potential benefits of a policy advocating universal annual influenza vaccination and outlines obstacles that need to be overcome to make such a recommendation feasible. The 5-year experience of a free influenza vaccination program for everyone ≥6 months of age in the Canadian province of Ontario is reviewed.

In the United States and other developed countries, influenza virus causes the greatest mortality of any microbial organism. On average, 36,000 influenza-related deaths occur annually in the United States, representing a death toll greater than that from all other vaccine-preventable diseases combined. Furthermore, in the United States, influenza results in an average of 150,000 hospitalizations and millions of physician visits each year [1]. Currently, the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) recommends influenza vaccination for individuals with certain underlying medical conditions that predispose them to severe complications of influenza infection, as well as for household members and other close contacts of such individuals. If fully implemented, these recommendations would result in ~190 million people, or approximately two-thirds of the US population, being vaccinated (table 1). However, fewer than 90 million people are vaccinated each year [1].

Realizing the limitations of the current policy, ACIP has begun discussions on the possibility of expanding from an influenza vaccination program that focuses on delivering vaccine to those at highest risk to a program that advocates annual vaccination of everyone ≥6 months of age. Currently, no country in the world recommends universal annual influenza vaccination, although in the fall of 2000, the Canadian province of Ontario implemented a universal program of free influenza vaccination, recommended for everyone ≥6 months of age. The purpose of this commentary is to highlight the potential benefits that could result from universal annual influenza vaccination on a national scale and obstacles that need to be overcome to make such a recommendation feasible.

A universal recommendation has the benefit of simplicity. The complexity of the influenza vaccination recommendations may contribute to the overall poor coverage levels. It is difficult for health care professionals and the public to determine who qualifies for influenza vaccination on the basis of a high-risk condition or on the basis of living or working with others with high-risk conditions. Among adults, influenza vaccination coverage rates have been consistently higher among individuals aged ≥65 years, compared with individuals <65 years old with high-risk conditions (table 2). During the 2004–2005 influenza season, approximately one-half of the expected influenza vaccine supply was never distributed because of vaccine contamination problems [2]. During this vaccine shortage, the differences in coverage rates between adults whose risk was determined by age and adults whose risk was determined by underlying medical condition was even more pronounced [3, 4]. Among children 6–23 months of age, 48.4% received the influenza vaccine during the 2004–2005 influenza season, an impressive coverage rate, given that this was the first year that the ACIP made a universal recommendation for this age group [4]. Remarkably, the rate of influenza vaccination among 6–23-month old children was higher than the vaccination rate among older children with high-risk medical conditions, a group for whom influenza vaccination has been recommended for many years (table 2). Past experience with other vaccines reinforces the concept that universal age-based recommenda-
Table 1. Priority and nonpriority groups approved for vaccination with inactivated influenza vaccine, United States, 2003.

<table>
<thead>
<tr>
<th>Group</th>
<th>Population in millions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Priority</strong></td>
<td></td>
</tr>
<tr>
<td>High-risk group</td>
<td></td>
</tr>
<tr>
<td>Persons aged ≥65 years</td>
<td>35.9</td>
</tr>
<tr>
<td>Persons aged 2–64 years with comorbid conditions</td>
<td>42.4</td>
</tr>
<tr>
<td>Children aged 6–23 months</td>
<td>6.0</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>4.0</td>
</tr>
<tr>
<td>Residents of long-term care facilities</td>
<td>1.7</td>
</tr>
<tr>
<td><strong>Contacts of high-risk group</strong></td>
<td></td>
</tr>
<tr>
<td>Health care personnel</td>
<td>7.0</td>
</tr>
<tr>
<td>Household contacts of children and adults at high risk</td>
<td>75.3</td>
</tr>
<tr>
<td>Healthy persons aged 50–64 years</td>
<td>17.7</td>
</tr>
<tr>
<td>All priority groups</td>
<td>190</td>
</tr>
<tr>
<td><strong>Nonpriority group for whom vaccine is licensed</strong></td>
<td>105.5</td>
</tr>
</tbody>
</table>

**NOTE.** Adapted from [1, 15].

Table 2. Vaccination priority status of adults reporting influenza vaccination, Behavioral Risk Factor Surveillance System, United States.

<table>
<thead>
<tr>
<th>Vaccination priority status group</th>
<th>Vaccination coverage, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>September 2004–January 2005</td>
</tr>
<tr>
<td>All persons ≥65 years old</td>
<td>65.5 62.7</td>
</tr>
<tr>
<td>High-risk persons 18–64 years old</td>
<td>34.2 25.5</td>
</tr>
<tr>
<td>High-risk children 2–17 years old</td>
<td>... 34.8</td>
</tr>
<tr>
<td>All children 6–23 months old</td>
<td>... 48.4</td>
</tr>
</tbody>
</table>

**NOTE.** Adapted from [1, 4].

Solutions are more likely to be successful than risk-based recommendations. With hepatitis B, for example, a major impact on disease occurred only after universal infant vaccination was recommended.

A universal recommendation should help stabilize the supply of influenza vaccine by providing further impetus for current licensed manufacturers to increase production and for new pharmaceutical companies to enter the US market. The 2004–2005 vaccine shortage prompted the US government to seek help from companies that make influenza vaccine but do not have a Food and Drug Administration (FDA)–licensed product approved for use in this country. Through an accelerated FDA approval process, GlaxoSmithKline was able to distribute some of its existing influenza vaccine supply within the United States. A stabler influenza vaccine manufacturing infrastructure would be able to more reliably produce the large quantity of vaccine needed for a universal recommendation. This would decrease the chance of shortages during years in which the disease is epidemic and would potentially improve the infrastructure for rapid production of large quantities of a pandemic influenza vaccine.

Insight into the effect that a universal recommendation might have on a vaccination program is provided by the experience in the Canadian province of Ontario. In fall 2000, a program of universal influenza vaccination was begun in Ontario, and free influenza vaccination was offered to all persons ≥6 months of age. The impetus for this new program was to decrease the number and severity of influenza cases, to reduce the seasonal impact of influenza on the health care system (especially emergency departments), to reduce the economic impact of influenza (especially in workplaces), and to improve pandemic preparedness. Although promoting herd immunity was not a stated program goal, the inclusion of healthy children in the program could decrease the spread of influenza to other vulnerable persons [5–8]. The provincial government purchases the vaccine and distributes it to local health departments, funds vaccine administration, promotes workplace campaigns, and conducts annual province-wide communications campaigns. Local health departments distribute vaccine to family doctors, hospitals, long-term care facilities, and workplaces, provide public and professional education, and conduct public clinics with community partners.

Statistics Canada has recently compared influenza vaccination coverage in all Canadian provinces by analyzing data from national surveys conducted in 1996–1997 and 2000–2001 [9]. Overall coverage increased to 37% in Ontario, compared with 23% in the rest of Canada. Coverage among persons ≥65 years old increased from 60% to 73% in Ontario and from 46% to 63% in the rest of Canada. Among persons <65 years old with
a high-risk condition (a group that is traditionally hard to reach), coverage almost doubled in Ontario, increasing from 25% to 47%, whereas coverage increased from 19% to 26% in the rest of Canada. In the United States in 2003, a year without a vaccine shortage, coverage rates for all persons ≥65 years old and for high-risk persons <65 years old were 65% and 34%, respectively (table 2). These results show an advantage to a universal approach in terms of reaching younger persons at high risk for influenza in Ontario. The most recent Ontario coverage survey found that 42% of the entire population of individuals ≥16 years old had been vaccinated in the 2002–2003 season [10]. This annual accomplishment has taught local health departments and their partners to coordinate and deliver large scale vaccination programs in a limited time period and has enhanced their pandemic preparedness in this regard.

Although the Ontario experience provides support for a universal vaccination program, there will be challenges to implementation on a national scale. To vaccinate large numbers of people within a short time period each year, it is anticipated that many individuals will need to receive vaccination outside of a physician’s office or public health clinic. This is already occurring in the adult population; many people receive vaccination at pharmacies, retail stores, and other community venues. In Ontario, ~60% of doses are given by family doctors, ~20% are given at various clinics, ~10% are given at workplaces, and ~10% are given at hospitals and other sites [10]. Although the trivalent inactivated influenza vaccine can be given to adults outside of traditional health care facilities, the use of this vaccine in nontraditional health care settings is more problematic for children, because of the need to give the vaccine by intramuscular injection. In addition, children <9 years of age who receive the vaccine for the first time are recommended to receive 2 doses of the vaccine administered at least 1 month apart. However, the Ontario model suggests that school-based programs can be successfully implemented. Some health departments provide school-based clinics for all ages using written parental consent, vaccinating up to 38% of schoolchildren at school each fall [11]. In addition, most Ontario health departments use schools as clinic sites, delivering vaccine to both schoolchildren and the public at large. The recent availability of live attenuated influenza vaccine should facilitate vaccination at schools and other nontraditional health care sites and should also facilitate the possibility of self-administration of the vaccine in the home. Furthermore, live attenuated influenza vaccine provides an alternative for people who are needle averse. The current usefulness of live attenuated influenza vaccine is limited by the fact that its US license is restricted to healthy people 5–49 years of age, and it is more expensive than trivalent inactivated influenza vaccine. Studies are currently underway to determine whether live attenuated influenza vaccine can be used in expanded age groups and in those with underlying conditions (e.g., people with asthma) [12].

Any improvements that shorten the manufacturing process will ease the delivery constraints by allowing influenza vaccine to be available sooner. Alternatives to the current egg-based vaccine manufacturing method could allow for both faster vaccine production and broader strain selection. Influenza vaccines based on virus grown in tissue culture rather than in eggs are currently licensed in Europe. Reverse genetic technology has recently been used to rapidly produce a reference vaccine to a potentially pandemic H5N1 strain (the vaccine was made within 1 month after the virus strain was isolated) [13]. A long-range research goal would be to develop an influenza vaccine that induces immunity to viral antigens that do not change over time, thus eliminating the need for annual vaccination.

Prior to implementation of a universal influenza vaccination recommendation, it is important to understand what the program will cost and which end points (e.g., deaths, hospitalizations, and health care visits) should be considered to be the most important criteria for determining whether the benefits justify the expense. A national steering committee, with support from the Public Health Agency of Canada, is coordinating studies of the impact of the Ontario program on health care use and health outcomes (Karim Kurji, Ontario Ministry of Health and Long-Term Care, personal communication). The results of these studies will be helpful in modeling the effect of a universal vaccination policy throughout Canada, the United States, and other countries. Economic modeling of the recent recommendation to administer influenza vaccination to all children 6–23 months of age in the United States suggested cost savings if the cost of vaccination, including the price of the vaccine and administration costs, was no more than $48 per dose [14]. Although it would be helpful if an annual universal vaccination program is cost saving, recent precedent with conjugated pneumococcal vaccine recommendations suggests that cost savings will not be the defining criteria for a vaccine against a disease such as influenza, which has the potential to save many lives [15].

Effective implementation of universal annual influenza vaccination will largely depend on the acceptance of the recommendation by health care workers and the public. Although a large body of evidence supports the safety of this vaccine, unanticipated rare adverse events might occur if the vaccine is given to everyone on an annual basis. Even adverse events that are temporally but not causally related to a vaccine can damage a vaccination program. Another major obstacle to success in the United States relates to who will pay for the vaccine. In Canada, influenza vaccine is provided free for targeted persons in all provinces and for all persons in Ontario. However, in the United States, where the government does not provide the vaccine for free, the cost of immunizing a family will be more
than some can afford. Physicians will want to be assured that
the full cost of vaccination, including the price of the vaccine
and the administration costs, will be adequately reimbursed by
private insurers and the government. Plans to address these
and other concerns need to be in place at the time of program
implementation

So where do things stand? There is little doubt that a rec-
ommendation for universal vaccination, coupled with the nec-
essary infrastructure and adequate resources, will help to sta-
bilize the supply of influenza vaccine and increase the number
of high-risk and healthy people receiving influenza vaccine. This
should lead to reductions in mortality, hospitalizations, office
visits, and missed school and work days that occur each year
due to influenza. However, before one can decide to undertake
what would be the most ambitious vaccination program ever
attempted (even when smallpox vaccine was administered to
everyone, it was not given on an annual basis), very careful
consideration needs to be given to effectiveness, cost, logistics,
and other issues. The 5-year experience in Ontario has shown
that a program of annual, universal vaccination is feasible, en-
courages vaccination in targeted and high-risk groups, and im-
proves pandemic preparedness. The final decision of whether
to provide annual, universal influenza vaccination in other
countries will greatly depend on the breadth and depth of the ensu-
ing debate by public health officials, health care profes-
sionals, and the public.

Acknowledgments

Potential conflicts of interest. K.M.N. has received research grants
from Sanofi-Aventis and MedImmune, both makers of influenza vaccine.
J.S.A. is currently the Chair of the Centers for Disease Control and Pre-
vention Advisory Committee on Immunization Practices. S.E.T.: no
conflicts.

References

1. Centers for Disease Control and Prevention. Prevention and control
of influenza: recommendations of the Advisory Committee on Im-
2. Centers for Disease Control and Prevention. Interim influenza vacci-
nation recommendation, 2004–2005 influenza season. MMWR Rec-
3. Centers for Disease Control and Prevention. Experience with obtaining
influenza vaccination among persons in priority groups during a vac-
cine shortage—United States, November, 2004. MMWR Morb Mortal
4. Centers for Disease Control and Prevention. Estimated influenza vac-
cination coverage among children and adults—United States, Septem-
5. Reichert TA, Sugaya N, Fedson DS, Glezen WP et al. The Japanese
experience with vaccinating schoolchildren against influenza. N Engl
6. Monto AS, Davenport FM. Modification of an outbreak of influenza
in Tecumseh, Michigan, by vaccination of school children. J Infect Dis
7. Gaglani MJ, Piedra PA, Herschler GB, et al. Direct and total effect-
iveness of the intranasal, live-attenuated, trivalent cold-adapted influ-
enza virus vaccine against the 2000–2001 influenza A(H1N1) and B
episode in healthy children. Arch Pediatr Adolesc Med 2004; 158:
65–73.
of routine vaccination of children against influenza. Vaccine 2005; 23:
1284–93.
10. Technology Survey International. Influenza immunization coverage
11. Cronsherry T, Tamblyn SE, Smith JB. Flu shots at school: a recipe for
more effective community coverage (poster P50). In: Program and
abstracts of the 6th Canadian Immunization Conference (Montreal,
12. Treanor J. Influenza vaccine: outmaneuvering antigenic shift and drift.
13. Webby RJ, Perez DR, Coleman JS, et al. Responsiveness to a pandemic
alert: use of reverse genetics for rapid development of influenza vac-
14. Meltzer M, Neuzil KM, Griffin MR, Fukuda K. An economic analysis
15. Lieu RA, Ray GT, Black SB, et al. Projected cost-effectiveness of pneu-
mococcal conjugate vaccination of healthy infants and young children.