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Increasing Immunization Coverage

Committee on Practice and Ambulatory Medicine and Council on Community
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Policy Statement—Increasing Immunization Coverage

COMMITTEE ON PRACTICE AND AMBULATORY MEDICINE AND
COUNCIL ON COMMUNITY PEDIATRICS

KEY WORDS

immunization, vaccines, immunization coverage, increasing immunization coverage, vaccine financing, vaccine supply, vaccine safety, immunization information system, reminder-recall, missed opportunities, risk communication, refusal to vaccinate

ABBREVIATIONS

AAP—American Academy of Pediatrics
VFC—Vaccines for Children
VIS—vaccine information statement
DTaP—diphtheria and tetanus toxoids and acellular pertussis
Hib—*Haemophilus influenzae* type b
HBV—hepatitis B virus
MMR—measles-mumps-rubella
IPV—inactivated poliovirus
VZV—varicella-zoster virus
Td—tetanus toxoids and diphtheria booster
Tdap—tetanus-diphtheria-acellular pertussis booster
HPV—human papillomavirus
CDC—Centers for Disease Control and Prevention
ISO—Immunization Safety Office
NVAC—National Vaccine Advisory Committee
WIC—Special Supplemental Nutrition Program for Women, Infants, and Children
IIS—immunization information system

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abstract

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In 1977, the American Academy of Pediatrics issued a statement calling for universal immunization of all children for whom vaccines are not contraindicated. In 1995, the policy statement “Implementation of the Immunization Policy” was published by the American Academy of Pediatrics, followed in 2003 with publication of the first version of this statement, “Increasing Immunization Coverage.” Since 2003, there have continued to be improvements in immunization coverage, with progress toward meeting the goals set forth in *Healthy People 2010*. Data from the 2007 National Immunization Survey showed that 90% of children 19 to 35 months of age have received recommended doses of each of the following vaccines: inactivated poliovirus (IPV), measles-mumps-rubella (MMR), varicella-zoster virus (VZB), hepatitis B virus (HBV), and *Haemophilus influenzae* type b (Hib). For diphtheria and tetanus and acellular pertussis (DTaP) vaccine, 84.5% have received the recommended 4 doses by 35 months of age. Nevertheless, the *Healthy People 2010* goal of at least 80% coverage for the full series (at least 4 doses of DTaP, 3 doses of IPV, 1 dose of MMR, 3 doses of Hib, 3 doses of HBV, and 1 dose of varicella-zoster virus vaccine) has not yet been met, and immunization coverage of adolescents continues to lag behind the goals set forth in *Healthy People 2010*. Despite these encouraging data, a vast number of new challenges that threaten continued success toward the goal of universal immunization coverage have emerged. These challenges include an increase in new vaccines and new vaccine combinations as well as a significant number of vaccines currently under development; a dramatic increase in the acquisition cost of vaccines, coupled with a lack of adequate payment to practitioners to buy and administer vaccines; unanticipated manufacturing and delivery problems that have caused significant shortages of various vaccine products; and the rise of a public antivaccination movement that uses the Internet as well as standard media outlets to advance a position, wholly unsupported by any scientific evidence, linking vaccines with various childhood conditions, particularly autism. Much remains to be accomplished by physician organizations; vaccine manufacturers; third-party payers; the media; and local, state, and federal governments to ensure dependable vaccine supply and payments that are sufficient to continue to provide immunizations in public and private settings and to promote effective strategies to combat unjustified misstatements by the antivaccination movement.

Pediatricians should work individually and collectively at the local, state, and national levels to ensure that all children without a valid contraindication receive all childhood immunizations on time. Pediatricians and pediatric organizations, in conjunction with government agencies such as the Centers for Disease Control and Prevention, must communicate effectively with parents to maximize their understanding of the overall safety and efficacy of vaccines. Most parents and children have not experienced many of the vaccine-preventable diseases, and the general public is not well informed about the risks and sequelae of these conditions. A number of recommendations are included for pediatricians, individually and collectively, to support further progress toward the goal of universal immunization coverage of all children for whom vaccines are not contraindicated. *Pediatrics* 2010;125:1295–1304

BACKGROUND INFORMATION

In 1977, the American Academy of Pediatrics (AAP) issued a statement calling for universal immunization of all children for whom vaccines are not contraindicated.¹ Most immunizations in the United States are provided by private health care providers. Data from the 2004 National Immunization Survey show that 60.4% of children were vaccinated solely by a private health care provider, and an additional 24.2% received at least some of their vaccinations from a private provider.² Immunizations protect the individual child being vaccinated, but for most vaccine-preventable diseases, achieving high levels of immunization in the community offers indirect protection to others, because they are not exposed to infectious organisms. Children with contraindications to some vaccines, such as children with immunodeficiencies, who cannot receive measles vaccine, are indirectly protected when there is high coverage with measles-containing vaccines around that child. The 1995 AAP policy statement "Implementation of the Immunization Policy"³ supported specific guidelines for improving the vaccine-delivery system and increase immunization rates. Many of the 1995 recommendations have been achieved, including the expansion of immunization financing through the Vaccines for Children (VFC) program,⁴ production of parent-friendly vaccine information statements (VISs), promotion of the standards for child and adolescent immunization practices,⁵ and development of safer and combination vaccines. Additional recommendations in the initial policy statement included (1) sending parent reminders for upcoming visits and implementation of client reminder/recall systems, (2) using prompts during all office visits to remind parents and staff about immunizations needed at that visit, (3) re-

peatedly measuring practice-wide immunization rates over time as part of a quality-improvement effort, and (4) having in place standing orders for nurses, physician assistants, and medical assistants to identify opportunities to administer immunizations, unless such standing orders are prohibited by statute or other regulation.⁶

Childhood immunization rates are one of the leading health indicators used to assess the health of the nation as part of the US Department of Health and Human Services' *Healthy People 2010* initiative.⁷ *Healthy People 2010* set targets for immunization coverage rates for children and adolescents, for individual vaccines, and for the aggregate series of vaccines. For children 19 through 35 months of age, *Healthy People 2010* set a target of 90% coverage for each of the following: 4 doses of diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine, 3 doses of *Haemophilus influenzae* type b (Hib) vaccine, 3 doses of hepatitis B virus (HBV) vaccine, 1 dose of measles-mumps-rubella (MMR) vaccine, 3 doses of inactivated poliovirus (IPV) vaccine, and 1 dose of varicella-zoster virus (VZV) vaccine.⁸ For children who attend licensed child care and children in kindergarten through first grade, an additional target of 95% coverage was set for the DTaP, MMR, and IPV vaccines.⁹ An aggregate target for children in the 19- to 35-month age group was set for a minimum of 80% coverage for the full set of vaccines, referred to as 4:3:1:3:3:1 (at least 4 doses of DTaP vaccine, 3 doses of IPV vaccine, 1 dose of MMR vaccine, 3 doses of Hib vaccine, 3 doses of HBV vaccine, and 1 dose of VZV vaccine).¹⁰ For teenagers 13 to 15 years of age, *Healthy People 2010* sets a target of 90% coverage for each of the following: at least 3 doses of HBV vaccine, 2 doses of MMR vaccine, 1 or more doses of a tetanus-

diphtheria booster (tetanus toxoids and diphtheria booster [Td] or tetanus-diphtheria-acellular pertussis booster [Tdap] vaccine), and 1 or more doses of VZV vaccine (excluding those who have had varicella disease).¹¹

CHALLENGES

With the implementation of many of the recommendations from the 1995 AAP policy statement³ as well as the revised version published in 2003,⁶ much progress has been made toward achieving universal immunization, which was announced as a goal of the AAP in 1977. According to data from the 2007 National Immunization Survey, although only 77.4% of US toddlers 19 to 35 months of age had completed the combined immunization series (4:3:1:3:3:1) described previously,⁷ individual coverage for each of these vaccines, with the exception of the 4-dose series of DTaP vaccine, exceeded 90% for the first time. In 2007, 95.5% of children 19 to 35 months of age had received at least 3 doses of DTaP vaccine, and 84.5% had received 4 doses of DTaP vaccine.¹² Although the Institute of Medicine, in its 2000 report on vaccine financing, cited differences in vaccination rates on the basis of race/ethnicity, poverty, and location in inner-city or rural areas versus suburban areas,¹³ data from the 2007 National Immunization Survey showed similar vaccination rates for the 4:3:1:3:3:1 series for all ethnic/racial groups after controlling for poverty status and a difference in immunization rate of only 3.2% when comparing children at or above the poverty level with children living below the poverty level.¹² Also encouraging are recent data that showed rates of immunization coverage for American Indian/Alaska Native children to be comparable to those of white children.¹² There have been, and will continue to be, challenges to the vaccine-delivery system in terms of the science, economics, and social impact

of immunization, and these challenges have only increased as new vaccines and new vaccine combinations have been developed. Although new vaccines have the potential to improve the health of America's children, they have increased the burden on an already strained vaccine-delivery system.¹⁴ Today's vaccine-delivery system is actually a poorly integrated set of separate systems that include vaccine production, distribution, and financing. Immunization coverage of adolescents is a special challenge, and rates for adolescent immunization remain below targets set by *Healthy People 2010*. For example, data from the National Immunization Survey showed that for teenagers 13 to 17 years of age, only 30.4% had received Tdap vaccine, and only 72% had received at least 1 dose of either Td or Tdap vaccine after 10 years of age.¹⁵ Only 32.4% of adolescents had received meningococcal conjugate vaccine, and only 25.1% of female adolescents had initiated the 3-dose human papillomavirus (HPV) series. Coverage rates for some vaccines were higher but still below the *Healthy People 2010* targets for adolescents 13 through 15 years of age; only 89% of these adolescents had received at least 3 doses of HBV vaccine, 69% had received at least 2 doses of MMR vaccine, and 80% of those without a history of varicella disease had received at least 1 dose of VZV vaccine.¹⁵

Disruptions of Vaccine Supply

Shortages of specific vaccines during 2001–2002 brought to light the fragile nature of the US childhood vaccine supply and resulted in significant disruptions to childhood immunizations. Subsequent to the last publication of this statement in 2003, there have been increasingly disruptive shortages in vital vaccines. Over the past 10 years, shortages of heptavalent pneumococcal conjugate, Hib, HBV, influenza, hepatitis A virus, VZV, and menin-

gococcal conjugate vaccines have led to missed opportunities to immunize and have placed a large administrative burden on the delivery system. Some of these disruptions have lasted for an extended period of time; for example, the recent shortage of Hib vaccine has left a cohort of children not fully immunized with their final dose of Hib vaccine. Shortages of vaccines may lead to parental anxiety and increased demands on the practice setting. Children who fall behind in their coverage because of these systemic delivery disruptions should be tracked and then encouraged to return for these missed vaccine doses by using a reminder/recall system, which will be more easily accomplished with the adoption of electronic health records.

High Vaccine-Acquisition Costs and Inadequate Payment

With the introduction of VZV and heptavalent pneumococcal conjugate vaccines, a new era of higher-cost vaccines began. The introduction of other new vaccines, such as rotavirus and HPV, and combination vaccines such as Pediarix (GlaxoSmithKline Biologicals, Rixensart, Belgium) (HBV, IPV, DTaP) and Pentacel (Aventis Pasteur, Toronto, Ontario, Canada) (Hib, IPV, DTaP), as well as new indications for additional doses of existing vaccines, further increased the acquisition cost and complexity of delivering childhood immunizations. The introduction of HPV vaccine, with its single-dose acquisition cost of more than \$120, brought this issue into acute focus. Estimates from the Centers for Disease Control and Prevention (CDC) for the cost of fully immunizing an otherwise healthy child through the age of 18 years, based on the VFC federal acquisition-cost data chart, indicate that the total acquisition cost has increased to more than \$900 for boys and more than \$1200 for girls, which represents more than a sixfold increase since 1995.¹⁶

These increased acquisition costs are primarily the result of the addition of new vaccines or substitution of newer vaccines for older products by vaccine manufacturers (eg, IPV replacing oral poliovirus vaccine), as well as regular increases in the acquisition cost of older products, which often go unrecognized and unpaid by third-party payers.

Although payment for nearly all vaccines is available through either public or private sources, the high cost of buying, storing, and administering these products has increased to the point that the financial viability of many clinics and private practices is threatened unless realistic payments are provided. For some physicians, the strong desire to provide complete and timely immunizations to their patients is no longer sufficient to overcome these financial barriers. Even with universal purchase of vaccines, the administrative payment level varies tremendously and is often inadequate to justify the actual cost of administering the recommended immunizations, particularly by the Medicaid program, but also by other third-party payers. Third-party payers do not consistently pay at a level adequate to cover the cost of acquisition, storage, and administration of recommended vaccines to their intended recipients. Private payers often delay their coverage of new vaccines and fail to maintain adequate payment as acquisition costs increase, thereby resulting in payments that are insufficient to cover the costs of procuring and delivering vaccines. In a recent survey, half of the pediatricians and family physicians responded that they had delayed purchase of specific new vaccines because of financial reasons, and 5% of pediatricians and 20% of family physicians reported that they were seriously considering discontinuing the vaccination of privately insured patients because of vaccine-

acquisition cost, administration, and payment issues.¹⁷ This will be a larger problem for rural children and children who live in sparsely populated areas with shortages of pediatricians, where family practitioners are called on to provide the bulk of pediatric care. Should the financial situation worsen, the potential remains for more physicians, including pediatricians, to discontinue providing immunization services.

The public sector now purchases more than half of all vaccines administered in the United States through 3 sources of public funding: the federal VFC program, Section 317 federal discretionary grants, and state funds. Children who are eligible for the VFC program include uninsured children and recipients of government-funded health coverage such as Medicaid and the Children's Health Insurance Program in some states, children identified as Alaska Native/American Indian, and underinsured children if they receive vaccine at federally qualified health centers or rural health clinics. States also use Section 317 discretionary funds and their own funds to provide vaccines to children who are not covered by the VFC program or private third-party insurance.

The availability of vaccines through the VFC program and other government sources can be confusing. The VFC program is governed by a set of federal rules that define eligibility. Although VFC eligibility rules do not vary according to state, rules that govern Medicaid eligibility do vary according to state, thereby leading to variation in eligibility for VFC vaccines. These different Medicaid eligibility rules lead to disparities in access, with some states allowing VFC use for children from families with income up to 400% of the federal poverty level, whereas other states may limit VFC use to families with income only 100% of the poverty

level. The burden of record-keeping in the practice setting and inconsistencies in vaccine supply for vaccines funded through Section 317 and other funds places a large administrative burden on practices that elect to participate in these programs. Although the VFC program includes coverage for all CDC-recommended vaccines, variations in supply of vaccines covered by other vaccine sources as well as privately sourced vaccines introduce further complexity for practices that participate in these programs. In some states, such as Georgia, state funds are used to expand the supply of publicly available vaccines by adding these additional vaccine types to their VFC inventory of vaccines, which leads to yet more confusion for providers. Many states prohibit the interchange of VFC-sourced vaccines with private-sourced vaccines, which leads to the uncomfortable situation of having different vaccines available in the office for different groups of patients. In practices that care for both publicly and privately insured patients, these differences in vaccine availability, acquisition cost, and delivery lead to administrative confusion, vaccine-administration errors, and financial uncertainty. In many states, payments for the administration of VFC vaccines are less than the actual costs of administration, further eroding physician participation in the VFC program. Also, although Medicaid may attempt to cover administration costs for its beneficiaries, providers who care for other children enrolled in the VFC program, such as those who are uninsured, are not entitled to payment for their administrative costs of vaccination. Clearly the current "public-private partnership" for purchase, distribution, and administration of immunizations must be redesigned to maintain a consistent supply of vaccines at an acquisition cost that is predictable. This partnership also needs

to provide funding to compensate providers for storage, administration, and overhead that is sufficient to motivate practitioners to continue to participate in immunization services. Given the fact that the vast majority of immunizations are now administered by private-sector providers, it is unlikely that the public sector has the infrastructure to immunize the numbers of children who would be referred to it if private providers stopped administering vaccines. Current levels of payment to pediatricians for administration of vaccines by Medicaid and many private payers are far less than Medicare payments for administration of vaccines to adults, although administering vaccines to consenting adult patients takes significantly less work than administering vaccines to children, who are frequently nonverbal and less cooperative. Furthermore, payment for the administration of combination vaccines should be increased above that of single-component vaccines, or calculated on a per-component basis, in recognition of the fact that the additional components require additional effort on the part of the provider to explain the risks and benefits of each, and the payment should not be lower than that for the individual-component vaccines. The National Vaccine Advisory Committee recently issued a report listing 24 recommendations to ensure adequate supply, distribution, and administration of vaccines in the United States, including the elimination of the financial barriers described previously.¹⁸

Safety Concerns and Media Distortion

Another significant challenge to immunization delivery is the increasing concern within a segment of the general public about the safety and potential adverse effects of childhood immunizations. New and existing organizations and Web sites that portray

themselves as official resources for credible information on vaccines continue to appear on the Internet. These sites provide flawed or biased information that serves to fuel public concern regarding the safety of childhood immunizations, which leads to increased rates of immunization refusal or delays in on-time immunization.¹⁹ Celebrity opponents to vaccination, who are given national coverage by broadcast and cable networks because of their celebrity status, argue their case without scientific support or expert rebuttal. Adding further confusion to the public debate, well-known physicians have also published books that make recommendations, without any scientific or evidentiary basis, for altered vaccine schedules that contradict AAP and CDC recommendations. As a result, pediatricians are seeing an increasing number of parents who are demanding alternate schedules or completely refusing immunizations.²⁰ Pediatricians find themselves spending large amounts of time convincing frightened parents to follow published evidence-based recommendations for vaccine administration, thereby reducing time available for other important components of anticipatory guidance. To counter these antivaccination advocates, the CDC, AAP, and other professional agencies and organizations are also making use of the Internet and other media to promote greater acceptance of universal vaccination by providing evidence-based information and culturally sensitive and language-appropriate educational materials concerning the benefits of immunizations and their risks (eg, www.vaccinateyourbaby.org). Social marketing techniques should also be explored as a promising strategy for promoting acceptance of immunizations among members of the general public who remain hesitant or resistant to vaccinate their children.²¹

In response to the need for greater transparency and accountability regarding vaccine safety and the need to maintain constant surveillance of adverse events after vaccination, the CDC has established the Immunization Safety Office (ISO). Along with the Vaccine Adverse Event Reporting System, a cooperative program between the Food and Drug Administration and CDC, the ISO provides an infrastructure for high-quality vaccine-safety research, surveillance, and effective clinical translation of important vaccine-research findings, with an emphasis on enhanced follow-up of potential adverse events by using innovative research methods. A new and growing area of interest in the field of vaccine safety is the use of genomic research techniques to identify potential gene-based individual differences in vaccine recipients who experience adverse but not causally related events, such as Guillain-Barré syndrome or wheezing episodes after influenza vaccination and rheumatoid arthritis after HBV vaccination. In 2009, the ISO issued a statement on the CDC Web site categorically denying any scientific evidence for the highly publicized alleged linkage between vaccines and autism.²²

OPPORTUNITIES FOR IMPROVEMENT IN IMMUNIZATION COVERAGE

Despite the many challenges described, opportunities exist to improve immunization coverage in the future. With widespread implementation of the VFC program and continued availability of federal Section 317 discretionary funds and state funds, fewer children remain unimmunized in the United States because of purely financial obstacles. It is unfortunate that the level of funding for Section 317 funds is at the discretion of the federal budget and has not always kept pace with the growing cost of vaccine delivery. Con-

tinued efforts at the local, state, and federal levels are needed to further reduce the financial barriers to physicians and families associated with the complex system of vaccine financing described previously.

As reported in the previous version of this policy statement,⁶ the Task Force on Community Preventive Services, convened by the US Department of Health and Human Services with support from the CDC, reviewed evidence from published reports of interventions designed to improve the timely immunization of children and adults.²³ On the basis of the strength of this evidence as applied to the pediatric age group, the task force recommended a number of strategies for increasing immunization coverage for children.²⁴ They grouped these recommendations into 3 overall strategies: increase in community demand for vaccinations; enhancement of access to vaccination services; and provider-based interventions (see Table 1). The task force did not evaluate the extent to which financial constraints on those that provide immunizations (clinics, private offices) also affect the availability of immunizations to their clients.

In 2003, the National Vaccine Advisory Committee (NVAC) published a report titled "Standards for Child and Adolescent Immunization Practices."⁵ This report highlighted 17 immunization practices that were recommended to enhance immunization practices in the United States, including standards for vaccine availability; assessment of vaccination status at every health care encounter; improved communication with parents and patients about vaccine benefits and risks; proper storage, handling, administration, and documentation of immunizations; and a number of specific strategies for increasing coverage, such as reminder systems, office- and clinic-based patient record reviews, and community-

TABLE 1 Quality of Evidence Available to Support Potential Strategies for Increasing Immunization Coverage²⁴

Evidence Sufficient to Strongly Recommend or to Recommend	Insufficient Evidence to Evaluate or to Recommend
Client reminder/recall systems	Community education
Requirements for child care, school, and college enrollment	Patient incentives
Multicomponent patient education	Patient-held medical records
Reducing out-of-pocket costs	Using schools and child care centers as vaccination sites
Increasing vaccination settings closer to patients' homes	Provider education
Expanding clinic hours	Using standing orders
Using emergency departments and subspecialty clinics	
Using WIC sites	
Offering drop-in vaccination services	
Home-visiting services	
Use of electronic records	
Office-based quality-improvement activities	

based approaches. This extensive list of recommended immunization practices overlaps with those recommended by the CDC task force, as described previously, but does not specifically include the task force's recommended strategies involving Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) offices, home-visitation programs, or requirements for entry into child care, school, and college.

In September 2008, the NVAC endorsed a set of principles and recommendations for increasing provider and patient participation in immunization information systems (IISs), formerly known as immunization registries, as another strategy for increasing immunization coverage. The AAP, in its own policy statement in 2006, also endorsed the continued development and implementation of IISs.²⁵ To be most effective, IISs must provide bidirectional flow of vaccination information, allowing providers to enter vaccination data and retrieve patient-specific vaccination histories. It is unfortunate that many current IISs are incompatible with existing electronic medical records and, thus, present an added cost to those practices that are required or wish to participate in these systems. The time and cost of entering vaccination information into an

IIS can be considerable; therefore, payments by government and private insurers to support the entry of patient immunization data into IISs will be necessary for clinical practices that currently use paper-based records to participate in these new systems. Although the deployment of IISs will make it easier to identify patients who are behind on their immunizations, the provision of vaccinations during sick visits or emergency department visits may not be desirable in all situations because of the possible impact on patient compliance with recommendations for well-child care.²⁶

RECOMMENDATIONS

Recommendations below are based on evidence reviewed by the CDC Task Force on Community Preventive Services²⁴ and in the NVAC "Standards for Child and Adolescent Immunization Practices" report⁵ and are updated to include newer recommendations for the use of IISs and to emphasize the importance of the pediatric medical home as the optimal location for the delivery of pediatric immunization services. Additional recommendations beyond those addressed directly in either of these previous publications acknowledge the extensive financial and administrative barriers that private pediatricians and pediatric clinics

face in purchasing and delivering an adequate supply of vaccines to their patients and the current use of various media to influence parental decision-making by those who oppose a policy of universal childhood immunizations. In its most recent report, the NVAC included a set of 24 recommendations that address financial barriers that continue to undermine efforts to reach the goal of universal immunization coverage for children in whom vaccinations are not contraindicated.¹⁸ Where appropriate, those recommendations have been incorporated into this policy statement.

1. Collectively, pediatricians and child health care professionals should join with the AAP and its chapters in the following activities.

- Advocate for all children to receive comprehensive health care, including childhood immunizations, in a medical home²⁷ and improve access for children who are most likely to experience barriers to comprehensive care in a medical home, including members of racial and ethnic minorities, poor or uninsured children, children who live in inner-city or rural areas, and children with chronic medical conditions. Pediatricians can further assist by collaborating with local public and private child health services to identify children without access to a medical home and providing assistance in referring them to an appropriate medical home. The medical home should maintain the children's health records, including immunization records; furthermore, the pediatric medical home requires a level of payment at least as great as that for the adult medical home.
- Assist in the identification of other venues in which vaccina-

tions can be delivered if a significant number of children in a community do not have convenient access to a medical home or if existing medical homes are not able to meet the demand. If sufficient pediatric medical homes are not available, additional venues could include public health department clinics, WIC program offices, child care centers, school-based health clinics, and, in those states that allow it, pharmacies. Elimination of the financial barriers to immunization delivery, as described in this statement, would reduce the need to consider such alternative venues.

- Advocate for reform in the distribution and payment systems that apply to the procurement, storage, and administration of immunizations and that often act as a barrier to physicians who wish to provide immunizations in their private offices and in their clinics. It is important that private- and public-sector payers provide payments to practitioners and clinics for immunization services sufficient not only to cover the direct and indirect costs of these services but also to provide a financial incentive for ongoing participation in this vital service to the community. Using “The Business Case for Vaccine Pricing” (available from Practice Management Online [PMO] at <http://practice.aap.org/content.aspx?aid=1808>), physicians and other child health providers can better understand and advocate for adequate payment for immunization services, including the direct costs of vaccine procurement, storage, and administration as well as the cost of related materials and the professional time involved in providing counseling to concerned parents. These payments must also be sufficient to cover the added indirect opportunity costs of stocking and purchasing expensive vaccines, as well as the predictable costs of wastage, refrigeration, and space. A vaccine-cost calculator is now available on the PMO Web site (<http://practice.aap.org/vaccinecalculator.aspx>). Private physicians should also be encouraged to participate in vaccine-purchasing pools.
- Advocate for a public-private partnership in the manufacture and distribution of vaccines so that purchasers of vaccines (eg, physicians, the VFC program) know what their acquisition costs will be and what to expect in payment for these services before exposing themselves to potential financial losses because of changes in pricing and third-party payment. These efforts would also include advocating for immediate recognition of and payment for newly recommended vaccines, adjustments in payments when prices increase on existing vaccines, and payment of administrative fees per component, not per injection, so as not to discourage the use of combination vaccines. When new vaccines are introduced or when price increases are announced, manufacturers should offer reasonable terms for payment to facilitate their introduction, thereby allowing physicians to purchase and receive payment for vaccines without experiencing excessive financial burden.
- Advocate for the removal of economic and administrative barriers for physicians who wish to participate in the VFC program and other state vaccination programs. Public health department clinics and private physician offices should be included as venues for underinsured VFC-eligible children to receive immunizations, rather than limiting access for these children to federally qualified health centers and rural health clinics.
- Advocate for the removal of economic barriers to immunizations for parents by minimizing their out-of-pocket expenses for immunizations. Public and private payers should provide first-dollar coverage for all recommended vaccines (ie, without copays or deductibles). Use of a uniform acquisition-price standard as the basis for acquisition cost for all vaccine products should be advocated. Such a basis could be the CDC Private Sector Price List, as posted on its Web site (www.cdc.gov/vaccines/programs/vfc/cdc-vac-price-list.htm). Funding is also encouraged to support studies that periodically estimate the actual financial burdens, both direct and indirect, of administering vaccines, and that third-party payers should be expected to honor and pay for these costs.
- Advocate with vaccine manufacturers and state and federal governments to maintain an adequate supply of all childhood vaccines at all times and to provide adequate notice, quick planning, and equitable distribution to all entities that administer immunizations to deal with shortages as they arise.
- Advocate for studies that ensure that the safest and most effective vaccines and combination products are available to children.
- Work with other physician organizations and their representa-

tives to advocate with state and federal governments, private payers, and employers who purchase health care to ensure that timely access to all immunizations recommended by the CDC, the AAP, and the American Academy of Family Physicians for all children remains a high public policy priority.

- Advocate for interoperability of IISs and electronic health records that accommodate bidirectional flow of information to facilitate pediatrician participation in these systems. IISs should also provide support for automated identification of vaccine products (eg, bar codes or radio-frequency tags) and include integrated, up-to-date VISs.
- Advocate for payment by commercial and government payers for the entry of patient immunization information into county and state IISs or for the interfaces necessary to allow transfer of these data from electronic health records to these IISs to support pediatric care provider participation in these systems. Likewise, schools must have adequate funding to cover the costs that arise from their mandate to verify immunization coverage for their students.
- Support ongoing education and quality-improvement programs for pediatricians and other child health care professionals about important vaccine-related issues, including the dissemination of peer-reviewed evidence for more effective immunization delivery. Educational programs should be offered to help physicians incorporate optimal business practices in their office or clinic setting to maximize their opportunities to offer

immunizations to all children for whom vaccines are not contraindicated.

- Vigorously mount a public relations campaign to better inform the public and counter the influence of misinformation spread by celebrities and others who participate in the antivaccination movement to minimize the negative impact of this false information on the health of children. The public must be educated with regard to the risks associated with vaccine-preventable diseases and the impact of immunizations on their prevalence by using culturally effective materials in English and other languages.
2. Individually, pediatricians and other child health professionals are encouraged to do the following to increase the immunization coverage of those under their care.
 - Expand opportunities to immunize in the setting of a medical home by extending office hours when possible, making vaccinations available during visits for minor illnesses (if appropriate), and maintaining accurate and up-to-date records of immunizations received by each patient. Participation in IISs, including those that cross political boundaries, is also recommended.
 - Implement reminder/recall systems based on office charts or electronic information systems and minimize out-of-pocket costs to patients being immunized.
 - Undertake office- and clinic-based assessment and improvement activities necessary to maximize their practices' effectiveness in immunizing children. Offices and clinics should main-

tain up-to-date protocols that are accessible wherever immunizations are delivered and ensure that medically accepted contraindications to immunizations are accurately identified. This goal can be supported by using an IIS that is easily updated with new vaccine information and changes in protocols for existing vaccines.

- Ensure that all those who administer immunizations are fully immunized (unless contraindicated), are knowledgeable about immunizations, and participate in continuing education activities regarding immunizations, including their proper administration, storage, and handling.
- Always provide and document the most current VIS to educate parents about vaccine risks and benefits of immunizations, in accordance with the Vaccine Injury Compensation Program and CDC recommendations (available on the AAP Web site at www.aap.org). Physicians are encouraged to discuss the benefits and risks of immunizations with parents who refuse or delay age-appropriate vaccinations and to document ongoing discussion and refusal by using a form such as the AAP "Refusal to Vaccinate" template (<http://practice.aap.org/popup.aspx?alD=2685&language>). Although the AAP strongly discourages pediatricians from discharging patients from their practices solely as a result of vaccine refusal, pediatricians may encourage a family to find another physician or practice if there is a substantial level of distrust, differences in philosophy of care, or persistent poor quality of communication.²⁸
- Provide their patients with the addresses (URLs) of reliable and

accurate immunization and vaccine-information Web sites that discuss immunization issues (eg, www.aap.org/healthtopics/immunizations.cfm, www.immunize.org, www.cdc.gov/vaccines, www.vaccinateyourbaby.org).

- Report all adverse events related to vaccines by using the Vaccine Adverse Event Reporting System (see <http://vaers.hhs.gov/index> for forms and instructions), as directed by the National Childhood Vaccine Injury Act.²⁹
- Support and implement the standards for child and adolescent immunization practices as

endorsed by the AAP and the NVAC.⁵

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Increasing Immunization Coverage

Committee on Practice and Ambulatory Medicine and Council on Community Pediatrics

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Committee on Infectious Diseases

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POLICY STATEMENT

Recommendations for Prevention and Control of
Influenza in Children, 2011–2012

COMMITTEE ON INFECTIOUS DISEASES

KEY WORDS

influenza, immunization, live-attenuated influenza vaccine, trivalent inactivated influenza vaccine, vaccine, children, pediatrics

ABBREVIATIONS

AAP—American Academy of Pediatrics
HCP—health care personnel
CDC—Centers for Disease Control and Prevention
TIV—trivalent inactivated influenza vaccine
LAIV—live-attenuated influenza vaccine

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abstract

The purpose of this statement is to update recommendations for routine use of trivalent seasonal influenza vaccine and antiviral medications for the prevention and treatment of influenza in children. The key points for the upcoming 2011–2012 season are that (1) the influenza vaccine composition for the 2011–2012 season is *unchanged* from the 2010–2011 season, (2) annual universal influenza immunization is indicated, (3) a *simplified* dosing algorithm for administration of influenza vaccine to children 6 months through 8 years of age has been created, (4) most children presumed to have egg allergy can safely receive influenza vaccine in the office without need for an allergy consultation, and (5) an intradermal trivalent inactivated influenza vaccine has been licensed for the 2011–2012 season for use in people 18 through 64 years of age. Pediatricians, nurses, and all health care personnel have leadership roles in the prevention of influenza through vaccine use and public education. In addition, pediatricians should promptly identify influenza infections to enable rapid treatment, when indicated, to reduce childhood morbidity and mortality. *Pediatrics* 2011;128:813–825

INTRODUCTION

The American Academy of Pediatrics (AAP) recommends annual trivalent seasonal influenza immunization for all children and adolescents 6 months of age and older during the 2011–2012 influenza season. Special outreach efforts should be made to vaccinate people in the following groups:

- All children, including infants born prematurely, 6 months of age and older with conditions that increase the risk of complications from influenza.
- All household contacts and out-of-home care providers of
 - children with high-risk conditions and
 - children younger than 5 years.
- All health care personnel (HCP).
- All women who are pregnant, considering pregnancy, or breastfeeding during the influenza season.

KEY POINTS RELEVANT FOR THE 2011–2012 INFLUENZA SEASON

1. All people 6 months of age and older should receive trivalent seasonal influenza vaccine each year, especially those who are at high

risk of influenza complications (eg, children with chronic medical conditions such as asthma, diabetes mellitus, immunosuppression, or neurologic disorders). In the United States, more than two-thirds of children younger than 6 years and almost all children older than 6 years spend significant time in child care and school settings outside the home. Exposure to groups of children increases the risk of infectious diseases. Children younger than 2 years are at an increased risk of hospitalization and complications attributable to influenza. School-aged children bear a large influenza disease burden and have a significantly higher chance of seeking influenza-related medical care compared with healthy adults. Therefore, reducing influenza transmission among children who attend child care or school should decrease the burden of childhood influenza and transmission of influenza to household contacts and community members. Most egg-allergic children can now receive influenza vaccine safely.

2. Annual trivalent seasonal influenza vaccine is recommended for household members and out-of-home care providers of children and adolescents at high risk of complications of influenza and healthy children younger than 5 years, especially infants younger than 6 months. Pediatric offices should consider serving as an alternate venue for parents and other adults who care for children to receive influenza vaccine, if this approach is acceptable to both the pediatrician and the adult to be immunized. Clinicians should still encourage adults to have a medical home and communicate their

immunization status to the primary care provider. Immunization of close contacts of children at high risk of influenza-related complications is intended to reduce their risk of contagion (ie, “cocooning”). The concept of cocooning is particularly important for helping to protect infants younger than 6 months, because they are too young to be immunized with influenza vaccine. The risk of influenza-associated hospitalization in healthy children younger than 24 months has been shown to be greater than the risk of hospitalization in previously recognized high-risk groups such as the elderly. Children 24 through 59 months of age have had increased rates of outpatient visits and antimicrobial use.

3. The 2009 pandemic influenza A (H1N1) virus emerged in March 2009 and was associated with 2 significant waves of influenza activity during 2009 and 2010, as defined by the World Health Organization. This virus strain disproportionately affected the pediatric population compared with the usual seasonal influenza strains. It was 1 of 3 circulating influenza viruses during the 2010–2011 influenza season, and it is expected to circulate again during the 2011–2012 influenza season in combination with 1 or more of the other seasonal influenza strains. During the 2010–2011 season, influenza A (H3N2) was the predominant circulating strain, but weekly virus subtype activity varied regionally.

4. Although the number of hospitalizations for younger persons and outpatient visits for influenza-like illness overall was lower during the 2010–2011 season compared with the influenza A (H1N1) pan-

demic period, at least 114 laboratory-confirmed influenza-associated pediatric deaths were recorded during the 2010–2011 season. Seventy-one deaths were associated with influenza A virus subtypes: 30 influenza A (2009 H1N1), 21 influenza A (H3N2), and 20 undetermined subtypes. Forty-three deaths were associated with influenza B viruses. More than half of all hospitalized pediatric patients (51.8%) did not have any known underlying conditions (Fig 1). Although children with certain conditions are at higher risk of complications, substantial proportions of seasonal influenza morbidity and mortality occur among healthy children.

5. The recommended trivalent vaccine for the 2011–2012 influenza season contains the following 3 virus strains:
- A/California/7/2009 (H1N1)–like antigen (derived from 2009 pandemic influenza A [H1N1] virus);
 - A/Perth/16/2009 (H3N2)–like antigen; and
 - B/Brisbane/60/2008–like antigen.
6. On the basis of ongoing global surveillance data, for only the fourth time in 25 years there is no need to change any of the influenza vaccine strains (Fig 2). The number of trivalent seasonal influenza vaccine doses to be administered this year depends on the child’s age at the time of the first administered dose and his or her vaccine history (Fig 3):
- Infants younger than 6 months are too young to be immunized with influenza vaccine.
 - Children 9 years of age and older need only 1 dose.
 - Children 6 months through 8 years of age should receive 2 doses of vaccine if they did not receive any dose of vaccine last

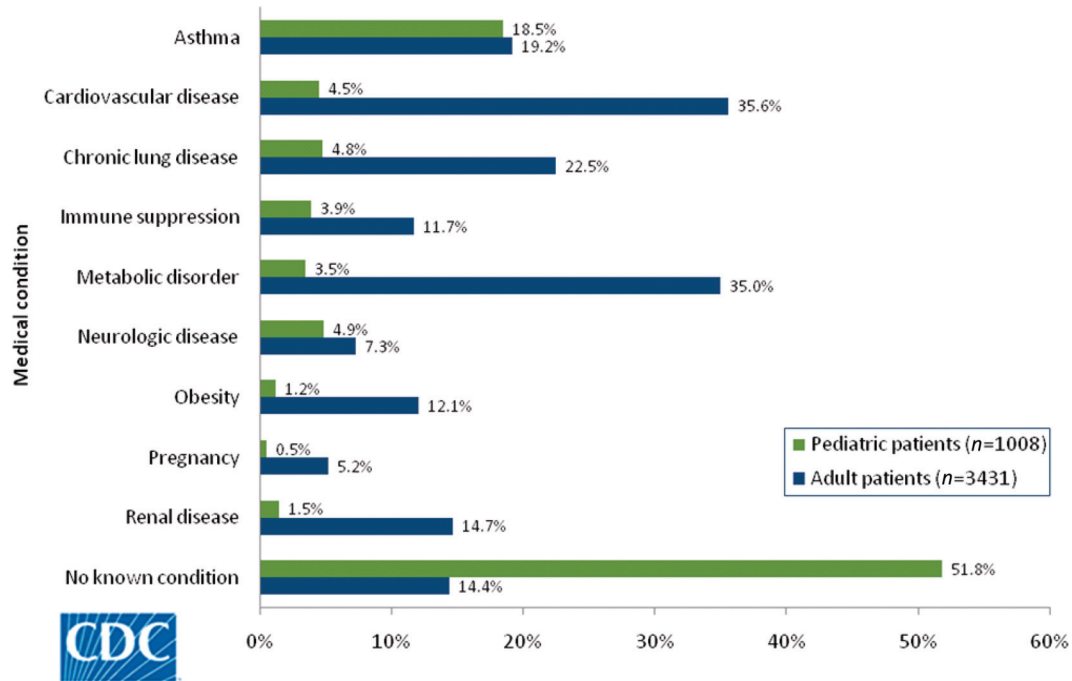


FIGURE 1 Selected underlying medical conditions in patients hospitalized with influenza, FluSurv-NET 2010–2011. Reprinted from: Centers for Disease Control and Prevention. FluView 2010–2011 influenza season week 15 ending April 16, 2010. Available at: www.cdc.gov/flu/weekly.

	H1N1-like strain	H3N2-like strain	B-like strain
1986-87	A/Chile/1/83 and A/Singapore/6/86	A/Christchurch/4/85- A/Mississippi/1/85	B/Ann Arbor/1/86
1987-88	A/Singapore/6/86	A/Leningrad/360/1986	B/Ann Arbor/1/86
1988-89	A/Singapore/6/86	A/Sichuan/2/87	B/Beijing/1/87
1989-90	A/Singapore/6/86	A/Shanghai/11/87	B/Yamagata/16/88
1990-91	A/Singapore/6/86	A/Guizhou/54/89	B/Yamagata/16/88
1991-92	A/Singapore/6/86	A/Beijing/353/89	B/Yamagata/16/88
1992-93 ^a	A/Singapore/6/86	A/Beijing/353/89	B/Yamagata/16/88
1993-94	A/Singapore/6/86	A/Beijing/32/92	B/Panama/45/90
1994-95	A/Singapore/6/86	A/Shangdong/9/93	B/Panama/45/90
1995-96	A/Singapore/6/86	A/Johannesburg/33/94	B/Beijing/184/93
1996-97	A/Singapore/6/86	A/Wuhan/359/95	B/Beijing/184/93
1997-98	A/Bayern/7/95	A/Wuhan/359/95	B/Beijing/184/93
1998-99	A/Beijing/262/95	A/Sydney/5/97	B/Beijing/184/93
1999-2000 ^a	A/Beijing/262/95	A/Sydney/5/97	B/Beijing/184/93
2000-01	A/New Caledonia/20/99	A/Moscow/10/99	B/Beijing/184/93
2001-02	A/New Caledonia/20/99	A/Moscow/10/99	B/Sichuan/379/99
2002-03	A/New Caledonia/20/99	A/Moscow/10/99	B/Hong Kong/330/2001
2003-04 ^a	A/New Caledonia/20/99	A/Moscow/10/99	B/Hong Kong/330/2001
2004-05	A/New Caledonia/20/99	A/Fujian/411/2002	B/Shanghai/361/2002
2005-06	A/New Caledonia/20/99	A/California/7/2004	B/Shanghai/361/2002
2006-07	A/New Caledonia/20/99	A/Wisconsin/67/2005	B/Malaysia/2506/2004
2007-08	A/Solomon Islands/3/2006	A/Wisconsin/67/2005	B/Malaysia/2506/2004
2008-09	A/Brisbane/59/2007	A/Brisbane/10/2007	B/Florida/4/2006
2009-10	A/Brisbane/59/2007	A/Brisbane/10/2007	B/Brisbane/60/2008
Pandemic	A/California/07/2009		
2010-11	A/California/07/2009	A/Perth/16/2009	B/Brisbane/60/2008
2011-12 ^a	A/California/07/2009	A/Perth/16/2009	B/Brisbane/60/2008

FIGURE 2 World Health Organization vaccine composition recommendations 1986 to present. ^a No change in influenza vaccine strains from previous influenza season. Data source: World Health Organization, Global Alert and Response. Recommendations for influenza vaccine composition. Available at: www.who.int/csr/disease/influenza/vaccinerecommendations1/en/index.html (for data from 1998 to present; previous years' data were obtained from *Weekly Epidemiologic Record*).

seasonal influenza vaccine last season need only 1 dose of the 2011–2012 influenza vaccine this season.

In most influenza seasons, children who received influenza vaccine for the *first time* the previous season but who received only 1 dose are recommended to receive 2 doses of vaccine in the current season, because the first vaccine dose primes the immune system, but no significant protection against disease is achieved until 1 week after the second dose. However, because the vaccine strains for the 2011–2012 season are *unchanged* from last season, 1 dose of last season will provide adequate protection (Fig 4). Previous recommendations for 2 doses of vaccine will resume for seasons in which 1 or more of the vaccine strains change.

season. The second dose should be administered at least 4 weeks after the first dose.

- Children 6 months through 8 years of age who received at least 1 dose of the 2010–2011 trivalent

7. Optimal protection is achieved through annual immunization. Antibody titers wane to 50% of their

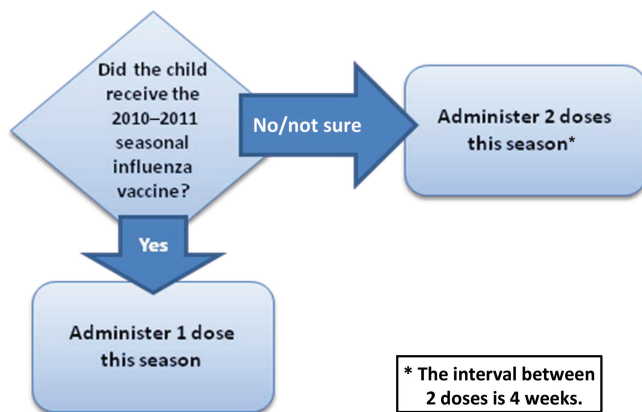


FIGURE 3

Number of 2011–2012 seasonal influenza vaccine doses for children 6 months through 8 years of age.

- This simplified approach is only possible because the 2011–2012 influenza vaccine contains the identical 3 influenza virus strains used last year in the 2010–2011 vaccine.
- The number of doses to be given is determined on the basis of the child's age at the time of the first dose.

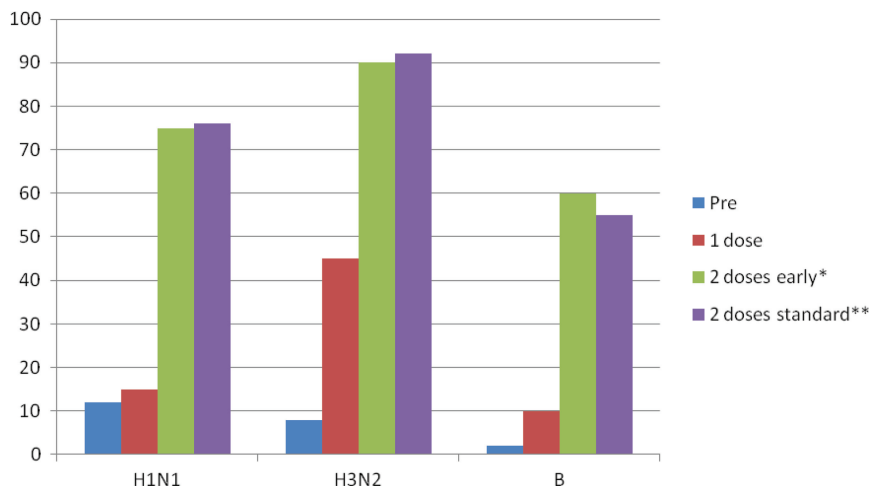


FIGURE 4

Percentage of children with titers greater than 1:32 during seasons with no change in vaccine antigen. * One dose administered in the spring; the second dose administered in the fall. ** Two doses administered 4 weeks apart in the fall. (Reprinted with permission from Englund JA, Fairchok MP, Monto AS, Neuzil KM. *Pediatrics*. 2005;115[4]:1039–1047.)

original levels 6 to 12 months after vaccination. Because the vaccine strains for the 2011–2012 season are unchanged from last season, a repeat dose this season is critical for maintaining protection in all populations.

8. As soon as the trivalent seasonal influenza vaccine is available locally, health care personnel (HCP) should be immunized, publicize vaccine availability to par-

ents and caregivers, and begin immunization of all children 6 months of age and older, especially children at high risk of complications from influenza. HCP endorsement plays a major role in vaccine uptake. A strong correlation exists between HCP endorsement of influenza vaccine and patient acceptance. Providers should continue to offer vaccine through the vaccine expiration

date. Protective immune responses persist throughout the influenza season, which can have >1 disease peak and often extends into March or later. Prompt initiation of influenza immunization and continuance of immunization throughout the influenza season, regardless of whether influenza is circulating (or has circulated) in the community, are critical components of an effective immunization strategy. This approach provides ample opportunity to administer a second dose of vaccine, because children younger than 9 years might require 2 doses to confer optimal protection.

9. HCP, influenza campaign organizers, and public health agencies should collaborate to develop improved strategies for planning, communication, and administration of vaccines.

- Plan to make trivalent seasonal influenza vaccine easily accessible for all children. Examples of such action include creating walk-in influenza clinics, extending office hours beyond routine times during peak vaccination periods, considering how to immunize parents and adult caregivers at the same time in the same office setting as children, and working with other institutions (eg, schools, child care centers, and religious organizations) or alternative care sites, such as emergency departments, to expand venues for administering vaccine while providing appropriate documentation of immunization for the child's medical home.

- Concerted efforts among the aforementioned groups, plus vaccine manufacturers, distributors, and payers, are also necessary to

TABLE 1 Antiviral Drug Sensitivities of Influenza Strains Expected to Circulate During the 2011–2012 Influenza Season

Seasonal Influenza Vaccine Strain (2011–2012)	Amantadine (Symmetrel ^a)/ Rimantadine (Flumadine ^b)	Oseltamivir (Tamiflu ^c)	Zanamivir (Relenza ^d)
Seasonal influenza A (H1N1) virus (derived from 2009 pandemic influenza A [H1N1] virus)	Resistant	Susceptible	Susceptible
Seasonal influenza A (H3N2) virus	Resistant	Susceptible	Susceptible
Seasonal influenza B virus	Resistant	Susceptible	Susceptible

For current recommendations about treatment and chemoprophylaxis of influenza, see www.cdc.gov/flu/professionals/antivirals/index.htm or www.aapredbook.org/flu. Circulating strains in local communities may vary from those found in the vaccine; antiviral sensitivities of these strains are reported weekly at www.cdc.gov/flu/weekly/summary.htm.

^a Endo Pharmaceuticals (Chads Ford, PA).

^b Forest Pharmaceuticals (St Louis, MO).

^c Roche Laboratories (Nutley, NJ).

^d GlaxoSmithKline (Research Triangle Park, NC).

appropriately prioritize distribution to the primary care office setting, especially when vaccine supplies are delayed or limited.

- Vaccine safety, effectiveness, and indications must be communicated properly to the public. HCP should act as role models by receiving influenza immunization annually and recommending annual immunizations to both their colleagues and patients.
10. The neuraminidase inhibitors oseltamivir (Tamiflu [Roche Laboratories, Nutley, NJ]) and zanamivir (Relenza [GlaxoSmithKline, Research Triangle Park, NC]) are the only antiviral medications routinely recommended for chemoprophylaxis or treatment during the 2011–2012 season. All strains of influenza currently anticipated to circulate are susceptible to neuraminidase inhibitors but have high rates of resistance to amantadine and rimantadine (Table 1). Resistance characteristics might change rapidly; clinicians should verify susceptibility information at the start of the influenza season and monitor it during the season through either the AAP Web site (www.aap.org or <http://aapredbook.aappublications.org/flu>) or the Centers for Disease

Control and Prevention (CDC) Web site (www.cdc.gov/flu/index.htm).

11. As the 2011–2012 influenza season unfolds, it is critically important for HCP to be aware of new or changing recommendations from the CDC or their local and state health departments. Up-to-date information can be found on the AAP Web site (www.aap.org or <http://aapredbook.aappublications.org/flu>), through state-specific AAP chapter Web sites, or on the CDC Web site (www.cdc.gov/flu/index.htm).

TRIVALENT SEASONAL INFLUENZA VACCINES

Tables 2 and 3 summarize information on the 2 types of 2011–2012 trivalent seasonal influenza vaccines licensed for immunization of children and adults: injectable trivalent inactivated influenza vaccine (TIV) and intranasally administered live-attenuated influenza vaccine (LAIV). Both vaccines contain the identical strains of influenza A subtypes (ie, H1N1 and H3N2) and influenza B anticipated to circulate during the 2011–2012 influenza season.

TIV is an inactivated vaccine that contains no live virus and cannot produce a viral infection. TIV formulations are now available for intramuscular and intradermal use. The intramuscular formulation of TIV is licensed and rec-

ommended for children 6 months of age and older and adults, including people with and without chronic medical conditions. The most common adverse events after administration are local injection-site pain and tenderness. Fever might occur within 24 hours after immunization in approximately 10% to 35% of children younger than 2 years but rarely in older children and adults. Mild systemic symptoms such as nausea, lethargy, headache, muscle aches, and chills might occur after administration of TIV.

An intradermal formulation of TIV has been licensed for the 2011–2012 season for use in people 18 through 64 years of age. This method of delivery involves a microinjection with a needle 90% shorter than needles used for intramuscular administration. The most common adverse events are redness, induration, swelling, pain, and itching at the site of administration at a slightly higher rate than occurs with the intramuscular formulation of TIV. Headache, myalgia, and malaise might occur and tend to occur at the same rate as that with the intramuscular formulation of TIV. There is no preference for intramuscular or intradermal immunization in people 18 years of age or older; therefore, pediatricians may choose to use either the intramuscular or intradermal product in their late adolescent and young adult patients.

Increased reports of febrile seizures in the United States were noted by the Vaccine Adverse Event Reporting System (VAERS) and were associated with TIV manufactured by Sanofi Pasteur (Fluzone), mainly in children in the 12-through 23-month age group (the peak age for febrile seizures), and included some who concurrently had received 13-valent pneumococcal conjugate vaccine (PCV13). All children fully recovered. On the basis of current data, prophylactic use of antipyretic agents in TIV-immunized children is not indi-

TABLE 2 Recommended Trivalent Seasonal Influenza Vaccines for Different Age Groups: United States, 2011–2012 Influenza Season

Vaccine	Trade Name	Manufacturer	Presentation	Ovalbumin Content, μg of Ovalbumin per 0.5-mL Dose	Thimerosal Mercury Content, μg of Hg per 0.5-mL Dose	Age Group
Inactivated						
TIV	Fluzone	Sanofi Pasteur, Swiftwater, PA	0.25-mL prefilled syringe	$\sim 0.1^a$	0.0	6–35 mo
			0.5-mL prefilled syringe	$\sim 0.1^a$	0.0	≥ 36 mo
			0.5-mL vial	$\sim 0.1^a$	0.0	≥ 36 mo
			5.0-mL multidose vial	$\sim 0.1^a$	25.0	≥ 6 mo
TIV	Fluzone intradermal	Sanofi Pasteur, Swiftwater, PA	0.1-mL prefilled microinjection	Not cited	0.0	18–64 y
TIV	Fluzone HD	Sanofi Pasteur, Swiftwater, PA	0.5-mL prefilled syringe	$\sim 0.1^a$	0.0	≥ 65 y
TIV	Fluvirin	Novartis, East Hanover, NJ	0.5-mL prefilled syringe	$\leq 1.0^b$	< 1.0	≥ 4 y
			5.0-mL multidose vial	$\leq 1.0^b$	25	≥ 4 y
TIV	Fluarix	GlaxoSmithKline, King of Prussia, PA	0.5-mL prefilled syringe	$\leq 0.05^b$	0.0	≥ 3 y
TIV	FluLaval	GlaxoSmithKline, King of Prussia, PA	5.0-mL multidose vial	$\leq 1.0^b$	25.0	≥ 18 y
TIV	Afluria	CSL Biotherapies, King of Prussia, PA	0.5-mL prefilled syringe	$\leq 1.0^b$	0	$\geq 9^c$
			5-mL multidose vial	$\leq 1.0^b$	25.0	$\geq 9^c$
Live-attenuated						
LAIV	FluMist	MedImmune, Gaithersburg, MD	0.2-mL sprayer	Not cited	0.0	2–49 y

^a Data obtained from Sanofi Pasteur (personal communication, 2011) suggests that the residual egg protein (expressed as ovalbumin) in Fluzone vaccine or in Fluzone High-Dose vaccine is typically on the order of 0.1 μg per dose.

^b Data are from the package inserts, many of which have been updated for the 2011–2012 season.

Data sources: American Academy of Pediatrics, Committee on Infectious Diseases. *Pediatrics*. 2010;126(4):816–826; Centers for Disease Control and Prevention. *MMWR Recomm Rep*. 2010;59(RR-8):1–62; and Centers for Disease Control and Prevention. *Morb Mortal Wkly Rep*. 2011;60 (Early Release):1–6.

^c Age indication per package insert is ≥ 5 years; however, the ACIP recommends Afluria not be used in children aged 6 months through 8 years because of increased reports of febrile reactions noted in this age group. If no other age-appropriate, licensed inactivated seasonal influenza vaccine is available for a child aged 5 through 8 years of age who has a medical condition that increases the child's risk for influenza complications, Afluria can be used; however, providers should discuss with the parents or caregivers the benefits and risks of influenza vaccination with Afluria before administering this vaccine.

cated, and current AAP and Advisory Committee on Immunization Practices (ACIP) recommendations for administration of TIV in this age group are unchanged. Febrile seizures can occur anytime a child has a fever, but the typical child who has a febrile seizure recovers quickly and fully.

Previous febrile seizures or seizure disorders are not a contraindication to use of TIV or LAIV in otherwise eligible children. Use of antipyretic agents in febrile children does not reduce the incidence of febrile seizures; therefore, routine use of antipyretic agents for avoiding febrile seizures in children who receive influenza vaccine is not recommended. Approximately 2% to 5% of children 6 months through 5 years of age will have at least 1 febrile seizure not associated with vaccines in their lifetime.

LAIV is a live-attenuated influenza vaccine that is administered intranasally and is licensed by the US Food

and Drug Administration for healthy people 2 through 49 years of age. It is not recommended for people with a history of asthma or other high-risk medical conditions associated with an increased risk of complications from influenza (see “Contraindications and Precautions”). LAIV has the potential to produce mild symptoms including rhinitis, headache, wheezing, vomiting, muscle aches, and fever. LAIV should not be administered to people with copious nasal congestion that would impede vaccine delivery.

Both TIV and LAIV are cost-effective strategies for preventing influenza among children and their families when circulating and vaccine strains are matched closely, but efficacy varies according to the age of the recipient. Current data from direct comparisons of the efficacy or effectiveness of these 2 vaccines are limited, because the studies were conducted in a variety of settings and in popula-

tions using several different clinical end points. In 1 study that compared LAIV with TIV in infants and young children without severe asthma or a recent history of wheezing, LAIV showed significantly better efficacy than TIV; results of other studies suggest that TIV might be more effective in young adults.

A large body of evidence demonstrates that thimerosal-containing vaccines are not associated with increased risk of autism spectrum disorders in children. However, some people might raise concerns about the minute amounts of thimerosal in TIV vaccines, and in some states, there is a legislated restriction on the use of thimerosal-containing vaccines for infants and/or children. The benefits of protecting children against the known risks of influenza are clear. Therefore, children should receive any available formulation of TIV rather than delay immunization while waiting for vaccines with reduced thimerosal content or for

TABLE 3 LAIV Compared With TIV

Vaccine Characteristic	LAIV	TIV
Route of administration	Intranasal spray	Intramuscular or intradermal injection ^a
Type of vaccine	Live virus	Killed virus
Product	Attenuated, cold-adapted	Inactivated subvirion or surface antigen
No. of included virus strains	3 (2 influenza A, 1 influenza B)	3 (2 influenza A, 1 influenza B)
Vaccine virus strains updated	Annually	Annually
Frequency of administration ^b	Annually	Annually
Approved age groups	All healthy persons aged 2–49 y	All persons aged ≥6 mo (intradermal 18–64 y)
Interval between 2 doses in children	4 wk	4 wk
Can be given to persons with medical risk factors for influenza-related complications	No	Yes
Can be given to children with asthma or children aged 2–4 y with wheezing in the previous year	No ^c	Yes
Can be simultaneously administered with other vaccines	Yes ^d	Yes ^d
If not simultaneously administered, can be administered within 4 wk of another live vaccine	No, prudent to space 4 wk apart	Yes
Can be administered within 4 wk of an inactivated vaccine	Yes	Yes

^a The preferred site of TIV intramuscular injection for infants and young children is the anterolateral aspect of the thigh.

^b See Fig 4 for decision algorithm to determine the number of doses of 2011–2012 seasonal influenza vaccine recommended for children this year.

^c LAIV is not recommended for children with a history of asthma. In the 2- through 4-year age group, there are children who have a history of wheezing with respiratory illnesses in whom reactive airways disease is diagnosed and in whom asthma may later be diagnosed. Therefore, because of the potential for increased wheezing after immunization, children 2 through 4 years of age with recurrent wheezing or a wheezing episode in the previous 12 months should *not* receive LAIV. When offering LAIV to children in this age group, a clinician should screen those who might be at higher risk of asthma by asking the parents/guardians of 2-, 3-, and 4-year-olds (24- to 59-month-olds) the question, “In the previous 12 months, has a health care professional ever told you that your child had wheezing?” If the parents answer “yes” to this question, LAIV is *not* recommended for these children.

^d LAIV coadministration has been evaluated systematically only among children 12 to 15 months of age with measles-mumps-rubella and varicella vaccines. TIV coadministration has been evaluated systematically only among adults with pneumococcal polysaccharide and zoster vaccines.

Data sources: American Academy of Pediatrics, Committee on Infectious Diseases. *Pediatrics*. 2010;126(4):816–826; and Fiore AE, Fry A, Shay D, Gubareva L, Bresee JS, Uyeku TM; Centers for Disease Control and Prevention. *MMWR Recomm Rep*. 2011;60(RR-1):1–24.

thimerosal-free vaccine. Although some formulations of TIV contain only a trace amount of thimerosal, certain types can be obtained with no thimerosal. LAIV does not contain thimerosal. Vaccine manufacturers are delivering increasing amounts of thimerosal-free influenza vaccine each year.

Administration to Egg-Allergic Individuals

Although both TIV and LAIV are produced in eggs, recent data have shown that influenza vaccine administered in a single, age-appropriate dose is well tolerated by nearly all recipients who

have egg allergy. More conservative approaches, such as skin testing or a 2-step graded challenge, are no longer recommended.

As a precaution, clinicians should determine if the presumed egg allergy is based on a mild or severe reaction. Mild reactions are defined as hives alone; severe reactions involve cardiovascular changes, respiratory and/or gastrointestinal tract symptoms, or reactions that require the use of epinephrine. Clinicians should consult with an allergist for children with a history of severe reaction. Most vac-

cine administration to people with egg allergy can happen without the need for referral. Data indicate that only approximately 1% of children have immunoglobulin E–mediated sensitivity to egg, and of those, a very small minority have a severe allergy.

Standard immunization practice should include the ability to respond to acute hypersensitivity reactions. Therefore, influenza vaccine should be given to people with egg allergy with the following preconditions (Fig 5):

- Appropriate resuscitative equipment must be readily available.¹
- Ovalbumin content up to 0.7 micrograms/0.5 mL per vaccine dose has been well tolerated (Table 2).
- After immunization, the vaccine recipient should be observed in the office for 30 minutes, the standard observation time after receiving immunotherapy.
- For children who need a second dose, the same product brand is preferred, if possible, but it does not need to be from the same lot as the first dose.

VACCINE STORAGE AND ADMINISTRATION

Intramuscular Vaccine

The intramuscular formulation of TIV is shipped and stored at 2°C to 8°C (35°F–46°F). It is administered intramuscularly into the anterolateral thigh of infants and young children and into the deltoid muscle of older children and adults. The volume of vaccine is age dependent; infants and toddlers older than 6 months but younger than 36 months should receive a dose of 0.25 mL, and all people aged 3 years (36 months) and older should receive 0.5 mL per dose.

Intradermal Vaccine

The intradermal formulation of TIV also is shipped and stored at 2°C to 8°C (35°F–46°F). The package insert

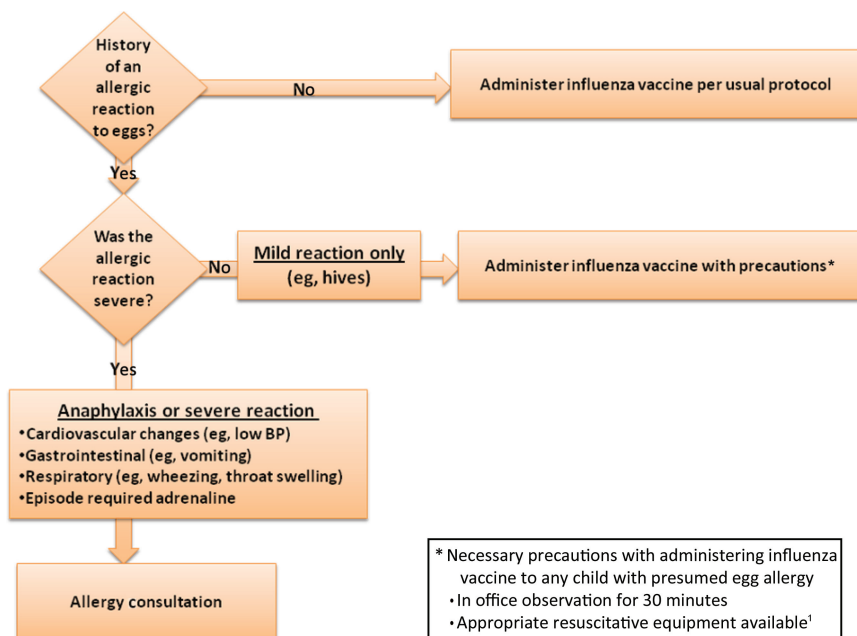


FIGURE 5
Precautions for administering influenza vaccine to presumed egg-allergic recipients.

should be reviewed for full administration details of this new product, which is licensed for the 2011–2012 season for persons 18 through 64 years of age.

Live-Attenuated (Intranasal) Vaccine

The cold-adapted LAIV formulation currently licensed in the United States must be shipped and stored at 2°C to 8°C and administered intranasally in a prefilled, single-use sprayer containing 0.2 mL of vaccine. A removable dose-divider clip is attached to the sprayer to administer 0.1 mL separately into each nostril. Any of the influenza vaccines can be administered at the same visit with all other recommended routine vaccines. After administration of any live-virus vaccine, at least 4 weeks should pass before another live-virus vaccine is administered.

CURRENT RECOMMENDATIONS

Trivalent seasonal influenza immunization is recommended for all children 6 months of age and older. Healthy chil-

dren 2 years of age and older can receive either TIV or LAIV. Particular focus should be on the administration of TIV for all children and adolescents who have underlying medical conditions associated with an increased risk of complications from influenza, including:

- Asthma or other chronic pulmonary diseases including cystic fibrosis.
- Hemodynamically significant cardiac disease.
- Immunosuppressive disorders or therapy.
- HIV infection.
- Sickle cell anemia and other hemoglobinopathies.
- Diseases that require long-term aspirin therapy, including juvenile idiopathic arthritis and Kawasaki disease.
- Chronic renal dysfunction.
- Chronic metabolic disease including diabetes mellitus.
- Any condition that can compromise respiratory function or handling of

secretions or can increase the risk of aspiration, such as neurodevelopmental disorders, spinal cord injuries, seizure disorders, or neuromuscular abnormalities.

Although universal immunization for all people 6 months of age and older is recommended for 2011–2012, particular immunization efforts with either TIV or LAIV should be made for the following groups to prevent transmission of influenza to those at risk, unless contraindicated:

- Household contacts and out-of-home care providers of children younger than 5 years and at-risk children of all ages (healthy contacts 2–49 years of age can receive either TIV or LAIV).
- Any female who is pregnant, considering pregnancy, or breastfeeding during the influenza season (TIV only). Studies have found that infants born to immunized women have better influenza-related health outcomes. However, data suggest that no more than one-half of pregnant women receive seasonal influenza vaccine, although both pregnant women and their infants are at higher risk of complications. In addition, there is limited evidence that influenza vaccination in pregnancy might decrease the risk of preterm birth.
- HCP or health care volunteers. Despite the recent AAP recommendation for mandatory influenza immunization for all HCP,² many HCP remain unvaccinated. As of January 2010, the CDC estimated that only 62% of HCP received the seasonal vaccine and only 37% received the 2009 H1N1 monovalent vaccine. HCP frequently come into contact with patients at high risk of influenza illness in their clinical settings, so it is paramount that HCP protect themselves against influenza to remain influenza free, to prevent disease

transmission to patient populations at high risk, and to avoid lost workplace productivity.

- Close contacts of immunosuppressed people.

CONTRAINDICATIONS AND PRECAUTIONS

Minor illnesses, with or without fever, are not contraindications to the use of influenza vaccines, particularly among children with mild upper respiratory infection symptoms or allergic rhinitis.

Children Who Should Not Be Vaccinated With TIV

- Infants younger than 6 months.
- Children who have a moderate-to-severe febrile illness, on the basis of clinical judgment of the provider.
- Children who are known to have experienced Guillain-Barré syndrome (GBS) within 6 weeks after a previous influenza vaccination; whether influenza vaccination specifically might increase the risk of recurrence of Guillain-Barré syndrome is unknown; the decision not to immunize should be thoughtfully balanced against the potential morbidity and mortality associated with influenza for that individual child.

Children Who Should Not Be Vaccinated With LAIV

- Children younger than 2 years.
- Children who have a moderate-to-severe febrile illness.
- Children with copious nasal congestion that would impede vaccine delivery.
- Children who are known to have experienced Guillain-Barré syndrome within 6 weeks after a previous influenza vaccination; whether influenza vaccination specifically might increase the risk of recurrence of Guillain-Barré syndrome is unknown; the decision not to immunize

should be balanced against the potential morbidity and mortality associated with influenza for that individual child.

- Children who have received other live-virus vaccines within the previous 4 weeks; however, other live-virus vaccines can be given on the same day as LAIV.
- Children with asthma, children with other chronic disorders of the pulmonary or cardiovascular systems, or children 2 through 4 years of age with a history of recurrent wheezing or a medically attended wheezing episode in the previous 12 months.
- Children with chronic underlying medical conditions including metabolic disease, diabetes mellitus, renal dysfunction, and hemoglobinopathies.
- Children who have known or suspected immunodeficiency disease or who are receiving immunosuppressive or immunomodulatory therapies.
- Children who are receiving aspirin or other salicylates.
- Any female who is pregnant or considering pregnancy.
- Children with any condition that can compromise respiratory function or handling of secretions or can increase the risk for aspiration, such as neurodevelopmental disorders, spinal cord injuries, seizure disorders, or neuromuscular abnormalities.

PRECAUTIONS

LAIV is not recommended for children with asthma. In the 2- through 4-year age range, many children have a history of wheezing with respiratory tract illnesses and are eventually diagnosed with asthma. Therefore, because of the potential for increased wheezing after immunization, children younger than 5 years with recurrent wheezing or a medically attended wheezing episode

in the previous 12 months of age should *not* receive LAIV.

When offering LAIV to children 24 through 59 months of age, the clinician should screen them by asking the parent/guardian the question, "In the previous 12 months, has a health care professional ever told you that your child had wheezing?" If a parent answers "yes" to this question, LAIV is *not* recommended for the child. TIV would be recommended for the child to whom LAIV is not given.

In addition, TIV is the vaccine of choice for anyone in close contact with a subset of severely immunocompromised people (ie, people in a protected environment). TIV is preferred over LAIV for contacts of severely immunocompromised people (ie, in a protected environment) because of the theoretical risk of infection in an immunocompromised contact of an LAIV-immunized person. Available data indicate that there is a very low risk of transmission of the virus in both children and adults vaccinated with LAIV. HCP immunized with LAIV may continue to work in most units of a hospital, including the NICU and general oncology wards, while using standard infection-control techniques. As a precautionary measure, people recently vaccinated with LAIV should restrict contact with severely immunocompromised patients (eg, hematopoietic stem cell transplant recipients during periods that require a protected environment) for 7 days after immunization, although there have been no reports of LAIV transmission from a vaccinated person to an immunocompromised person. In the theoretical scenario in which symptomatic LAIV infection develops in an immunocompromised host, oseltamivir or zanamivir could be prescribed, because LAIV strains are susceptible to these antiviral medications.

Information about influenza surveillance is available through the CDC

TABLE 4 Recommended Dosage and Schedule of Influenza Antiviral Medications for Treatment and Chemoprophylaxis for the 2011–2012 Influenza Season: United States

Medication	Treatment (5 d)	Chemoprophylaxis (10 d)
Oseltamivir^a		
Adults	75 mg twice daily	75 mg once daily
Children > 12 mo		
Body weight		
≤15 kg (≤33 lb)	30 mg twice daily	30 mg once daily
>15 to 23 kg (33 to 51 lb)	45 mg twice daily	45 mg once daily
>23 to 40 kg (>51 to 88 lb)	60 mg twice daily	60 mg once daily
>40 kg (>88 lb)	75 mg twice daily	75 mg once daily
Children 3 to <12 mo ^b	3 mg/kg per dose twice daily	3 mg/kg per dose once per day
Children 0 to <3 mo ^c	3 mg/kg per dose twice daily	Not recommended unless situation judged critical because of limited data on use in this age group
Zanamivir^d		
Adults	10 mg (two 5-mg inhalations) twice daily	10 mg (two 5-mg inhalations) once daily
Children (≥7 y for treatment, 5 y for chemoprophylaxis)	10 mg (two 5-mg inhalations) twice daily	10 mg (two 5-mg inhalations) once daily

^a Oseltamivir is manufactured by Roche Laboratories (Nutley, NJ) and is administered orally without regard to meals, although administration with meals may improve gastrointestinal tolerability. Oseltamivir is available as Tamiflu in 30-, 45-, and 75-mg capsules and as a powder for oral suspension that is reconstituted to provide a final concentration of 6 mg/mL. The volume of oral suspension is being changed from 12 mg/mL to 6 mg/mL this year to reduce frothing when shaken. **Oral suspensions in 12 mg/mL concentrations will remain available until supplies run out. For the 6-mg/mL suspension, a 30-mg dose is given with 5 mL of oral suspension, 45-mg dose is given with 7.5 mL oral suspension, 60-mg dose is given with 10 mL oral suspension, and 75-mg dose is given with 12.5 mL oral suspension.** If the commercially manufactured oral suspension is not available, the capsules may be opened and the contents mixed with a sweetened liquid to mask the bitter taste, or a suspension can be compounded by retail pharmacies (final concentration: 15 mg/mL). For patients with renal insufficiency, the dose should be adjusted on the basis of creatinine-clearance rate. For treatment of patients with a creatinine-clearance rate of 10 to 30 mL/min: 75 mg once daily for 5 days. For chemoprophylaxis of patients with a creatinine-clearance rate of 10 to 30 mL/min: 30 mg once daily for 10 days after exposure or 75 mg once every other day for 10 days after exposure (5 doses). (See www.cdc.gov/flu/professionals/antivirals/antiviral-drug-resistance.htm.)

^b Weight-based dosing is preferred; however, if weight is not known, dosing according to age for treatment (give 2 doses per day) or prophylaxis (give 1 dose per day) of influenza in term infants younger than 1 year may be necessary: 0 to 3 months (treatment only), 12 mg (2 mL of 6 mg/mL commercial suspension); 4 to 5 months, 17 mg (2.8 mL of 6 mg/mL of commercial suspension); 6 to 11 months, 24 mg (4 mL of 6 mg/mL commercial suspension). Although Emergency Use Authorization recommendations for use of oseltamivir in children younger than 1 y expired on June 23, 2010, this drug remains appropriate for use when indicated.

^c Current weight-based dosing recommendations are not intended for preterm infants. Preterm infants may have slower clearance of oseltamivir because of immature renal function, and doses recommended for term infants may lead to very high drug concentrations in this age group. Limited data from a cohort of preterm infants who received an average dose of 1.7 mg/kg twice daily revealed drug concentrations higher than those observed with the recommended treatment dose in term infants (3 mg/kg twice daily). Observed drug concentrations were highly variable among preterm infants. These data are insufficient to recommend a specific dose of oseltamivir for preterm infants.

^d Zanamivir is manufactured by GlaxoSmithKline (King of Prussia, PA) and is administered by inhalation using a proprietary "Diskhaler" device distributed together with the medication. Zanamivir is a dry powder (not an aerosol) and should not be administered by using nebulizers, ventilators, or other devices typically used for administering medications in aerosolized solutions. Zanamivir is not recommended for persons with chronic respiratory diseases such as asthma or chronic obstructive pulmonary disease that increase the risk of bronchospasm. Data source: Fiore AE, Fry A, Shay D, Gubareva L, Bresee JS, Uyeki TM; Centers for Disease Control and Prevention. *MMWR Recomm Rep*. 2011;60(RR-1):1–24.

Voice Information System (influenza update, 888-232-3228) or at www.cdc.gov/flu/index.htm. Although current influenza season data on circulating strains do not necessarily predict which and in what proportion strains will circulate in the subsequent season, it is instructive to be aware of 2010–2011 influenza surveillance data and use them as a guide to empiric therapy until current seasonal data are available from the CDC. Information is posted weekly by the CDC (www.cdc.gov/flu/weekly/fluactivitysurv.htm). During the 2010–2011 season, most activity was attributable to influenza A; approximately 66% was attributable to influenza A (H3N2) activity, and 34% was attributable to 2009 (H1N1) activity. Activity varied widely on a local level.

VACCINE IMPLEMENTATION

These updated recommendations for prevention and control of influenza in children will have considerable operational and fiscal effect on pediatric practice. Therefore, the AAP has developed implementation guidance on supply, payment, coding, and liability issues; these documents can be found at www.aapredbook.org/implementation.

USE OF ANTIVIRAL MEDICATIONS

Antiviral resistance can emerge quickly from one season to the next. If local or national influenza surveillance data indicate a predominance of a particular influenza strain with a known antiviral-susceptibility profile, then empiric treatment can be directed to-

ward that strain. For example, during the 2010–2011 season, only 1.3% of influenza viruses tested were resistant to oseltamivir, and none were resistant to zanamivir. High levels of resistance to amantadine and rimantadine persist, and these drugs should not be used in the upcoming season unless resistance patterns change significantly (Table 1).

- Oseltamivir is available in capsule and oral-suspension formulations. The manufactured liquid formulation has a concentration of 6 mg/mL. Oral suspensions in 12 mg/mL concentrations will remain available until supplies run out. If the commercially manufactured oral suspension is not available, the capsule might be

TABLE 5 Persons at Higher Risk Recommended for Antiviral Treatment for Suspected/Confirmed Influenza

Children <2 y of age
Adults ≥65 y of age
Persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematologic (including sickle cell disease), or metabolic (including diabetes mellitus) disorders or neurologic and neurodevelopmental conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle, such as cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability [mental retardation], moderate-to-severe developmental delay, muscular dystrophy, or spinal cord injury)
Persons with immunosuppression, including that caused by medications or by HIV infection
Women who are pregnant or in the postpartum period (within 2 wk after delivery)
Persons aged <19 y who are receiving long-term aspirin therapy
American Indian/Alaska Native persons
Persons who are morbidly obese (ie, BMI ≥ 40)
Residents of nursing homes and other chronic care facilities

Data source: Fiore AE, Fry A, Shay D, Gubareva L, Bresee JS, Uyeki TM; Centers for Disease Control and Prevention. *MMWR Recomm Rep*. 2011;60(RR-1):1–24.

opened and the contents mixed with a sweetened liquid by retail pharmacies to a final concentration of 15 mg/mL (Table 4, footnote “a”).

- Current treatment guidelines (Table 4) are applicable to infants and children with suspected influenza when known virus strains are circulating in the community or when infants or children are confirmed to have seasonal influenza.
- Continuous monitoring of the epidemiology, change in severity, and resistance patterns of influenza strains might lead to new guidance.

Treatment should be offered for:

- Any child hospitalized with presumed influenza or with severe, complicated, or progressive illness, regardless of influenza immunization status.
- Influenza infection of any severity in children at high risk of complications of influenza infection (Table 5).

Treatment should be considered for:

- Any otherwise healthy child with influenza infection for whom a decrease in duration of clinical symptoms is felt to be warranted by his or her provider if treatment can be initiated within 48 hours of illness onset.

Earlier treatment provides more optimal clinical responses, although treatment after 48 hours of symptoms in the child with moderate-to-severe disease or with progressive disease might still provide some benefit. Doses for antiviral agents for both treatment and chemoprophylaxis in children can be found in Table 4 and on the CDC Web site <http://www.cdc.gov/flu/professionals/antivirals/index.htm>. Children younger than 1 year are at increased risk of influenza-related complications. Although there are no antiviral medications licensed by the Food and Drug Administration for this age group and the 2009 H1N1 pandemic Emergency Use Authorization has expired, recommendations for use of oseltamivir in this young age group can still be followed and are provided in Table 4.

Clinical judgment (based on underlying conditions, disease severity, time since symptom onset, and local influenza activity) is an important factor in treatment decisions for pediatric patients who present with influenza-like illness. Antiviral treatment should be started as soon as possible after illness onset and should not be delayed while waiting for a definitive influenza test result. Currently available rapid antigen tests have low sensitivity, particularly for the 2009 pandemic influenza A (H1N1) virus strain and should not be used to rule out influenza. Negative results from rapid antigen tests should not be used to make treatment or infection-control decisions.

People with suspected influenza who

present with an uncomplicated febrile illness typically do not require treatment with antiviral medications unless they are at higher risk of influenza complications, especially in situations with limited antiviral medication availability. Should there be a shortage of antiviral medications, local public health authorities might provide additional guidance about testing and treatment. Rapid antigen tests are not helpful in the management of children with suspected influenza.

Recommendations for chemoprophylaxis during an influenza outbreak:

- For children at high risk of complications from influenza for whom influenza vaccine is contraindicated.
- For children at high risk during the 2 weeks after influenza immunization.
- For family members or HCP who are unimmunized and are likely to have ongoing, close exposure to:
 - unimmunized children at high risk; or
 - infants and toddlers who are younger than 24 months.
- For control of influenza outbreaks for unimmunized staff and children in a closed institutional setting with children at high risk (eg, extended care facilities).
- As a supplement to immunization among children at high risk, including children who are immunocompromised and might not respond to vaccine.
- As postexposure prophylaxis for family members and close contacts of an infected person if those people are at high risk of complications from influenza.
- For children at high risk and their family members and close contacts, as well as HCP, when circulating strains of influenza virus in the community are not matched with triva-

lent seasonal influenza vaccine strains, on the basis of current data from the CDC and local health departments.

These recommendations apply to routine circumstances, but it should be noted that guidance might change on the basis of updated recommendations from the CDC in concert with antiviral-agent availability, local resources, clinical judgment, recommendations from local or public health authorities, risk of influenza complications, type and duration of exposure contact, and change in epidemiology or severity of influenza.

Chemoprophylaxis should not be considered a substitute for immunization. Influenza vaccine should always be offered when not contraindicated, even when influenza virus is circulating in the community. Antiviral medications currently licensed are important adjuncts to influenza immunization for control and prevention of influenza disease, but indiscriminate use might promote resistance and/or limit availability (Table 1). Providers should inform recipients of antiviral chemoprophylaxis that risk of influenza is lowered but still remains while taking medication, and susceptibility to influenza returns when medication is discontinued. For recommendations about treatment and chemoprophylaxis against influenza, see Table 4. Updates will be available at www.aapredbook.org/flu and www.cdc.gov/flu/professionals/antivirals/index.htm.

FUTURE NEEDS

Manufacturers anticipate being able to provide adequate supplies of vaccine. Efforts should be made to create adequate outreach and infrastructure to ensure an optimal distribution of vaccine so that more people are immunized. Health care for children should be provided in the child's medical

home. However, medical homes might have limited capacity to accommodate all patients (and their families) who seek influenza immunization. Because of the increased demand for immunization during each influenza season, the AAP and the CDC recommend vaccine administration at any visit to the medical home during influenza season when it is not contraindicated, at specially arranged "vaccine-only" sessions, and through cooperation with community sites, schools, and child care centers to provide influenza vaccine. If alternate venues are used, a system of patient record transfer is beneficial for ensuring maintenance of accurate immunization records. Immunization-information systems should be used whenever available.

Cost-effectiveness and logistic feasibility of vaccinating everyone continue to be concerns. With universal immunization, particular attention is being paid to vaccine supply, distribution, implementation, and financing. Potential benefits of more widespread childhood immunization among recipients, their contacts, and the community include fewer influenza cases, fewer outpatient visits and hospitalizations for influenza infection, and a decrease in the use of antimicrobial agents, absenteeism from school, and lost parent work time.

Continued evaluation of the safety, immunogenicity, and effectiveness of influenza vaccine, especially for children younger than 2 years, is important. Development of a safe, immunogenic vaccine for infants younger than 6 months is essential. Consideration of how best to offer to immunize parents and adult child care providers in the pediatric office setting continues to be investigated. Mandatory annual influenza immunization has been implemented successfully at pediatric institutions, and future efforts should include broader implementation of mandatory

immunization programs. Optimal prevention of influenza in the health care setting depends on coverage of at least 90% of HCP. Finally, efforts are underway to improve the vaccine-development process to allow for a shorter interval between identification of vaccine strains and vaccine production.

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Recommendations for Prevention and Control of Influenza in Children, 2011–2012

Committee on Infectious Diseases

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ORIGINAL ARTICLE

Live Attenuated versus Inactivated Influenza Vaccine in Infants and Young Children

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ABSTRACT

BACKGROUND

Universal vaccination of children 6 to 59 months of age with trivalent inactivated influenza vaccine has recently been recommended by U.S. advisory bodies. To evaluate alternative vaccine approaches, we compared the safety and efficacy of intranasally administered live attenuated influenza vaccine with those of inactivated vaccine in infants and young children.

METHODS

Children 6 to 59 months of age, without a recent episode of wheezing illness or severe asthma, were randomly assigned in a 1:1 ratio to receive either cold-adapted trivalent live attenuated influenza vaccine (a refrigeration-stable formulation of live attenuated intranasally administered influenza vaccine) or trivalent inactivated vaccine in a double-blind manner. Influenza-like illness was monitored with cultures throughout the 2004–2005 influenza season.

RESULTS

Safety data were available for 8352 children, and 7852 children completed the study according to the protocol. There were 54.9% fewer cases of cultured-confirmed influenza in the group that received live attenuated vaccine than in the group that received inactivated vaccine (153 vs. 338 cases, $P < 0.001$). The superior efficacy of live attenuated vaccine, as compared with inactivated vaccine, was observed for both antigenically well-matched and drifted viruses. Among previously unvaccinated children, wheezing within 42 days after the administration of dose 1 was more common with live attenuated vaccine than with inactivated vaccine, primarily among children 6 to 11 months of age; in this age group, 12 more episodes of wheezing were noted within 42 days after receipt of dose 1 among recipients of live attenuated vaccine (3.8%) than among recipients of inactivated vaccine (2.1%, $P = 0.076$). Rates of hospitalization for any cause during the 180 days after vaccination were higher among the recipients of live attenuated vaccine who were 6 to 11 months of age (6.1%) than among the recipients of inactivated vaccine in this age group (2.6%, $P = 0.002$).

CONCLUSIONS

Among young children, live attenuated vaccine had significantly better efficacy than inactivated vaccine. An evaluation of the risks and benefits indicates that live attenuated vaccine should be a highly effective, safe vaccine for children 12 to 59 months of age who do not have a history of asthma or wheezing. (ClinicalTrials.gov number, NCT00128167.)

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HOSPITALIZATION RATES FOR CULTURE-confirmed influenza among young children are similar to those among the elderly, and outpatient visits for confirmed influenza are more frequent among infants and young children than in any other age group.¹ For these reasons, U.S. advisory bodies have recently recommended the routine vaccination of all children 6 to 59 months of age with the licensed trivalent inactivated influenza vaccine.² The implementation of this recommendation will be challenging because of the limited supplies of inactivated vaccine during many influenza seasons,³⁻⁵ the modest efficacy of inactivated vaccine in young children,⁶ and the frequent need to administer the inactivated vaccine by injection concurrent with multiple other parenteral vaccines.

Previous clinical trials of live attenuated trivalent influenza vaccine in young children have shown it to be highly effective.⁷⁻⁹ Live attenuated influenza vaccine showed high efficacy when epidemic influenza viruses were not well matched to the recommended vaccine antigens.⁷ Initial studies comparing the efficacy of cold-adapted trivalent live attenuated influenza vaccine with trivalent inactivated vaccine have shown the former to be more effective (35 to 53% reduction in the influenza attack rate with live attenuated vaccine, as compared with inactivated vaccine).^{10,11} Although the safety of live attenuated influenza vaccine was assessed in children in both prospective and database studies,¹²⁻¹⁵ additional prospective studies of both inactivated vaccine and live attenuated vaccine were needed. In one study,¹⁵ but not in others,^{10,11,16} wheezing events were more frequent among young children given formulations of live attenuated vaccine. The present trial was designed to assess the safety and relative efficacy of live attenuated intranasal influenza vaccine and inactivated vaccine in children 6 to 59 months of age.

METHODS

STUDY DESIGN

The study was proposed by a subgroup of the authors, and the protocol was developed by all the authors in collaboration with an advisory committee. Data were gathered at each study site by the local principal investigator and the local staff.

The data were monitored by PPD in the United States and Europe and by Quintiles at the Asian sites. A data and safety monitoring board oversaw the study. The analysis was performed by biostatisticians employed by the sponsor. All authors had complete access to all data and all individual case-report forms, including data on all serious adverse events. All the authors vouch for the accuracy and completeness of the reported data.

The study was conducted at 249 sites (physicians' offices and primary care clinics) in 16 countries: the United States (49% of subjects), 12 countries in Europe and the Middle East (45% of subjects), and 3 countries in Asia (6% of subjects). The protocol and the informed consent forms were approved by the institutional review board at each participating center, and the study was conducted in accordance with the Declaration of Helsinki and the Guidelines for Good Clinical Practice.

After written informed consent had been obtained from a parent or guardian, children 6 to 59 months of age were randomly assigned on a 1:1 basis to receive either live attenuated vaccine or inactivated vaccine with the use of a centrally managed computer-generated randomization schedule. Subjects were stratified according to age on receipt of the first dose, the presence or absence of previous influenza vaccination, the presence or absence of a history of recurrent wheezing (defined as three or more wheezing episodes, each requiring medical follow-up or hospitalization, according to the parent's report or chart review), and country of residence. Children with a history of hypersensitivity to any component of the live attenuated vaccine or the inactivated vaccine were excluded; other exclusion criteria were a known immunosuppressive condition, medically diagnosed or treated wheezing within 42 days before enrollment, a history of severe asthma (as judged by the investigator), body temperature higher than 37.8°C (100°F) measured orally or the equivalent within 3 days before enrollment, and the use of aspirin or salicylate-containing products within 30 days before enrollment. Children with mild or moderate asthma or a history of wheezing (i.e., more than 42 days before enrollment) were included in the trial.

Children who had not previously been vaccinated against influenza were given two doses of

the assigned study vaccine; the first dose (dose 1) was administered on day 0 of the trial, and the second dose was administered 28 to 42 days later. Those who had previously been vaccinated against influenza were given only one dose. Subjects who were assigned to receive live attenuated vaccine, which was administered intranasally, also received a concurrent injection of intramuscular saline, and those assigned to receive inactivated vaccine, which was administered intramuscularly, also received a concurrent intranasal mist of saline.

VACCINES AND PLACEBO

The live attenuated intranasal vaccine was a refrigeration-stable (2 to 8°C) formulation of the currently licensed frozen FluMist (LAIV, MedImmune). This vaccine consisted of three cold-adapted reassortant influenza viruses grown in specific pathogen-free chicken eggs. Each dose of vaccine contained approximately 10^7 fluorescence focus assay units of each of the three strains of the 2004–2005 influenza season, as recommended by the Food and Drug Administration (A/New Caledonia/20/99 [H1N1], A/Wyoming/3/2003 [an A/Fujian/411/2002 (H3N2)-like virus], and B/Jilin/20/2003 [a B/Shanghai/361/2002-like virus]). A total of 0.2 ml of vaccine was administered (0.1 ml into each nostril with the use of an intranasal-spray device).

The licensed inactivated vaccine consisted of the recommended 2004–2005 influenza strains (A/New Caledonia/20/99 [H1N1], A/Wyoming/3/2003 [an A/Fujian/411/2002 (H3N2)-like virus], and B/Jiangsu/10/2003 [a B/Shanghai/361/2002-like virus]), and the vaccine was administered by intramuscular injection, according to the manufacturer's dosing instructions. In the United States and Asia, Fluzone (Aventis Pasteur) was used, and in Europe and the Middle East, Vaxigrip (Aventis Pasteur) was used. Children 6 to 35 months of age received 0.25 ml of intramuscular inactivated vaccine, and those 36 to 59 months of age received 0.5 ml of intramuscular inactivated vaccine.

Intranasal and intramuscular placebos were composed of physiologic saline and were given in a manner identical to the administration of the corresponding study vaccine. The subject, the subject's parent or guardian, the staff at the clinical site who were evaluating the subjects (including the investigators, study nurses, and coordinators),

and the clinical, biostatistical, and data-management staff employed by the sponsor were unaware of the treatment assignments. The vaccines and placebos were maintained at 2 to 8°C and were shipped by express courier to the study sites.

SURVEILLANCE FOR OUTCOMES AND SYMPTOMS OF INFLUENZA

Parents or guardians recorded local reactions, daily temperatures (oral, axillary, or rectal), systemic adverse events, and concomitant medications on worksheets from the time that dose 1 was administered until 42 days after the administration of the second dose, or until 42 days after dose 1 among subjects who received only one dose. Data on medically significant wheezing and serious adverse events (defined as events that were life-threatening or that resulted in death, hospitalization or prolonged hospitalization, significant disability or incapacity, or another important medical event requiring intervention to prevent one of these outcomes) were collected from the day of dose 1 until the end of the influenza surveillance period, extending through May 31, 2005. Medically significant wheezing was prospectively defined as the presence of wheezing on a physical examination conducted by a health care provider, with a prescription for a daily bronchodilator; respiratory distress; or hypoxemia. Study staff contacted the children's parents or guardians every 7 to 10 days throughout the influenza surveillance period, and if symptoms defined in the study protocol as suggestive of influenza were reported, nasal swabs for viral cultures were obtained either at the study site or at the child's home. Virologic methods are summarized in the Supplementary Appendix (available with the full text of this article at www.nejm.org).

STATISTICAL ANALYSIS

Assuming a 3.0% attack rate in the group that received inactivated vaccine and a 1.8% attack rate in the group that received live attenuated vaccine (relative efficacy rate, 40%) and assuming that sufficient data would be collected for 90% of the children to be included in the according-to-protocol population, we calculated that a sample of 8500 children would provide more than 90% power to demonstrate the superiority of live attenuated vaccine to inactivated vaccine (see the Statistics

section in the Supplementary Appendix). The primary end point was the efficacy of live attenuated vaccine, as compared with that of inactivated vaccine, in preventing culture-confirmed influenza-like illness as defined by the Centers for Disease Control and Prevention (CDC), modified to account for the subject's age, caused by well-matched influenza strains. The modified CDC definition of influenza-like illness was an oral temperature of 37.8°C or higher or the equivalent in the presence of cough, sore throat, or runny nose or nasal congestion occurring on the same or consecutive days; the addition of runny nose or nasal congestion to the case definition accounts for the age modification. Culture-positive influenza strains were assessed according to whether the isolated virus was well matched or significantly drifted to the vaccine strains. For detailed information on the statistical methods, see the Supplementary Appendix.

Secondary efficacy end points included the efficacy of live attenuated vaccine, as compared with that of inactivated vaccine, in preventing culture-confirmed influenza-like illness (according to the modified CDC definition) caused by antigenically mismatched influenza viruses and by all influenza viruses. Other efficacy end points included any culture-confirmed symptomatic influenza infection (as distinguished from influenza-like illness that met the modified CDC definition), medically diagnosed acute otitis media with fever and antibiotic use, and medically diagnosed lower respiratory illness, all associated with a positive nasal-swab culture for influenza virus at any time during the interval between the seventh day before the onset of the illness and the seventh day after the end of the illness.

RESULTS

STUDY POPULATION AND FOLLOW-UP

From October 20 to October 29, 2004, a total of 8475 children were enrolled (for details on the study populations, see Fig. 1 in the Supplementary Appendix). On average, 34 children (range, 1 to 270; median, 26) underwent randomization at each study site. Safety data were available for 8352 children, 7852 of whom were included in the analysis of the according-to-protocol population. Demographic and other characteristics, including num-

ber of days of follow-up, were well balanced between the group that received live attenuated vaccine and the group that received inactivated vaccine (Table 1). A total of 1880 of the children had previously received an influenza vaccine, and 6472 had not previously been vaccinated. Of those who received dose 1 of the vaccine and were assigned to receive a second dose, 3002 (92.4%) in the live-attenuated-vaccine group and 3034 (94.0%) in the inactivated-vaccine group received both doses. Overall on entry into the trial, 5.7% of the children in each group had underlying medical conditions, 21% had a history of any wheezing (as reported by a parent, guardian, or health care provider), and 6% had recurrent wheezing. More than 20,000 nasal specimens were cultured during the surveillance period (2.4 cultures per child).

EFFICACY

Kaplan–Meier curves for the time of the acquisition of a culture-confirmed influenza-like illness (according to the modified CDC definition) in the two groups are shown in Figure 1, and the attack rates are summarized in Table 2. There were 185 (54.9%) fewer cases of influenza in the live-attenuated-vaccine group (153 cases; attack rate, 3.9%) than in the inactivated-vaccine group (338 cases; attack rate, 8.6%) ($P < 0.001$). According to the virus subtype, vaccination with live attenuated vaccine resulted in 89.2% fewer cases of influenza A/H1N1 ($P < 0.001$), 79.2% fewer cases of influenza A/H3N2 ($P < 0.001$), and 16.1% fewer cases of influenza B ($P = 0.19$). The live attenuated vaccine was significantly more protective against both well-matched and mismatched influenza A viruses (Table 2). All isolates of H1N1 virus were regarded as antigenically matched. All isolates of H3N2 virus were antigenically mismatched. In contrast, the circulating B strains were divided into two lineages, Yamagata-like (strains that were antigenically matched and mismatched to vaccine) and Victoria-like (antigenically mismatched to vaccine). Although the difference was not significant, live attenuated vaccine showed a relative efficacy of 27%, as compared with inactivated vaccine, against the matched B strains, but there was no significant difference in efficacy against mismatched B strains.

For all culture-confirmed symptomatic influenza, the overall attack rates were 5.0% in the group

that received live attenuated vaccine and 10.0% in the group that received inactivated vaccine, with a 50.6% reduction in the live-attenuated-vaccine group, as compared with the inactivated-vaccine group ($P<0.001$). Significant reductions were also seen in the overall attack rates of acute otitis media and lower respiratory illness associated with positive influenza cultures, as diagnosed by a health care provider, with a relative efficacy in the live-attenuated-vaccine group of 50.6% ($P=0.004$) and 45.9% ($P=0.046$), respectively (see Table 1 in the Supplementary Appendix).

ADVERSE EVENTS

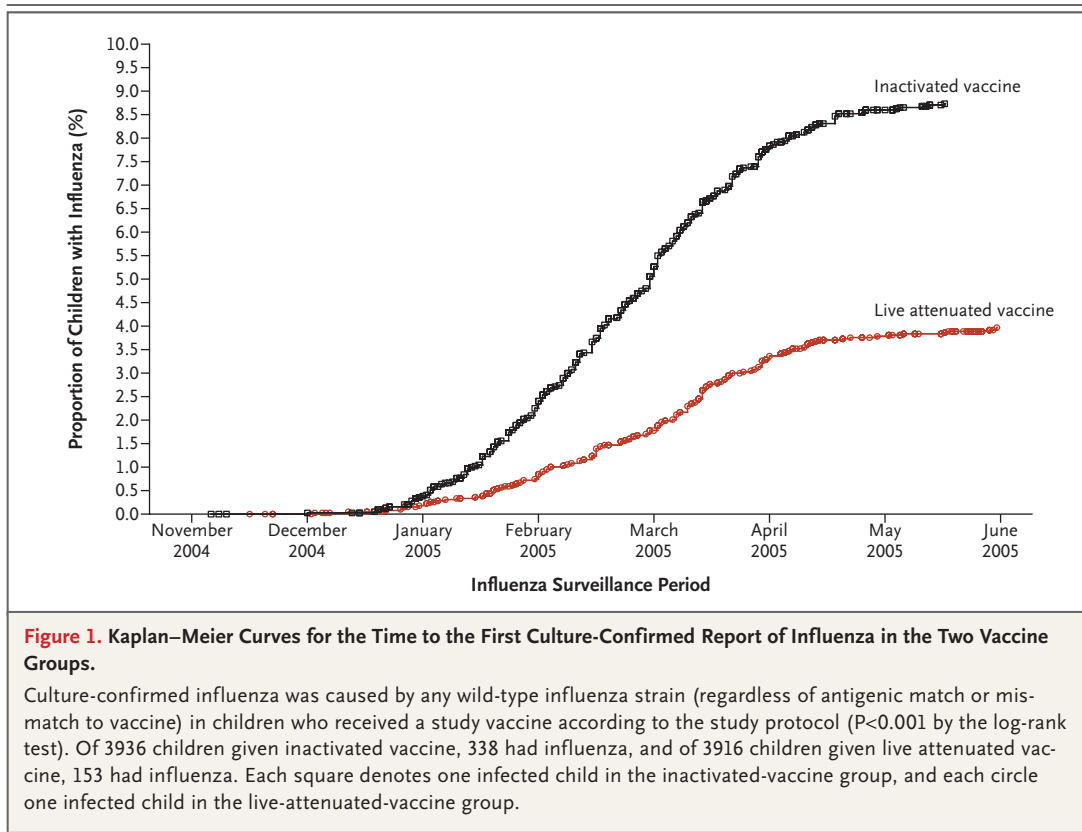
The incidence of pain, redness, and swelling at the injection site, with most instances reported as mild to moderate in severity, was higher in the group that received inactivated vaccine than in the group that received intramuscular placebo. Among subjects being vaccinated for the first time, 57.0% of those receiving intramuscular placebo and 46.3% of those receiving intranasal placebo had a runny or stuffy nose within 10 days after vaccination. With fever defined as a temperature of more than 37.8°C, fever occurred in 5.4%

Table 1. Characteristics and Follow-up of Subjects Included in the Safety Population.*

Variable	Live Attenuated Vaccine	Inactivated Vaccine	Total
No. of subjects	4179	4173	8352
History of influenza vaccination — no. (%)	933 (22.3)	947 (22.7)	1880 (22.6)
Mean age at first vaccination — mo	25.7	25.6	25.6
Age distribution — no. (%)			
6–23 mo	1992 (47.7)	1975 (47.3)	3967 (47.5)
6–11 mo	684 (16.4)	683 (16.4)	1367 (16.4)
12–23 mo	1308 (31.3)	1292 (31.0)	2600 (31.1)
24–35 mo	1372 (32.8)	1379 (33.0)	2751 (32.9)
36–59 mo	815 (19.5)	818 (19.6)	1633 (19.6)
60 mo	0	1 (<0.1)	1 (<0.1)
Sex — no. (%)			
Male	2142 (51.3)	2147 (51.4)	4289 (51.4)
Female	2037 (48.7)	2026 (48.6)	4063 (48.6)
Race or ethnic group — no. (%)†			
White and non-Hispanic	3351 (80.2)	3356 (80.4)	6707 (80.3)
Black	171 (4.1)	156 (3.7)	327 (3.9)
Hispanic	267 (6.4)	272 (6.5)	539 (6.5)
Asian	309 (7.4)	307 (7.4)	616 (7.4)
Other	81 (1.9)	82 (2.0)	163 (2.0)
History of any wheezing — no. (%)	899 (21.5)	863 (20.7)	1762 (21.1)
History of recurrent wheezing — no. (%)	271 (6.5)	239 (5.7)	510 (6.1)
History of asthma — no. (%)	164 (3.9)	169 (4.0)	333 (4.0)
Duration of follow-up — days			
Median	219	219	219
Range	0–224	0–224	0–224

* The categories of any wheezing, recurrent wheezing, and asthma were not mutually exclusive.

† Race or ethnic group was reported by the child's parent or guardian.



of the live-attenuated-vaccine group and 2.0% of the inactivated-vaccine group on day 2 after receipt of dose 1 of vaccine ($P < 0.001$). With the use of a higher temperature cutoff (fever defined as 38.9°C [$>102^{\circ}\text{F}$]), the incidence of fever was low ($<1\%$ on day 2, after receipt of dose 1) in both vaccine groups. No significant differences in fever were found between the two groups after the second dose (see Fig. 2 in the Supplementary Appendix).

The rates of medically significant wheezing during the 42-day period after each dose of vaccine are shown in Table 3. Overall, there was no significant difference in medically significant wheezing between the two groups. In previously unvaccinated children, after dose 1, there were 74 cases of medically significant wheezing (2.3%) among children given live attenuated vaccine, as compared with 48 cases (1.5%) among those given inactivated vaccine, with a significant adjusted rate difference of 0.77% (95% confidence interval [CI], 0.12 to 1.46). The increase in medically significant wheezing was seen primarily dur-

ing the second, third, and fourth weeks after vaccination (Fig. 3 in the Supplementary Appendix). Among previously unvaccinated children 24 months of age or older, there was no significant difference in the rates of medically significant wheezing between the two groups. Among those younger than 24 months of age, 55 children (3.2%) in the live-attenuated-vaccine group and 34 children (2.0%) in the inactivated-vaccine group had medically significant wheezing after receipt of dose 1, with an adjusted difference of 1.18 (95% CI, 0.13 to 2.29). The difference in the incidence of medically significant wheezing was seen primarily in children less than 12 months of age (see Fig. 4 in the Supplementary Appendix), with 12 more episodes of wheezing after dose 1 in children in this age group who received live attenuated vaccine than in those who received inactivated vaccine (3.8% vs. 2.1%, $P = 0.08$).

A review of hospital records for children less than 24 months of age who were hospitalized with medically significant wheezing indicated a

Table 2. Influenza Attack Rates in the According-to-Protocol Population.*

Variable	Similarity to Vaccine†	Live Attenuated Vaccine (N=3916)‡		Inactivated Vaccine (N=3936)§		Reduction in Attack Rate with Live Vaccine¶ % (95% CI)
		Cases	Attack Rate	Cases	Attack Rate	
		no.	%	no.	%	
Virus	Well matched	53	1.4	93	2.4	44.5 (22.4 to 60.6)
A/H1N1		3	0.1	27	0.7	89.2 (67.7 to 97.4)
A/H3N2		0	0	0	0	—
B		50	1.3	67	1.7	27.3 (–4.8 to 49.9)
Age at first vaccination (any influenza virus)	Well matched					
6–23 mo		23	1.3	32	1.7	29.1 (–21.2 to 59.1)
24–35 mo		17	1.3	24	1.8	32.6 (–25.8 to 64.5)
36–59 mo		13	1.7	37	4.7	65.6 (36.3 to 82.4)
Previous vaccination (any influenza virus)	Well matched					
Yes		18	1.9	29	3.1	39.3 (–9.2 to 66.9)
No		35	1.2	64	2.1	46.9 (20.0 to 65.2)
Virus	Not well matched	102	2.6	245	6.2	58.2 (47.4 to 67.0)
A/H1N1		0	0	0	0	—
A/H3N2		37	0.9	178	4.5	79.2 (70.6 to 85.7)
B		66	1.7	71	1.8	6.3 (–31.6 to 33.3)
Virus	Regardless of match	153	3.9	338	8.6	54.9 (45.4 to 62.9)
A/H1N1		3	0.1	27	0.7	89.2 (67.7 to 97.4)
A/H3N2		37	0.9	178	4.5	79.2 (70.6 to 85.7)
B		115	2.9	136	3.5	16.1 (–7.7 to 34.7)

* Children had influenza-like illness and culture-positive infection. Modified CDC influenza-like illness was defined as the presence of an increased oral temperature (>100°F [37.8°C] or the equivalent) in the presence of cough, sore throat, runny nose, or nasal congestion occurring on the same or consecutive days. The analysis of the primary end point in subgroups (stratified according to age, vaccination status, and presence or absence of a history of recurrent wheezing) provided estimates of the relative efficacy of live attenuated vaccine of 24.0 to 65.6%, a finding consistent with the relative efficacy of 44.5% observed in the overall according-to-protocol population. Higher estimates of the relative efficacy of live attenuated vaccine, as compared with inactivated vaccine, against matched influenza strains were seen in 13 of the 15 countries in which matched strains were isolated.

† Viruses were characterized as antigenically similar to vaccine or not well matched to vaccine. Reference antiserum provided by the CDC was used to characterize isolates antigenically and a difference by a factor of 4 or more in the hemagglutination-inhibition titers was considered indicative of antigenic variation between two viruses.

‡ Four subjects had both influenza A/H3N2 and influenza B virus infections; two isolates could not be characterized as antigenically well matched or not well matched to vaccine virus antigen.

§ Two subjects had both influenza A/H1N1 and influenza B virus infections; six subjects had both influenza A/H3N2 and influenza B virus infections; five isolates could not be characterized as antigenically well matched or not well matched to vaccine virus antigen.

¶ The analysis of subjects in the intention-to-treat population confirmed the results in the according-to-protocol population. The observations were robust in all subgroups (stratified according to age, vaccination status, presence or absence of a history of recurrent wheezing, and country of residence). Among children 6 to 23 months of age, in whom the overall attack rates of influenza were 3.2% in the live-attenuated-vaccine group and 7.2% in the inactivated-vaccine group, the relative efficacy of live attenuated vaccine of 55.7% was significant.

Table 3. Incidence in the Safety Population of Medically Significant Wheezing within 42 Days after Receiving Vaccine.*

Variable	Live Attenuated Vaccine no./total no. of cases (%)	Inactivated Vaccine no./total no. of cases (%)	Adjusted Rate Difference (95% CI)†
All children (6–59 mo of age)			
Previously vaccinated			
After dose 1	19/933 (2.0)	17/947 (1.8)	0.03 (–1.24 to 1.38)
Not previously vaccinated			
After dose 1	74/3246 (2.3)	48/3226 (1.5)	0.77 (0.12 to 1.46)
After dose 2	73/3002 (2.4)	67/3034 (2.2)	0.20 (–0.56 to 0.97)
Children <24 mo‡			
Previously vaccinated			
After dose 1	7/267 (2.6)	3/269 (1.1)	1.34 (–1.11 to 4.30)
Not previously vaccinated			
After dose 1	55/1725 (3.2)	34/1706 (2.0)	1.18 (0.13 to 2.29)
After dose 2	57/1578 (3.6)	39/1595 (2.4)	1.15 (–0.04 to 2.38)
Children ≥24 mo‡			
Previously vaccinated			
After dose 1	12/666 (1.8)	14/678 (2.1)	–0.49 (–2.07 to 1.10)
Not previously vaccinated			
After dose 1	19/1521 (1.2)	14/1520 (0.9)	0.30 (–0.46 to 1.09)
After dose 2	16/1424 (1.1)	28/1439 (1.9)	–0.85 (–1.83 to 0.05)
Children with a history of recurrent wheezing (6–59 mo of age)			
Previously vaccinated			
After dose 1	10/98 (10.2)	7/78 (9.0)	1.08 (–8.52 to 10.26)
Not previously vaccinated			
After dose 1	12/173 (6.9)	12/161 (7.5)	–0.43 (–6.31 to 5.38)
After dose 2	10/148 (6.8)	14/140 (10.0)	–3.26 (–10.10 to 3.33)
Children without a history of recurrent wheezing (6–59 mo of age)			
Previously vaccinated			
After dose 1	9/835 (1.1)	10/869 (1.2)	–0.07 (–1.14 to 1.02)
Not previously vaccinated			
After dose 1	62/3073 (2.0)	36/3065 (1.2)	0.84 (0.21 to 1.50)
After dose 2	63/2854 (2.2)	53/2894 (1.8)	0.37 (–0.35 to 1.13)

* The health care provider documented the wheezing as accompanied by tachypnea, retractions, or dyspnea, an oxygen saturation of less than 95%, while breathing ambient air, or receipt of a new prescription for daily bronchodilators.

† Differences in rates were adjusted for the subject's age and the presence or absence of a history of recurrent wheezing.

‡ The proportion of subjects with medically significant wheezing who were younger than 24 months of age in the two study groups who had tachypnea, dyspnea, retractions, or hypoxemia after dose 1 was similar (27% in the live-attenuated-vaccine group and 26% in the inactivated-vaccine group). A total of 12 subjects younger than 24 months of age (9 [0.5%] and 3 [0.2%], respectively) were hospitalized in association with medically significant wheezing within 42 days after receiving a dose of vaccine. No child was treated in an intensive care unit, received mechanical ventilation, or died because of medically significant wheezing. The difference in the rate of medically significant wheezing after dose 1 among previously unvaccinated children 6 to 23 months of age occurred primarily among those who were 6 to 11 months of age (3.8% in the live-attenuated-vaccine group vs. 2.1% in the inactivated-vaccine group; adjusted rate difference, 1.61% [95% CI, –0.18 to 3.53]); among children 12 to 23 months of age who had medically significant wheezing (2.8% in the live-attenuated-vaccine group vs. 2.0% in the inactivated-vaccine group), the adjusted rate difference (0.9% [95% CI, –0.42 to 2.27]) was not significant.

Table 4. Medically Significant Wheezing, Serious Adverse Events, and Rates of Hospitalization According to Age Group, through 180 Days after the Last Dose of Vaccine.*

Age	Event	Live Attenuated Vaccine		Inactivated Vaccine	
		<i>no./total no. (%)</i>		<i>no./total no. (%)</i>	
6–11 mo	Medically significant wheezing	93/684 (13.6)		71/683 (10.4)	
	Any serious adverse event	44/684 (6.4)		23/683 (3.4)	
	Hospitalization for any cause	42/684 (6.1)		18/683 (2.6)	
12–59 mo	Medically significant wheezing	272/3495 (7.8)		255/3490 (7.3)	
	Any serious adverse event	92/3495 (2.6)		105/3490 (3.0)	
	Hospitalization for any cause	88/3495 (2.5)		101/3490 (2.9)	
6–59 mo	Medically significant wheezing	365/4179 (8.7)		326/4173 (7.8)	
	Any serious adverse event	136/4179 (3.3)		128/4173 (3.1)	
	Hospitalization for any cause	130/4179 (3.1)		119/4173 (2.9)	

* Medically significant wheezing, serious adverse events, and hospitalizations were analyzed from the day of the first dose through 180 days after the last dose of vaccine (for a breakdown according to causes of hospitalization and diagnostic category, see Table 4 in the Supplementary Appendix).

similar severity of illness among those receiving live attenuated vaccine and those receiving inactivated vaccine and in the duration of stay in the hospital, associated diagnoses, and treatment (Table 2 and Table 3 in the Supplementary Appendix). Beyond 42 days after vaccination, the rates of medically significant wheezing did not differ significantly between the two groups among children less than 24 months of age (7.6% in the live-attenuated-vaccine group and 7.1% in the inactivated-vaccine group). The proportion of those less than 24 months of age who had medically significant wheezing within 42 days after vaccination and who had at least one additional medically significant wheezing episode during the study period was similar in the two groups (32% in the live-attenuated-vaccine group and 28% in the inactivated-vaccine group); the proportion of these children who had two or more additional medically significant wheezing episodes was 4.3% and 5.3%, respectively.

The incidence of serious adverse events in the two groups was similar (136 in the live-attenuated-vaccine group and 128 in the inactivated-vaccine group) (Table 4). Six serious adverse events in the live-attenuated-vaccine group (bronchiolitis in two children, and asthma exacerbation, wheezing, acute gastroenteritis, and reactive airway disease in one child each) and five in the inactivated-vaccine group (pneumonia, wheezing, febrile convulsion, febrile convulsion and pneumonia, and viral gastroenteritis in one child each) were

considered by the investigator, who was unaware of the treatment assignments, to be potentially related to the study vaccine. One death occurred in each vaccine group — one because of aspiration of a foreign body and one because of a house fire. New diagnoses of chronic diseases assessed within 180 days after the last dose of vaccine were infrequent in the two groups, with overall incidence rates of 1.7% in the live-attenuated-vaccine group and 1.3% in the inactivated-vaccine group.

A post hoc analysis for the study period through 180 days after the last dose of vaccine showed that children 6 to 11 months of age were hospitalized for any cause at a higher rate in the live-attenuated-vaccine group than in the inactivated-vaccine group (6.1% vs. 2.6%; difference in rate, 3.5% [95% CI, 1.4 to 5.8]) (Fig. 2 and Table 4, and Table 4 in the Supplementary Appendix). The rate of hospitalization for respiratory diagnoses in this age group was 3.2%, as compared with 1.2% in the two groups, respectively (absolute difference, 2.0% [95% CI, 0.5 to 3.8]). The differences in hospitalization rates among children 12 to 23 months of age (3.2% in the live-attenuated-vaccine group and 3.5% in the inactivated-vaccine group) and among children 24 to 59 months of age were not significant. Although not statistically significant, there was a trend toward a higher rate of hospitalization for any cause among children receiving live attenuated vaccine who were 6 to 47 months of age and had a history

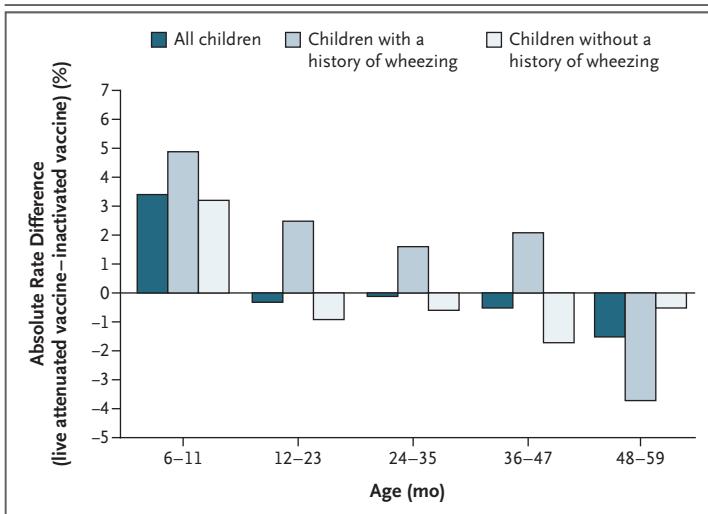


Figure 2. Difference in Rates of Hospitalization between the Two Vaccine Groups, According to Age and the Presence or Absence of a History of Wheezing Illness before Vaccination.

Among children 6 to 11 months of age, for the comparison between live attenuated vaccine and inactivated vaccine among all children regardless of whether there was a history of wheezing illness, $P=0.002$, and for the comparison between live attenuated vaccine and inactivated vaccine among children with a history of wheezing illness, $P=0.004$. Among children 48 to 59 months of age, for the comparison between live attenuated vaccine and inactivated vaccine among children without a history of wheezing, $P=0.039$. For all other comparisons, $P>0.05$. P values were calculated by inverting two one-sided tests on the basis of asymptotic methods and with the use of StatXact software, version 6.2 (Statistical Solutions).

of wheezing than among those receiving inactivated vaccine who were in the same age group and had a history of wheezing. Among children 12 to 59 months of age who did not have a history of wheezing, the rates of hospitalization for any cause were lower in the live-attenuated-vaccine group than in the inactivated-vaccine group ($P=0.07$).

DISCUSSION

Many believe that the successful control of annual influenza epidemics depends on vaccinating a high proportion of children.¹⁶⁻¹⁸ As U.S. public health authorities move toward this goal, highly effective vaccines are needed, including vaccines with efficacy against antigenically drifted influenza strains. The live attenuated influenza vaccine we used has many of the characteristics that are desirable for the control of epidemic influenza. In addition to its high acceptability because of the mode of administration, the significantly

higher efficacy of this live attenuated vaccine than of the licensed inactivated vaccine suggests that it can play an important role in the control of influenza. This higher efficacy was seen not only for well-matched strains but also for viruses that were antigenically drifted from the antigen in the vaccine.

Some earlier studies have suggested the potential for wheezing in young children after receipt of live attenuated influenza vaccine,¹⁵ whereas others have not.^{10,16} Our comprehensive, prospective safety study showed an increased risk of medically significant wheezing (within 42 days after vaccination) among recipients of live attenuated vaccine who were younger than 12 months of age. The pathogenesis of wheezing in some children given live attenuated vaccine remains unknown, although in our study, the wheezing developed after the peak of viral replication and at the time when immune responses to the viruses are expected — that is, during weeks 2, 3, and 4 after vaccination.

The incidence of serious adverse events did not differ significantly between the two groups. However, in post hoc analyses, rates of hospitalization for any cause among infants 6 to 11 months of age were significantly higher in the live-attenuated-vaccine group than in the inactivated-vaccine group. In addition, higher, but not significantly higher, rates of hospitalization were observed among children in the age groups of 12 to 23 months, 24 to 35 months, and 36 to 47 months who had a history of wheezing illness before entering the study. These observations require further study. Children 12 months of age or older who had no history of wheezing illness before vaccination and who received live attenuated vaccine had lower rates of hospitalization for any cause during the study than those who received inactivated vaccine. On the basis of our results, the risk-benefit ratio for live attenuated vaccine appears favorable among children 12 to 47 months of age who have no history of wheezing.

Until additional data are available, the observations related to medically significant wheezing and rates of hospitalization will restrict the use of live attenuated vaccine in children younger than 1 year and in children 12 to 47 months of age who have a history of asthma or wheezing. Additional studies to determine the optimal use of both vaccines in infants and young children are warranted.

The high influenza attack rate among children in the inactivated-vaccine group who were less than 12 months of age and had a history of wheezing (14%) suggests that inactivated vaccine has low efficacy in this group. Further studies might show whether an initial dose of inactivated vaccine followed by live attenuated vaccine would provide optimal protection for children younger than 1 year of age while also ensuring maximum vaccine safety.

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APPENDIX

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Influenza Vaccine Given to Pregnant Women Reduces Hospitalization Due to Influenza in Their Infants

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Background. Infants aged <12 months are at high risk of hospitalization for influenza. Influenza vaccine is recommended for pregnant women and for most children; however, no vaccine is approved for infants aged <6 months. Effective approaches are needed to protect this vulnerable population. Vaccination of women during pregnancy may protect the infant through transfer of antibodies from the mother. Few studies have examined the effectiveness of this strategy, and those studies produced mixed results.

Methods. In a matched case-control study, case patients were infants aged <12 months admitted to a large urban hospital in the northeastern United States because of laboratory-confirmed influenza from 2000 to 2009. For each case, we enrolled 1 or 2 control subjects who were infants who tested negative for influenza and matched cases by date of birth and date of hospitalization (within 4 weeks). Vaccine effectiveness was calculated on the basis of matched odds ratios and was adjusted for confounding.

Results. The mothers of 2 (2.2%) of 91 case subjects and 31 (19.9%) of 156 control subjects aged <6 months, and 1 (4.6%) of 22 case subjects and 2 (5.6%) of 36 control subjects aged ≥6 months, had received influenza vaccine during pregnancy. The effectiveness of influenza vaccine given to mothers during pregnancy in preventing hospitalization among their infants, adjusted for potential confounders, was 91.5% (95% confidence interval [CI], 61.7%–98.1%; $P = .001$) for infants aged <6 months. The unadjusted effectiveness was 90.7% (95% CI, 59.9%–97.8%; $P = .001$).

Conclusions. Influenza vaccine given to pregnant women is 91.5% effective in preventing hospitalization of their infants for influenza in the first 6 months of life.

Influenza is the leading cause of vaccine-preventable death in the United States [1], responsible for 200,000 hospitalizations and 36,000 deaths per year [2]. The highest burden of disease is among infants, pregnant women, elderly persons, and people with certain chronic medical conditions. In children, the highest incidence of hospitalization attributable to influenza is among infants aged <1 year, with those aged <6 months at highest risk [3]. Rates of hospitalization of healthy infants for influenza are similar to those of high-risk adults, and rates are even higher among infants with underlying chronic medical problems, particularly respiratory conditions [3].

Inactivated influenza vaccine is recommended by the Centers for Disease Control and Prevention (CDC) for all pregnant women and children, except for infants aged <6 months (for whom the vaccine is poorly immunogenic) and for persons with a serious allergy to egg protein [4, 5]. Strategies for protecting these groups have included only washing hands, avoiding contact with persons infected with influenza, and vaccinating close contacts [4], but the effectiveness of these strategies is unknown.

One potential approach to protecting young infants against influenza infection is to vaccinate their mothers during pregnancy [6, 7]. Both animal and human studies support the possibility of protecting the offspring against influenza by immunization of the mother. Antibodies (immunoglobulin G) cross the placenta via active transport from the mother to the fetus, particularly in the final weeks of pregnancy [8–11]. Additional antibodies (immunoglobulin A) are transferred from the mother to the infant via breastmilk [12].

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One study showed that an infant's concentration of influenza antibodies at birth correlated with that of the mother. Although the study failed to find a protective effect, infants with higher concentrations of influenza antibodies had delayed onset and decreased severity of influenza infection [13]. The same protection could be achieved via influenza vaccination of pregnant women [13–16]. Another study showed influenza vaccination during pregnancy resulted in influenza-specific antibody concentrations in the infants at birth that were higher than those in their mothers, suggesting active transport from mother to infant [14]. The presence of maternally derived antibodies in infancy does not inhibit development of natural immunity later in life from vaccination or natural infection [16, 17].

Two previous studies of hospitalized infants have compared rates of influenza-like illness or medically attended acute respiratory infections between infants whose mothers had received influenza vaccine during pregnancy and infants whose mothers had not received this vaccine; however, neither study found a protective effect [18, 19]. Recently, a clinical trial evaluated women who received inactivated influenza vaccine during their third trimester of pregnancy in Bangladesh, where influenza circulates year-round, and followed up their infants for up to 24 weeks after birth. Researchers in that study found a 63% decrease in the number of laboratory-confirmed influenza infections in those infants, compared with infants of women in a control group who received a conjugate pneumococcal vaccine during pregnancy. However, the study did not assess the vaccine's effectiveness for either hospitalization or severity of illness in the infants [20].

We conducted a matched case-control study of infants at Yale–New Haven Children's Hospital, a large urban hospital in the northeastern United States, to assess the effectiveness of influenza vaccine given to pregnant women in decreasing the number of hospitalizations for laboratory-documented influenza among their infants.

METHODS

Eligibility requirements. Subjects were infants aged <12 months who were hospitalized for laboratory-confirmed influenza between October 2000 and April 2009 (prior to the arrival of the 2009 pandemic influenza in this region).

We excluded infants who were adopted at birth, infants whose mothers had a contraindication to inactivated influenza vaccine or were unable to consent to participate (eg, were deceased or had unknown whereabouts), infants who were hospitalized for reasons unrelated to respiratory infection (as determined by review of medical records), infants whose parents could not complete the interview in English or Spanish, and infants with influenza infection acquired when the patient was already in the hospital (ie, nosocomial). Infants who received influenza vaccine at least 2 weeks prior to admission to the

hospital were excluded from the analyses, because it would be impossible to separate the effect of vaccination of the mother from that of vaccination of the infant.

Identification of potential cases. Cases were infants hospitalized for influenza with documentation of either a nasal swab or aspirate sample that was positive for influenza by direct fluorescent antibody (DFA) test. Case subjects were identified from the list of all patients who had a nasal swab or aspirate sample submitted to the hospital's clinical virology laboratory for the DFA test (Light Diagnostics). This test has been shown to be 96.2% sensitive and 99.0% specific for influenza, compared with PCR, in our clinical virology laboratory [21]. Samples deemed inadequate by the laboratory were not included. Data collection started in 2007. Subjects hospitalized between 2000 and early 2007 were identified historically from the clinical virology laboratory list of all tests for influenza and were enrolled by telephone. During the 2007–2008 and 2008–2009 influenza seasons, research staff identified cases prospectively by reviewing clinical virology laboratory lists of all tests for influenza and the daily list of new hospital admissions, to enroll patients in the hospital setting and to collect a nasal aspirate sample.

The nasal samples obtained from the case subjects identified prospectively (2007–2009) were all confirmed to be negative for 2009 pandemic influenza A H1N1. RNA was extracted from the clinical specimens using RNeasy Mini Kit (Qiagen) per the manufacturer's instructions. Reverse transcription and polymerase chain reaction were performed using primers and parameters described by the World Health Organization/CDC protocol [22] and the AccessQuick RT-PCR System (Promega).

Selection of controls. For each case, we enrolled 1 or 2 matched control subjects, who were hospitalized infants with DFA results negative for influenza. Control subjects from the list of all patients who had a DFA test for influenza were matched to cases by date of birth and date of hospitalization. Matching started with the subjects born within 2 weeks (before or after the case date of birth) and who were admitted within 2 weeks (before or after the case date of hospital admission) and then, if necessary, proceeded to those born within 4 weeks and admitted within 2 weeks from the case, then those born within 2 weeks and admitted within 4 weeks, and finally those born within 4 weeks and admitted within 4 weeks. We used lists of random numbers to determine the order in which to contact potential eligible subjects within each case-control group. We used risk-set sampling in our selection of cases and controls [23].

Collection of data and ascertainment of vaccinations. We conducted interviews with the parents of all study subjects for information about demographic characteristics, possible confounders (such as breast-feeding or susceptible individuals in the household), and comorbidities and to identify all possible

locations where vaccination was given. Interviews were conducted in person when a case subject or control subject was identified prior to discharge from the hospital, if possible, or otherwise by phone. All interviews were conducted in English or Spanish.

Information about vaccinations and comorbidities of the infants was obtained by reviewing records of all providers of medical care. We reviewed mothers' medical records from primary medical providers, obstetricians, pharmacies, and anywhere the mother stated that she had received influenza vaccine. We used this information to ascertain whether a woman had received influenza vaccine during pregnancy, whether she had received the vaccine at any time prior to that pregnancy, and whether she had received the vaccine during the same influenza season as the infant's hospital admission. A woman was considered vaccinated if there was written documentation of receipt of influenza vaccine during her pregnancy, excluding vaccinations received within 14 days of delivery.

We also collected clinical data from the hospital medical record, including any abnormal vital signs (highest temperature and respiratory rates and lowest oxygen saturation levels), clinical signs of increased work of breathing, results of chest radiographs, and the need for intubation and/or admission to the intensive care unit (ICU). We classified the severity of each case subject's symptoms on a scale of 0–16 points, based on our modification of a validated scale of severity of respiratory symptoms in infants (Table 1) [24].

Statistical analysis. We calculated a matched odds ratio for vaccination of mothers of case subjects, compared with mothers of matched control subjects. The vaccine's effectiveness was calculated as 1 minus the matched odds ratio, multiplied by 100. Conditional logistic regression was used to adjust for potential confounders, including race, ethnicity, sex, age, day care attendance, prematurity, vaccination of household contacts, breast-feeding, and relevant chronic illness (asthma/reactive airways disease, chronic lung disease, conditions requiring medical equipment to facilitate breathing, heart defects, blood disorders, seizures, metabolic or endocrine disorders, severe gastrointestinal disease, kidney disease, or spinal cord injury).

A stratified analysis was also conducted to assess for effect modification by age of the subject (≥ 6 months vs < 6 months) on the basis of the CDC recommendation to begin influenza vaccination at age 6 months. Whether the subject was identified at the time of hospitalization or historically via billing data was also evaluated as a possible confounder or effect modifier.

We also assessed the significance of the clinical severity of influenza of the cases using Student's *t* test or the Wilcoxon rank-sum test, as appropriate. Analyses were conducted using SAS, version 9.1.3 for Microsoft Windows (SAS Institute).

RESULTS

We identified a total of 220 eligible case subjects (infants aged < 12 months who were hospitalized for influenza) between October 2000 and April 2009. Of these, 36 (16%) could not be contacted by researchers (eg, had an incorrect or outdated phone number or had moved with no forwarding information). Of the remaining 184 potential case subjects, parents of 27 (15%) declined to participate, and 157 (85%) were enrolled. Enrollment for this study started in July 2007. Of all case subjects, 33 were hospitalized between January 2008 and April 2009 (identified prospectively via active surveillance of laboratory data and hospital admissions), and 124 were hospitalized between October 2000 and May 2007 (identified historically via laboratory data). Of the case subjects, 130 (82.8%) were infected with influenza A and 27 (17.2%) were infected with influenza B; none were infected with the 2009 pandemic influenza A H1N1. For the case subjects, 430 potentially suitable matched control subjects were identified; of these, 114 (26.5%) could not be contacted. Of those that we were able to reach, 45 (14.2%) declined to participate, and 270 (85.7%) were enrolled. Data are presented on the 113 cases and 192 controls in matched groups, with complete data for the case and at least 1 matched control. Demographic characteristics of subjects identified prospectively and historically differed statistically significantly only for report of sick household members during the month before hospitalization (59.8% vs 23.3%; $P < .001$) and length of hospital stay (5.0 ± 13.2 vs 2.9 ± 3.7 days; $P = .030$).

Table 1. Clinical Severity Scale Used to Assess Severity of Influenza

Parameter	Point value		
	0	1	2
Heart rate, max no. of beats/min			
Age 0–7 days	<130	130–160	>160
Age 1–4 weeks	<135	135–170	>170
Age 1–6 months	<140	140–170	>170
Age ≥ 6 months	<130	130–160	>160
Respiratory rate, max no. of breaths/min			
Age 0–1 month	<50	50–70	>70
Age 1–6 months	<30	30–50	>50
Age ≥ 6 months	<20	20–40	>40
Oxygen saturation (by pulse oximeter), %	≥ 94	...	<94
Wheezing	No	Yes	...
Retractions (intercostal, subcostal, etc)	No	...	Yes
Nasal flaring	No	Yes	...
Required intubation/mechanical ventilation	No	...	Yes
Required ICU care	No	...	Yes
Abnormal chest radiograph	No	...	Yes

NOTE. Value range is 0–16 (mild, 0–3; moderate, 4–5; severe, 6–16). ICU, intensive care unit; max, maximum.

Table 2. Characteristics of Infants Hospitalized with Influenza and Matched Control Subjects

Characteristic	No. (%) of case subjects (n = 113)	No. (%) of control subjects (n = 192)	P
Age, months			.998
0 to <3	40 (35.4)	69 (35.9)	
3 to <6	51 (45.1)	87 (45.3)	
6 to <9	12 (10.6)	19 (9.9)	
9 to <12	10 (8.9)	17 (8.9)	
Mean age \pm SD, months	3.2 \pm 2.8	3.1 \pm 2.9	
Median age, months	2.0	2.0	
Male sex	57 (50.4)	101 (52.6)	.715
Hispanic ethnicity	45 (39.8)	59 (30.7)	.106
Race			.135
White	73 (64.6)	129 (67.2)	
Black	21 (18.6)	21 (10.9)	
Other	19 (16.8)	42 (21.9)	
Ever breast-fed	59 (55.7)	115 (67.3)	.052
Attends day care	11 (9.8)	18 (9.4)	.898
Environmental tobacco smoke exposure	35 (31.0)	56 (29.2)	.739
Premature (gestational age \leq 37 weeks)	13 (11.6)	37 (19.3)	.082
Gestational age <32 weeks	1 (0.9)	10 (3.5)	
Gestational age 32 to \leq 37 weeks	12 (10.7)	27 (14.1)	
Chronic medical conditions ^a	41 (36.3)	74 (38.5)	.695
Respiratory conditions	25 (22.1)	25 (24.5)	.640
Type of residence			.028
Single family home	56 (49.6)	110 (57.3)	
Multifamily home	22 (19.5)	26 (13.5)	
Apartment	31 (27.4)	56 (29.2)	
Other setting ^b	4 (3.5)	0 (0.0)	
No. of people living at home (including subject)			
Mean \pm SD	4.9 \pm 2.1	4.4 \pm 1.3	.015
Median	5.0	4.0	
Household contacts received influenza vaccine			.001
None	64 (56.6)	67 (34.9)	
Some	37 (32.7)	96 (50.0)	
All	12 (10.6)	29 (15.1)	

NOTE. SD, standard deviation.

^a Includes respiratory conditions (asthma, reactive airways disease, chronic lung disease, and conditions requiring medical equipment to facilitate breathing) as well as heart defects, blood disorders, seizures, metabolic or endocrine problems, severe stomach problems, kidney disease, and spinal cord injuries.

^b Other settings include dormitories, shelters, and mobile homes.

Case subjects and matched control subjects were comparable for most demographic characteristics and risk factors (Table 2). Of the case subjects, 81% were aged <6 months. Case subjects came from households with a larger number of household members, compared with those of control subjects (4.9 \pm 2.0 vs 4.4 \pm 1.3 persons; $P = .015$), and they were significantly less likely to live with household members who had received influenza vaccine (32.7% vs 50.0% for any household members vaccinated; 10.6% vs 15.1% for all household members vac-

inated; $P = .001$). The mothers of 2 (2.2%) of 91 case subjects and 31 (19.9%) of 156 control subjects aged <6 months and mothers of 1 (4.6%) of 22 case subjects and 2 (5.6%) of 36 control subjects aged \geq 6 months had received influenza vaccine during pregnancy (Table 3).

The unadjusted effectiveness of influenza vaccine given to mothers during pregnancy in preventing hospitalization for influenza among their infants was 90.7% (95% confidence interval [CI], 59.9%–97.8%; $P = .001$) for infants aged <6

Table 3. Receipt of Influenza Vaccine by Subjects' Mothers

Characteristic	No. (%) of case subjects (n = 113)	No. (%) of control subjects (n = 192)	P
Vaccination status during pregnancy			<.001
Not vaccinated	110 (97.4)	159 (82.8)	
Vaccinated	3 (2.7)	33 (17.2)	
During hospitalization season	2 (1.8)	32 (16.7)	
During prior season	1 (0.9)	1 (0.5)	
For those vaccinated during pregnancy, vaccination occurred			.541
First trimester	0 (0.0)	0 (0.0)	
Second trimester	1 (33.3)	7 (21.2)	
Third trimester	2 (66.7)	26 (78.8)	
During influenza season when infant was hospitalized			<.001
Mother was not vaccinated	109 (96.5)	155 (80.7)	
Mother was vaccinated	4 (3.5)	37 (19.3)	

months. In the final adjusted model, immunization of household contacts (ie, persons other than the subject's mother residing in the household at the time of admission) (adjusted odds ratio, 0.420; 95% CI, 0.221–0.798; $P = .008$) and prematurity (adjusted odds ratio, 0.375; 95% CI, 0.153–0.918; $P = .032$) were retained, resulting in an adjusted effectiveness of the vaccine of 91.5% (95% CI, 61.7%–98.1%; $P = .001$) for this age group. The effectiveness of the vaccine for infants aged ≥ 6 months was -41.4% (95% CI, -2257.3% to 91.5%; $P = .809$). The effectiveness of the vaccine did not differ significantly when we compared those identified prospectively with those identified historically (for historically identified subjects: effectiveness, 88.9%; 95% CI, 13.1%–98.6%; $P = .036$; for prospectively identified subjects: effectiveness, 92.0%; 95% CI, 37.0–99.0; $P = .016$; for the Breslow Day test for homogeneity of the odds ratios, $P = .767$). Also, exclusion of subjects born before 32 weeks gestational age did not significantly affect the estimate.

There were no significant differences in demographic char-

acteristics between mothers who received influenza vaccine and those who did not (Table 4). Among vaccinated mothers, the 2 groups did not differ significantly in the trimester of pregnancy during which vaccination occurred, with 2 (66.7%) of the case subjects' mothers and 26 (78.8%) of the control subjects' mothers receiving vaccines during the third trimester. A mother's chance of being offered influenza vaccine during pregnancy will vary depending on the time of year when the pregnancy begins, but we expect that this variability did not differ significantly between case and control subjects, because these 2 groups were closely matched by the infants' dates of birth.

The median clinical severity scores of the case subjects enrolled was 4, on a scale of 0–16 (Figure 1). There were 11 case subjects (9.7%) admitted to the ICU. Case subjects aged ≥ 6 months at the time of hospitalization had a significantly higher mean severity score than did those aged < 6 months (6.3 ± 3.1 vs 4.1 ± 2.7 ; $P = .001$), and those with chronic medical conditions had higher severity scores than did those without (5.3 ± 2.5 vs 3.5 ± 2.2 ; $P = .003$). Differences in clinical se-

Table 4. Effectiveness of Influenza Vaccine Given to Mothers During Pregnancy in Preventing Hospitalization for Influenza among Their Infants

Measure	Subjects aged <6 months	Subjects aged ≥ 6 months
No. (%) of case infants; no. (%) of control infants		
Mother was vaccinated	2 (2.2); 31 (19.9)	1 (4.6); 2 (5.6)
Mother was not vaccinated	89 (97.8); 125 (80.1)	21 (95.5); 34 (94.4)
Vaccine effectiveness (95% CI), %		
Unadjusted	90.7 (59.9–97.8) ^a	$-41.4 (-2257.3 \text{ to } 91.5)$ ^b
Adjusted ^c	91.5 (61.7–98.1) ^a	...

NOTE. CI, confidence interval.

^a $P = .001$.

^b $P = .809$.

^c The adjusted model for subjects aged < 6 months retained vaccination of household contacts and prematurity.

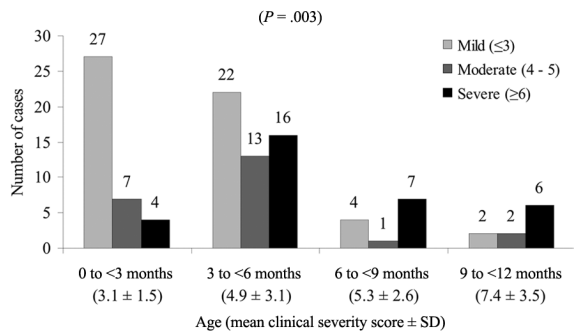


Figure 1. Clinical severity score by age group

verity scores of the case subjects by mother’s vaccination status during pregnancy were not statistically significant.

DISCUSSION

Our study shows that inactivated influenza vaccine given to pregnant women is highly effective (91.5%) in preventing hospitalization for laboratory-confirmed influenza among their infants aged <6 months. These results have great clinical relevance, because they provide a strategy to confer protection to young infants at high risk for the disease and for whom no vaccine is currently available. Furthermore, this strategy has important public health implications, because vaccination protects not only young infants but also their mothers, who are in the high-risk category for severe influenza. Our results on the effectiveness of this approach in the United States, where influenza is seasonal, are consistent with findings of a randomized trial of influenza vaccine in Bangladesh, a tropical, developing country where the pattern and transmission of influenza is perennial [20].

Although there was inadequate statistical power to assess the vaccine’s effectiveness for infants aged ≥6 months, an estimate of –41.4% with wide confidence intervals indicates that a null effect in this age group is plausible. This difference in protective effect for infants aged ≥6 months and infants aged <6 months at hospitalization could be explained by the decrease in the concentration of passively transferred antibodies, which one would expect to have dropped to negligible levels by age 6–9 months. The interpretation of this effect is, however, complicated by small numbers of subjects.

There were several possible limitations to our study. We lacked statistical power to estimate the effectiveness of influenza vaccine for infants aged ≥6 months. It also was not possible to assess independent effects of second trimester vaccination versus third trimester vaccination, because of small numbers. Furthermore, our study did not have adequate power to assess the vaccine’s effectiveness by influenza season, allowing us to assess for year-to-year variability. Future prospective studies are needed to evaluate longer-term effectiveness, in subsequent in-

fluenza seasons, of this novel strategy. We did not type strains to determine whether influenza infections were caused by strains included in the vaccine, and further research is needed to evaluate differences in vaccine effectiveness by circulating strain and vaccine strain match. It is possible that recall bias could have influenced the ability of mothers to recall information that could not be verified by the medical record, such as the length of time they breast-fed their infant.

The CDC and the American College of Obstetricians and Gynecologists (ACOG) recommend inactivated influenza vaccination for women who will be pregnant during the influenza season [4], and inactivated influenza vaccine given to pregnant women is safe and immunogenic [25]. Despite data on safety and the potential benefit to both mother and infant, rates of vaccination with influenza vaccine among pregnant women are poor and vary widely for different health care providers and regions [26]. In spite of the ACOG’s recommendation of influenza vaccination for pregnant women as a means of protection for women against severe infection, in 2003 only one-third of obstetricians offered this vaccine to their patients during pregnancy [27]. In our sample, only 17.2% of mothers of control subjects received influenza vaccine during pregnancy. It is notable, however, that rates of influenza vaccination during pregnancy have improved steadily in the past few years; 10% control subjects in 2000–2004, 15% of control subjects in 2005–2007, and 35% control subjects in 2008–2009 were born to mothers who had received influenza vaccine during pregnancy, a trend similar to that in national data from these years [4].

The public health implications of our findings are important, because the effective strategy of the protection of the infant through vaccination during pregnancy may also serve as an incentive for pregnant women (who are also at high risk for complications from severe influenza) to accept influenza vaccine and for their care providers to offer it. Hopefully, this evidence could also be used in community and public campaigns to improve the overall vaccination rates in these high-risk groups. Also, this strategy improves on the cost-effectiveness of influenza vaccine in pregnant women [28]. Influenza vaccine given to pregnant women is an effective approach to decreasing the number of hospitalizations for influenza among their infants aged <6 months.

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Potential conflicts of interest. All authors: no conflicts.

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Prevention and Control of Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2011

This document provides updated guidance for the use of influenza vaccines in the United States for the 2011–12 influenza season. In 2010, the Advisory Committee on Immunization Practices (ACIP) first recommended annual influenza vaccination for all persons aged ≥ 6 months in the United States (1,2). Vaccination of all persons aged ≥ 6 months continues to be recommended. Information is presented in this report regarding vaccine strains for the 2011–12 influenza season, the vaccination schedule for children aged 6 months through 8 years, and considerations regarding vaccination of persons with egg allergy. Availability of a new Food and Drug Administration (FDA)–approved intradermally administered influenza vaccine formulation for adults aged 18 through 64 years is reported. For issues related to influenza vaccination that are not addressed in this update, refer to the 2010 ACIP statement on prevention and control of influenza with vaccines and associated updates (1,2).

Methodology for the formulation of the ACIP annual influenza statement has been described previously (1). The ACIP Influenza Work Group meets every 2–4 weeks throughout the year. Work Group membership includes several voting members of the ACIP, as well as representatives from ACIP Liaison Organizations. Meetings are held by teleconference and include discussion of influenza-related issues, such as vaccine effectiveness and safety, coverage in groups recommended for vaccination, feasibility, cost-effectiveness, and anticipated vaccine supply. Presentations are requested from invited experts, and published and unpublished data are discussed. CDC's Influenza Division provides influenza surveillance and antiviral resistance data, and the Immunization Safety Office and Immunization Services Division provide information on vaccine safety and distribution and coverage, respectively.

Vaccine Strains for the 2011–12 Influenza Season

The 2011–12 U.S. seasonal influenza vaccine virus strains are identical to those contained in the 2010–11 vaccine. These include A/California/7/2009 (H1N1)-like, A/Perth/16/2009 (H3N2)-like, and B/Brisbane/60/2008-like antigens. The influenza A (H1N1) vaccine virus strain is derived from a 2009 pandemic influenza A (H1N1) virus (3).

Recommendations for Vaccination

Routine annual influenza vaccination is recommended for all persons aged ≥ 6 months (1). To permit time for production of protective antibody levels (4,5), vaccination should optimally occur before onset of influenza activity in the community, and providers should offer vaccination as soon as vaccine is available. Vaccination also should continue to be offered throughout the influenza season.

Although influenza vaccine strains for the 2011–12 season are unchanged from those of 2010–11, annual vaccination is recommended even for those who received the vaccine for the previous season. Although in one study of children vaccinated against A/Hong Kong/68 (H3N2) virus, vaccine efficacy remained high against this strain 3 years later, the estimated efficacy of vaccine decreased over the seasons studied (6). Moreover, several studies have demonstrated that postvaccination antibody titers decline over the course of a year (7–10). Thus, annual vaccination is recommended for optimal protection against influenza.

Vaccine Doses for Children Aged 6 Months Through 8 Years

Children aged 6 months through 8 years require 2 doses of influenza vaccine (administered a minimum of 4 weeks apart) during their first season of vaccination to optimize immune

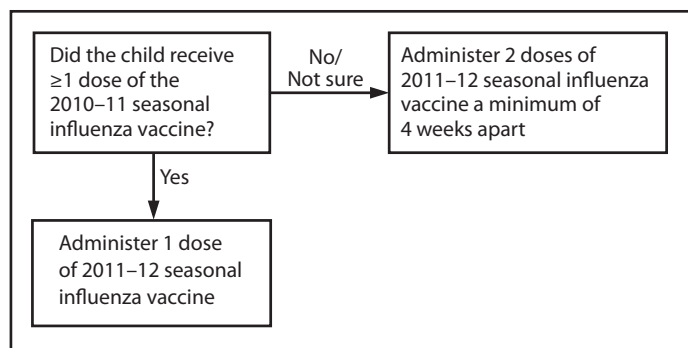


response. In a study of children aged 5 through 8 years who received trivalent inactivated vaccine (TIV) for the first time, the proportion of children with protective antibody responses was significantly higher after 2 doses than after 1 dose (11).

The importance of vaccine priming might depend more on the similarity of the antigenic composition between the priming and second dose than the temporal interval between doses. From the 2003–04 to 2004–05 influenza seasons, the A(H1N1) virus antigen remained unchanged; however, the A(H3N2) virus antigen changed to a drifted strain, and the B virus antigen changed more substantially to a different lineage. In a study conducted over those two seasons, influenza-vaccine naïve children aged 6 through 23 months who received 1 dose of TIV in the spring of their first year of vaccination followed by a second dose in the fall were less likely to have protective antibody responses to the A(H3N2) and B virus antigens when compared with children who received 2 doses of identical vaccine in the fall (12). Response to the unchanged A(H1N1) virus antigen was comparable between the groups. In another study conducted over the same two seasons, unprimed children aged 10 through 24 months who received 1 dose of TIV during the fall of each season had similar responses to the unchanged A(H1N1) virus antigen as well as to the drifted A(H3N2) virus antigen when compared with children aged 6 through 24 months who received 2 doses of the same TIV during the latter season; however, the first group had significantly lower response to the B virus antigen (13). During two seasons in which all influenza vaccine virus antigens were identical, unprimed children aged 6 through 23 months had similar responses when they received 1 dose in the spring followed by a second dose in the fall, as compared with 2 doses received 1 month apart in the fall (14). Studies of inactivated monovalent pandemic 2009 (H1N1) vaccine in children aged <9 years also have demonstrated improved response to this antigen when 2 doses are administered (15–17).

Vaccination providers should note that, in previous seasons, children aged 6 months through 8 years who received only 1 dose of influenza vaccine in their first year of vaccination required 2 doses the following season. However, because the 2011–12 vaccine strains are unchanged from the 2010–11 season, children in this age group who received at least 1 dose of the 2010–11 seasonal vaccine will require only 1 dose of the 2011–12 vaccine. Children in this age group who did not receive at least 1 dose of the 2010–11 seasonal influenza vaccine, or for whom it is not certain whether the 2010–11 seasonal vaccine was received, should receive 2 doses of the 2011–12 seasonal influenza vaccine (Figure 1). Recommendations regarding the number of doses for this age group might change for the 2012–13 season if vaccine antigens change.

FIGURE 1. Influenza vaccine dosing algorithm for children aged 6 months through 8 years — Advisory Committee on Immunization Practices (ACIP), 2011–12 influenza season



Available Vaccine Products and Indications

Multiple influenza vaccines are expected to be available during the 2011–12 season (Table). All contain the same antigenic composition. Package inserts should be consulted for information regarding additional components of various vaccine formulations.

TIV preparations, with the exception of Fluzone Intradermal (Sanofi Pasteur), should be administered intramuscularly. For adults and older children, the deltoid is the preferred site. Infants and younger children should be vaccinated in the anterolateral thigh. Specific guidance regarding site and needle length can be found in the ACIP's *General Recommendations on Immunization* (18).

A new intradermally administered TIV preparation, Fluzone Intradermal, was licensed in May 2011. This vaccine is indicated for persons aged 18 through 64 years and contains less antigen than intramuscular TIV preparations (9 µg rather than 15 µg of each strain per dose) in a smaller volume (0.1 mL rather than 0.5 mL). The vaccine is administered intradermally via a single-dose, prefilled microinjection syringe. The preferred site for administration is over the deltoid muscle (19). The most common adverse reactions include injection-site erythema, induration, swelling, pain, and pruritus. With the exception of pain, these reactions occurred more frequently than with intramuscular vaccine, but generally resolved within 3–7 days. This vaccine is an alternative to other TIV preparations for those in the indicated age range, with no preferential recommendation.

As during the 2010–11 season, a vaccine containing 60 µg of hemagglutinin per vaccine strain (rather than 15 µg per strain as in other intramuscular TIV preparations), Fluzone High-Dose (Sanofi Pasteur), is available as an alternative TIV for persons aged ≥65 years. No preference is indicated for this TIV versus other TIV preparations (1).

The intranasally administered live attenuated influenza vaccine (LAIV), FluMist (MedImmune) is indicated for

TABLE. Influenza vaccine information, by age group — United States, 2011–12 influenza season*

Vaccine	Trade name	Manufacturer	Presentation	Mercury content ($\mu\text{g Hg}/0.5\text{ mL dose}$)	Ovalbumin content ($\mu\text{g}/0.5\text{ mL dose}$)	Age group	No. of doses	Route
TIV	Fluzone	Sanofi Pasteur	0.25 mL prefilled syringe	0.0	— [†]	6–35 mos	1 or 2 [§]	IM [¶]
			0.5 mL prefilled syringe	0.0	— [†]	≥ 36 mos	1 or 2 [§]	IM [¶]
			0.5 mL vial	0.0	— [†]	≥ 36 mos	1 or 2 [§]	IM [¶]
			5.0 mL multidose vial	25.0	— [†]	≥ 6 mos	1 or 2 [§]	IM [¶]
TIV	Fluvirin	Novartis Vaccines	0.5 mL prefilled syringe	≤ 1	≤ 1	≥ 4 yrs	1 or 2 [§]	IM [¶]
			5.0 mL multidose vial	25.0	≤ 1			
TIV	Fluarix	GlaxoSmithKline	0.5 mL prefilled syringe	0	≤ 0.05	≥ 3 yrs	1 or 2 [§]	IM [¶]
TIV	FluLaval	ID Biomedical Corporation of Quebec (distributed by GlaxoSmithKline)	5.0 mL multidose vial	25.0	≤ 1	≥ 18 yrs	1	IM [¶]
TIV	Afluria	CSL Biotherapies (distributed by Merck)	0.5 mL prefilled syringe	0.0	≤ 1	≥ 9 yrs ^{**}	1	IM [¶]
			5.0 mL multidose vial	24.5	≤ 1			
TIV High-Dose ^{††}	Fluzone High-Dose	Sanofi Pasteur	0.5 mL prefilled syringe	0.0	— [†]	≥ 65 yrs	1	IM [¶]
TIV Intradermal	Fluzone Intradermal	Sanofi Pasteur	0.1 mL prefilled microinjection system	0.0	— [†]	18–64 yrs	1	ID
LAIV	FluMist ^{§§}	MedImmune	0.2 mL prefilled intranasal sprayer	0.0	— ^{¶¶}	2–49 yrs ^{***}	1 or 2 [§]	IN

Abbreviations: TIV = trivalent inactivated vaccine; LAIV = live attenuated influenza vaccine; IM = intramuscular; ID = intradermal; IN = intranasal.

* Vaccination providers should check Food and Drug Administration–approved prescribing information for 2011–12 influenza vaccines for the most updated information.

[†] Information not included in package insert but is available upon request from the manufacturer, Sanofi Pasteur, by telephone, 1-800-822-2463, or e-mail, MIS.Emails@sanofipasteur.com.

[§] Children aged 6 months through 8 years who did not receive seasonal influenza vaccine during the 2010–11 influenza season should receive 2 doses at least 4 weeks apart for the 2011–12 season. Those children aged 6 months through 8 years who received ≥ 1 dose of the 2010–11 seasonal vaccine require 1 dose for the 2011–12 season.

[¶] For adults and older children, the recommended site of vaccination is the deltoid muscle. The preferred site for infants and young children is the anterolateral aspect of the thigh.

^{**} Age indication per package insert is ≥ 5 years; however, the Advisory Committee on Immunization Practices recommends Afluria not be used in children aged 6 months through 8 years because of increased reports of febrile reactions in this age group. If no other age-appropriate, licensed inactivated seasonal influenza vaccine is available for a child aged 5–8 years who has a medical condition that increases the child's risk for influenza complications, Afluria can be used; however, providers should discuss with the parents or caregivers the benefits and risks of influenza vaccination with Afluria before administering this vaccine. Afluria may be used in persons aged ≥ 9 years.

^{††} TIV high-dose: A 0.5-mL dose contains 60 μg each of A/California/7/2009 (H1N1)-like, A/Perth/16/2009 (H3N2)-like, and B/Brisbane/60/2008-like antigens.

^{§§} FluMist is shipped refrigerated and stored in the refrigerator at 35°F–46°F (2°C–8°C) after arrival in the vaccination clinic. The dose is 0.2 mL divided equally between each nostril. Health-care providers should consult the medical record, when available, to identify children aged 2–4 years with asthma or recurrent wheezing that might indicate asthma. In addition, to identify children who might be at greater risk for asthma and possibly at increased risk for wheezing after receiving LAIV, parents or caregivers of children aged 2–4 years should be asked: "In the past 12 months, has a health-care provider ever told you that your child had wheezing or asthma?" Children whose parents or caregivers answer "yes" to this question and children who have asthma or who had a wheezing episode noted in the medical record within the past 12 months should not receive FluMist.

^{¶¶} Insufficient data available for use of LAIV in egg-allergic persons.

^{***} FluMist is indicated for healthy, nonpregnant persons aged 2–49 years.

healthy, nonpregnant persons aged 2 through 49 years. Within the indicated groups specified for each vaccine in the package inserts, no preference is indicated for LAIV versus TIV (1).

Vaccination of Persons Reporting Allergy to Eggs

Allergy to eggs must be distinguished from allergy to influenza vaccine. Severe allergic and anaphylactic reactions can occur in response to a number of influenza vaccine components, but such reactions are rare. A review of reports to the Vaccine Adverse Events Reporting System (VAERS) of

adverse events in adults noted four reports of death caused by anaphylaxis following influenza vaccine during 1990–2005; the vaccine components potentially responsible for these reactions were not reported (20). A prior severe allergic reaction to influenza vaccine, regardless of the component suspected to be responsible for the reaction, is a contraindication to receipt of influenza vaccine.

All currently available influenza vaccines are prepared by inoculation of virus into chicken eggs. Hypersensitivity to eggs has been listed as a contraindication to receipt of

influenza vaccine on most package inserts. However, several recent studies have documented safe receipt of TIV in persons with egg allergy (21–29), and recent revisions of some TIV package inserts note that only a severe allergic reaction (e.g., anaphylaxis) to egg protein is a contraindication. In general, these studies include relatively fewer persons reporting a history of anaphylactic reaction to egg, compared with less severe reactions. Several documents providing guidance on use of influenza vaccine in persons with egg allergy have been published recently (30–32).

The quantity of egg protein in vaccine is expressed as the concentration of ovalbumin per dose or unit volume. Among studies in which the ovalbumin content of the administered vaccine was reported, up to 1.4 µg/mL (0.7 µg/0.5 mL dose) was tolerated without serious reactions (22,23,25–29); however, a safe maximum threshold of ovalbumin, below which no anaphylactic reactions would be expected, is not known.

Although ovalbumin content is not required to be disclosed on package inserts for vaccines used in the United States, manufacturers either report maximum albumin content in the package inserts or will provide this information on request. Ovalbumin concentration can vary from season to season and from lot to lot for a given vaccine. Independent assessments of ovalbumin content of commercially available vaccines have noted lower concentrations than those listed on package inserts (33,34).

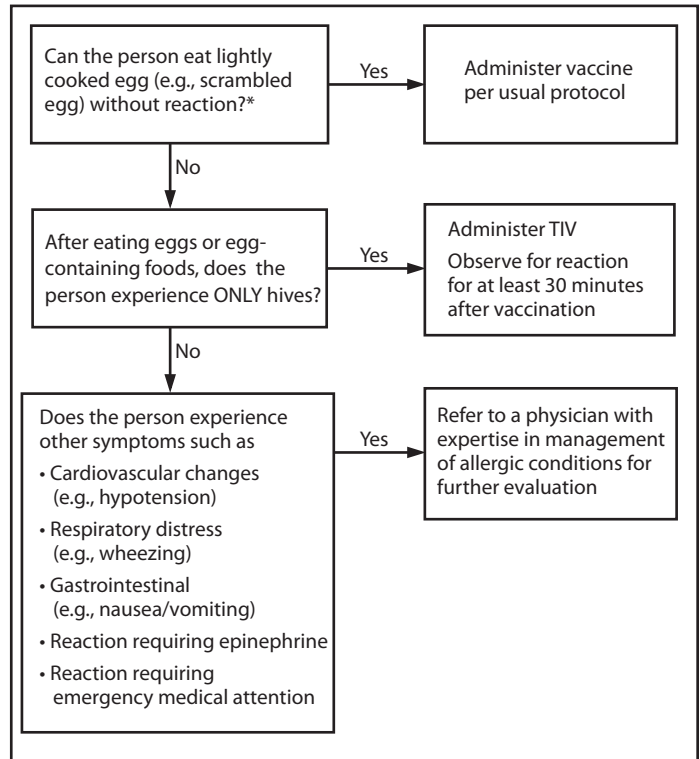
In several studies evaluating influenza vaccine in persons with egg allergy, additional safety measures have been taken, such as skin prick testing with vaccine (21–24,26,28,29) and administering the vaccine in 2 doses (e.g., 10% of the dose initially, followed by the remaining 90% if no reaction has occurred during a 30-minute observation period) (22,24–29). Skin prick testing with vaccine was poorly predictive of allergic reactions in these studies (22–24,26). In general, administration of both full doses and split doses have been well-tolerated without serious reactions, although systemic reactions (e.g., wheezing, eczema exacerbation, and hives on face/chest) were observed with the initial 10% dose among six (3.5%) of 171 participants in one study (24).

Recommendations Regarding Persons with Egg Allergy

Each of the following recommendations applies when considering influenza vaccination of persons who have or report a history of egg allergy.

1. Persons who have experienced only hives following exposure to egg should receive influenza vaccine with the following additional measures (Figure 2):
 - a) Because studies published to date involved use of TIV, TIV rather than LAIV should be used.

FIGURE 2. Recommendations regarding influenza vaccination for persons who report allergy to eggs — Advisory Committee on Immunization Practices (ACIP), 2011–12 influenza season



* Persons with egg allergy might tolerate egg in baked products (e.g., bread or cake). Tolerance to egg-containing foods does not exclude the possibility of egg allergy.

- b) Vaccine should be administered by a health-care provider who is familiar with the potential manifestations of egg allergy.
- c) Vaccine recipients should be observed for at least 30 minutes for signs of a reaction following administration of each vaccine dose.

Other measures, such as dividing and administering the vaccine by a two-step approach and skin testing with vaccine, are not necessary.

2. Persons who report having had reactions to egg involving angioedema, respiratory distress, lightheadedness, or recurrent emesis, or persons who required epinephrine or other emergency medical intervention, particularly those that occurred immediately or within minutes to hours after egg exposure are more likely to have a serious systemic or anaphylactic reaction upon reexposure to egg proteins. Before receipt of vaccine, such persons should be referred to a physician with expertise in the management of allergic conditions for further risk assessment (Figure 2).

3. All vaccines should be administered in settings in which personnel and equipment for rapid recognition and treatment of anaphylaxis are available. ACIP recommends that all vaccination providers be familiar with the office emergency plan (18).
4. Some persons who report allergy to egg might not be egg allergic. Those who are able to eat lightly cooked egg (e.g., scrambled eggs) without reaction are unlikely to be allergic. Conversely, egg-allergic persons might tolerate egg in baked products (e.g., bread or cake); tolerance to egg-containing foods does not exclude the possibility of egg allergy (35). Egg allergy can be confirmed by a consistent medical history of adverse reactions to eggs and egg-containing foods, plus skin and/or blood testing for immunoglobulin E antibodies to egg proteins.
5. A previous severe allergic reaction to influenza vaccine, regardless of the component suspected to be responsible for the reaction, is a contraindication to receipt of influenza vaccine.

Reported by

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* Roster available at <http://www.cdc.gov/vaccines/recs/acip/members-archive.htm>.

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Influenza-Associated Pediatric Deaths — United States, September 2010–August 2011

Influenza-associated pediatric mortality has been a nationally notifiable condition since October 2004. This report summarizes the 115 cases of influenza-associated pediatric mortality reported to CDC that occurred from September 1, 2010, through August 31, 2011. Deaths occurred in 33 states. Nearly half of the deaths (46%) occurred in children aged <5 years. Of the children who died, 49% had no known Advisory Committee on Immunization Practices (ACIP)-defined* high-risk medical conditions, and 35% died at home or in the emergency department. Of the 74 children aged ≥6 months for whom vaccination data were available, 17 (23%) had been fully vaccinated. ACIP recommends that all children aged ≥6 months receive vaccination against influenza annually (1,2). These findings underscore the importance of vaccinating children to prevent influenza virus infection and its potentially severe complications. Health-care providers should develop a comprehensive strategy to increase vaccination coverage among children.

A case is defined as a death from a clinically compatible illness confirmed to be influenza by a diagnostic test in a U.S. resident aged <18 years, with no period of complete recovery between illness and death. Cases are identified by state and local health departments, which collect demographic, clinical, and laboratory information using a standard form and transmit the information to CDC via a secure, web-based interface for data entry. Confirmatory influenza testing methods include commercial rapid diagnostic tests, viral culture, fluorescent antibody, enzyme immunoassay, reverse transcription–polymerase chain reaction, and immunohistochemistry. Although influenza vaccination

* Children receiving long-term aspirin therapy who might be at risk for experiencing Reye syndrome after influenza virus infection or those with chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematologic, or metabolic disorders (including diabetes mellitus), and children with immunosuppression (including immunosuppression caused by medications or by human immunodeficiency virus) or any neurologic condition (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration. Morbid obesity is a risk factor for adults.

of women during pregnancy has been shown to be effective in reducing hospitalizations (1) and deaths among infants aged <6 months (3), data on maternal vaccination during pregnancy were not available for infants aged <6 months.

Of the 115 influenza-associated pediatric deaths reported, 72 (63%) occurred in males (Table). The majority of cases were in non-Hispanic white children (52%), followed by non-Hispanic black (18%) and Hispanic (15%) children. The highest numbers of deaths occurred in late January and early February 2011 (Figure 1). The median age of patients was 6 years, and 53 cases (46%) were in children aged <5 years (Table). Seventy-one (62%) of these cases were associated with influenza A virus infection: 30 (26%) 2009 influenza A (H1N1), 21 (18%) influenza A (H3N2), and 20 (18%) influenza A viruses for which the subtype was not determined. The remaining 44 (38%) cases were associated with influenza B virus infections. In comparison, U.S. national viral surveillance data from World Health Organization (WHO) and National Respiratory and Enteric Virus Surveillance System (NREVSS) collaborating laboratories indicated that 74% of circulating viruses were influenza A and 26% were influenza B viruses.[†]

Nearly half of the children who died (49%) had no known ACIP-defined high-risk medical conditions, 57 (50%) children were reported with medical conditions recognized by ACIP that

[†] Data available at <http://www.cdc.gov/flu/weekly>.

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placed them at increased risk for influenza-related complications, and the medical history of two children was unknown (2%) (Table). Of the 57 children with at least one ACIP-defined high-risk condition, 31 (54%) had a neurologic disorder, 17 (30%) had pulmonary disease, 14 (25%) had a chromosomal abnormality or genetic disorder, 11 (19%) had congenital heart disease or other cardiac disease, and 11 (19%) had asthma or reactive airway disease. Obesity was reported in two (4%) of the 57 children.

Information on the location of death was available for 114 children; 20 (18%) died outside the hospital, 20 (18%) died in the emergency department, and 74 (65%) died in the hospital after admission (Table). Duration of illness ranged from 0 to 57 days (Figure 2); 33 (31%) children died within 3 days of illness onset, and 69 (65%) died within 7 days. When compared with pediatric deaths among children with at least one ACIP-defined high-risk condition, children without high-risk conditions were significantly more likely to die at home or in the emergency department ($p < 0.01$ by chi-square test). The median illness duration before death was 7 days among children with at least one ACIP-defined high-risk condition and 4 days among children without a high-risk condition ($p < 0.01$ by Wilcoxon rank-sum test).

Of 64 children who had specimens collected for bacterial culture from normally sterile sites (including 58 blood cultures), 25 (39%) had positive cultures; *Staphylococcus aureus* was detected in nine (36%) patients (six with methicillin-resistant *S. aureus*, two with methicillin-sensitive *S. aureus*, and one with unknown sensitivity), *Streptococcus pneumoniae*

was detected in six patients, and Group A streptococcus was detected in three. Of the 25 cases with positive cultures, 17 (68%) were in children without high-risk conditions. When compared with children with at least one ACIP-defined high-risk condition, children without a high-risk condition were significantly more likely to have a positive bacterial culture from a sterile site ($p < 0.01$ by chi-square test).

The most frequent complications reported were radiographically confirmed pneumonia (62%), shock or sepsis (40%), and acute respiratory distress syndrome (34%). Encephalopathy or encephalitis was reported in 12 children (14%). The antiviral medications approved by the Food and Drug Administration (FDA) for treatment of influenza are oseltamivir for children aged ≥ 1 year and zanamivir for children aged ≥ 7 years (4). Of the 47 children who received antiviral therapy, three (6%) died in the emergency department, and 44 (94%) died after being admitted to the hospital. All three children who died in the emergency department received oseltamivir. Of the children who died after being admitted to the hospital, 41 received oseltamivir only, two received oseltamivir and zanamivir, and one received zanamivir only.

Information about influenza vaccination was available for 74 children aged ≥ 6 months; 17 (23%) received influenza vaccine in the appropriate number of doses at least 14 days before illness onset. Of 39 vaccine-eligible children with ACIP-defined high-risk medical conditions who had vaccination data available, 12 (31%) had been vaccinated according to 2010 ACIP recommendations (1).

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TABLE. Number and percentage of children who died from influenza-associated illness (N = 115), by selected characteristics — United States, September 1, 2010–August 31, 2011

Characteristic	No.	(%)
Sex		
Male	72	(63)
Female	43	(38)
Median age (range) (yrs)	6 (0–17)	
Age group		
<6 mos	16	(14)
6–23 mos	17	(15)
24–59 mos	20	(19)
5–8 yrs	21	(18)
9–12 yrs	18	(16)
13–17 yrs	23	(20)
Race/Ethnicity		
White, non-Hispanic	60	(52)
Black, non-Hispanic	21	(18)
Hispanic	17	(15)
Asian	4	(3)
Native Hawaiian or Pacific Islander	2	(2)
American Indian or Alaska Native	3	(3)
Unknown	8	(7)
Influenza isolates		
Influenza A	71	(62)
Influenza A, 2009 (H1N1)	30	(26)
Influenza A, (H3N2)	21	(18)
Influenza A, subtype not determined	20	(17)
Influenza B	44	(38)
ACIP-defined high-risk condition*		
Yes	57	(50)
No	56	(49)
Unknown	2	(2)
Type of ACIP-defined high-risk conditions†		
Neurologic disorder	31	(27)
Moderate or severe developmental delay	22	(19)
Seizure disorder	13	(12)
Cerebral palsy	9	(8)
Neuromuscular disorder	4	(4)
Other neurologic disorder	8	(7)
Pulmonary disease	17	(15)
Asthma or reactive airway disease	11	(10)
Chronic pulmonary disease	8	(7)
Chromosome/Genetic disorder	14	(12)
Congenital heart disease or other cardiac disease	11	(10)
Immunosuppressive condition	9	(8)
Received steroids before illness	6	(5)
Cancer (received chemotherapy or radiation)	3	(3)
Endocrine disorder	5	(4)
Diabetes mellitus	1	(1)
Mitochondrial disorder	3	(3)
Renal disease	2	(2)
Pregnant	1	(1)
Obesity	2	(2)

See table footnotes on page 1236.

Reported by

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TABLE. (Continued) Number and percentage of children who died from influenza-associated illness (N = 115), by selected characteristics — United States, September 1, 2010–August 31, 2011

Characteristic	No.	(%)
Location of death[§]		
Outside hospital (i.e., at home or in transit)	20	(18)
Emergency department	20	(18)
Hospital, admitted [¶]	74	(65)
Duration of disease (days)**	6 (0–57)	
Duration of disease ≤3	33	(31)
Duration of disease ≤7	69	(66)
≥1 high-risk condition, median (range)	7 (0–57)	
No high-risk condition, median (range)	4 (0–21)	
Bacterial testing from sterile site performed		
Yes	64	(56)
No	43	(37)
Unknown	8	(7)
≥1 bacterial coinfection^{††}	25	(39)
Bacteria isolated from sterile site^{§§}		
<i>Staphylococcus aureus</i>	9	(36)
Methicillin-resistant <i>S. aureus</i>	6	(24)
Methicillin-sensitive <i>S. aureus</i>	2	(8)
Sensitivity testing not performed	1	(4)
<i>Streptococcus</i> species ^{¶¶}		
<i>Streptococcus pneumoniae</i>	6	(24)
Group A streptococcus	3	(12)
Group B streptococcus	2	(8)
Group C streptococcus, beta hemolytic	1	(4)
Group D streptococcus, non-hemolytic	1	(4)
Viridans group streptococcus ^{***}	2	(8)
Other or not specified streptococcus ^{†††}	2	(8)
<i>Pseudomonas aeruginosa</i>	2	(8)
Complications during acute illness		
Yes	85	(74)
No	19	(17)
Unknown	11	(10)
Complications^{§§§}		
Pneumonia	53	(62)
Shock or sepsis	34	(40)
Acute respiratory distress syndrome	29	(34)
Other complication	19	(22)
Encephalopathy/Encephalitis	12	(14)
Seizures	11	(13)
Hemorrhagic pneumonia/pneumonitis	5	(6)
Croup	4	(5)
Cardiomyopathy/Myocarditis	3	(4)
Bronchiolitis	2	(2)
Received antibiotic therapy^{¶¶¶}	49	(52)
Received antiviral therapy^{¶¶¶}	47	(50)
Received oseltamivir	46	(49)
Received zanamivir	3	(3)

See table footnotes on page 1236.

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Editorial Note

Nearly half of the children who died from influenza virus infections during the 2010–11 influenza season and whose deaths were reported to CDC had no known ACIP-defined high-risk medical conditions. Of children with ACIP-defined high-risk

TABLE. (Continued) Number and percentage of children who died from influenza-associated illness (N = 115), by selected characteristics — United States, September 1, 2010–August 31, 2011

Characteristic	No.	(%)
Vaccination status		
Ineligible for vaccine	16	(14)
Eligible for vaccine	99	(86)
Fully vaccinated****	17	(23)
Not vaccinated****	57	(77)
Eligible for vaccine, ≥1 ACIP-defined high-risk condition††††		
Fully vaccinated	12	(31)
Not fully vaccinated	27	(69)
Eligible for vaccine, no ACIP-defined high-risk condition††††		
Fully vaccinated	4	(12)
Not fully vaccinated	30	(88)
Unknown vaccination status	25	(22)

Abbreviation: ACIP = Advisory Committee on Immunization Practices.

* Children receiving long-term aspirin therapy who might be at risk for experiencing Reye syndrome after influenza virus infection or those with chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematologic, or metabolic disorders (including diabetes mellitus), and children with immunosuppression (including immunosuppression caused by medications or by human immunodeficiency virus) or any neurologic condition (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration. Morbid obesity is a risk factor for adults.

† Percentage reported out of 113 children with a known medical history; conditions are not mutually exclusive.

‡ Location of death was known for 114 children.

§ Includes inpatient ward (10), intensive-care unit (62), operating room (one), and hospice (one).

** Illness onset date was not available for nine deaths.

†† Percentage reported out of 64 children with specimen collected for bacterial culture from a normally sterile site.

‡‡ Percentage reported out of 25 children with positive bacteria culture from a normally sterile site.

§§ More than one *Streptococcus* species could be isolated from each patient.

*** Includes one *Streptococcus parasanguinis* and one not specified.

††† Includes one non-hemolytic and one alpha-hemolytic.

§§§ Percentage reported out of 85 children with known complications; complications were not mutually exclusive.

¶¶ Percentage reported out of 94 children who died in a health-care facility.

**** Percentage reported out of 74 children who had a known vaccination history and were eligible for vaccine.

†††† Percentage reported out of children with known vaccination status.

medical conditions, neurologic disorders and pulmonary disease were identified most frequently. The underlying reason for the vulnerability of patients with neurologic disorders remains unclear but likely is attributable, in part, to compromised respiratory function and decreased ability to handle secretions (5). These data are consistent with findings from the 2004–05 through 2008–09 influenza seasons (5–7). Children with no high-risk conditions had a shorter interval between illness onset and death (4 days versus 7 days), and were more likely to die at home or in the emergency department, and were more likely to have a positive bacterial culture from a sterile site. In children with no high-risk conditions, the development of a secondary bacterial coinfection might have been the immediate cause for

What is already known on this topic?

Since influenza-associated pediatric deaths became a nationally notifiable condition in 2004, the number of deaths reported to CDC has ranged from 46 during the 2005–06 influenza season to 282 during the 2009–10 season.

What is added by this report?

A total of 115 influenza-associated pediatric deaths were reported to CDC that occurred from September 1, 2010 to August 31, 2011. Fifty-six (49%) children who died from influenza virus infections during the 2010–11 influenza season had no reported Advisory Committee on Immunization Practices (ACIP)-defined high-risk medical conditions. Children without high-risk conditions had a shorter interval between illness onset and death (4 days versus 7 days), were more likely to die at home or in the emergency department, and were more likely to have a positive bacterial culture from a sterile site. Among children who died from influenza, few (23%) were vaccinated, and 50% received antiviral therapy.

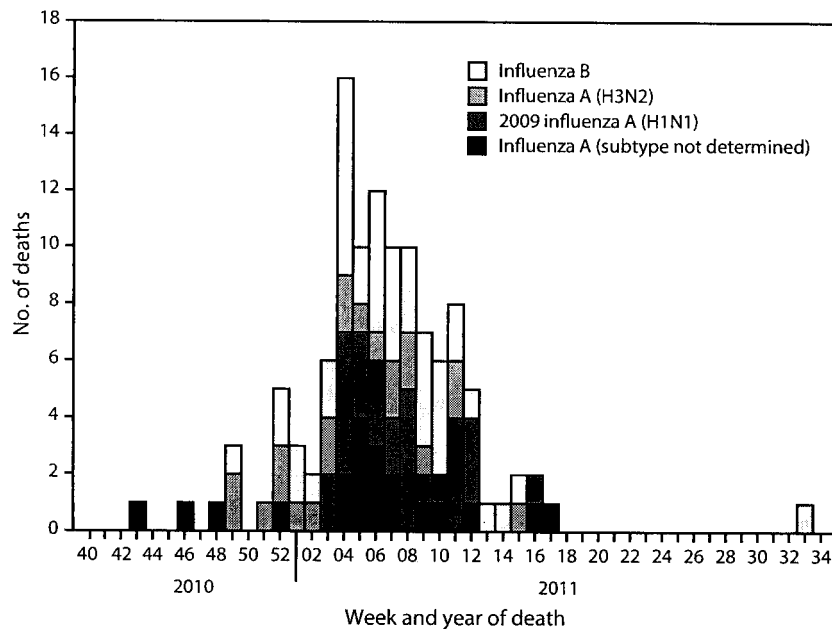
What are the implications for public health practice?

Continued efforts are needed to ensure annual influenza vaccination in all persons aged ≥6 months, and children with high-risk medical conditions should be specially targeted for vaccination. Health-care providers should be aware that severe complications of influenza can occur in children without high-risk medical conditions. Early and aggressive treatment with oseltamivir or zanamivir is recommended as soon as possible after symptom onset in patients with confirmed or suspected influenza who are hospitalized; who have severe, complicated, or progressive illness; or who are at a higher risk for influenza complications.

seeking medical care. Physicians of children with ACIP-defined high-risk conditions might have been more likely to hospitalize their patients early in their illness, given their perceived greater risk of influenza-related complications. Health-care providers should be aware that severe complications of influenza can occur in children without high-risk medical conditions. Information for parents, including guidance on influenza vaccination and danger signs in children with influenza-like illness symptoms, is available at http://www.cdc.gov/flu/pdf/freeresources/family/a_flu_guide_for_parents.pdf.

This report highlights several important points about influenza epidemiology, vaccination, and treatment in children. Although influenza-associated pediatric mortality is rare, influenza B was identified in a disproportionate number of pediatric influenza-associated deaths (38%). During the 2010–11 influenza season, only 26% of circulating influenza viruses were influenza B. In previous seasons, the percentage of influenza B viruses among children with influenza-associated mortality has been comparable to or higher than the percentage of influenza B viruses circulating for that season (6,7).

FIGURE 1. Number of influenza-associated pediatric deaths (N = 115), by week of death and type of influenza virus — United States, September 1, 2010–August 31, 2011



Annual influenza vaccination for all children aged ≥ 6 months is recommended and is the most effective way to prevent influenza and its complications. Influenza vaccination campaigns should proceed for all persons (children and adults) as soon as vaccine is available. Since 2010, ACIP has recommended annual influenza vaccination for all persons aged ≥ 6 months, and children with ACIP-defined high-risk medical conditions should be specially targeted for vaccination (1,2). Healthy children aged 2–18 years may receive either live, attenuated influenza vaccine (LAIV) or trivalent inactivated influenza vaccine (TIV) (1). Children aged 6–23 months and those aged 2–4 years who have asthma or wheezing, or who have medical conditions that put them at higher risk for influenza complications should receive TIV (1). Children aged 6 months–8 years who did not receive at least 1 dose of the 2010–11 seasonal influenza vaccine should receive 2 doses of the 2011–12 seasonal influenza vaccine administered at least 4 weeks apart. Children in this age group who did receive at least 1 dose of the 2010–11 vaccine, as well as persons aged ≥ 9 years, should receive 1 dose of the 2011–12 vaccine (2).

In the United States, influenza vaccination coverage for the 2010–11 season was estimated at 49% in children aged 6 months–17 years.[§] Among children who died from influenza described in this report, 23% were vaccinated. Vaccination coverage was higher among children with ACIP-defined

[§] Data available at <http://www.cdc.gov/flu/professionals/vaccination/vaccinecoverage.htm>.

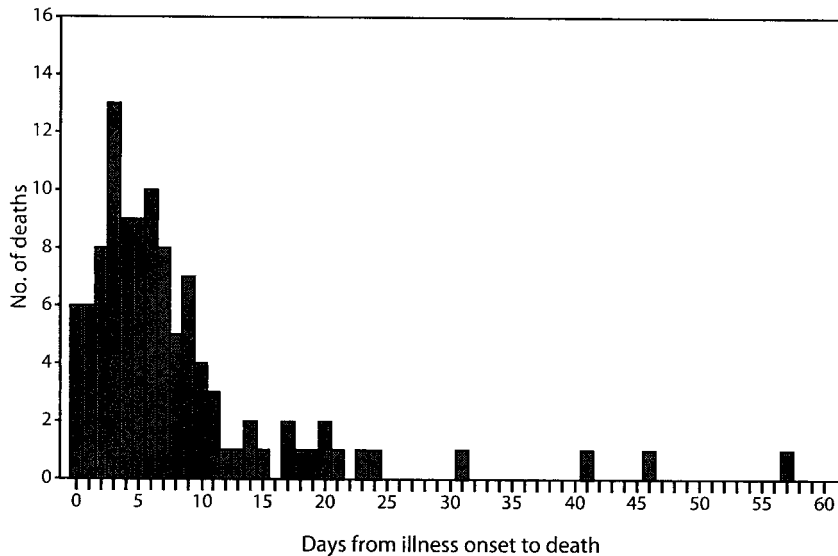
high-risk medical conditions than among children without high-risk medical conditions (31% versus 12%). These findings emphasize the need to improve vaccination coverage among all children, especially those at increased risk for influenza-related complications. To protect infants aged < 6 months who are too young to be vaccinated, ACIP recommends that pregnant women (3) and household contacts and out-of-home caregivers of such infants receive vaccination against influenza (1). Because influenza vaccination of women during pregnancy has been shown to be effective in reducing hospitalizations (1) and deaths among infants aged < 6 months (3), improving vaccination rates among pregnant women is a priority.

Half of the children described in this report received influenza antiviral therapy. Early and aggressive treatment with oseltamivir or zanamivir[†] is recommended as soon as possible after symptom onset in a patient with confirmed or suspected influenza who is hospitalized; who has severe, complicated, or progressive illness; or who is at higher risk for influenza complications,** even if influenza testing is negative (4). In outpatients without risk factors for complications, influenza antiviral treatment should be considered if treatment can be initiated within 48 hours of symptom onset. Results of one randomized, controlled trial of oseltamivir treatment among children aged 1–3 years indicated that when oseltamivir was started within 24 hours of illness onset, the median time to illness resolution was shortened by 3.5 days compared with placebo (8). Treatment with influenza antiviral therapy of any person with confirmed or suspected influenza who requires hospitalization is recommended, even if the patient enters care > 48 hours after illness onset (4,9).

[†] Oseltamivir is FDA-approved for treatment and chemoprophylaxis of influenza among children aged ≥ 1 year. Zanamivir is FDA-approved for treatment of influenza among children aged ≥ 7 years. Zanamivir is approved for chemoprophylaxis of influenza among children aged ≥ 5 years.

** Persons at higher risk include children aged < 5 years (especially those aged < 2 years); adults aged ≥ 65 years; persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematologic (including sickle cell disease), metabolic disorders (including diabetes mellitus), or neurologic and neurodevelopmental conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle, such as cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability [mental retardation], moderate to severe developmental delay, muscular dystrophy, or spinal cord injury); persons with immunosuppression, including that caused by medications or by human immunodeficiency virus infection; women who are pregnant or postpartum (within 2 weeks after delivery); persons aged ≤ 18 years who are receiving long-term aspirin therapy; American Indians/Alaska Natives; persons who are morbidly obese (i.e., body mass index ≥ 40); and residents of nursing homes and other chronic-care facilities.

FIGURE 2. Number of influenza-associated pediatric deaths (N = 106),* by number of days from influenza illness onset until death — United States, September 1, 2010–August 31, 2011



* Illness onset date not available for nine deaths.

S. aureus, *S. pneumoniae*, and Group A streptococcus were the pathogens most commonly identified in children with invasive bacterial coinfection. Empiric antibiotic therapy and early influenza antiviral therapy are recommended in patients with community-acquired pneumonia and suspected influenza coinfection (4). In 2010, ACIP recommended the use of the 13-valent pneumococcal polysaccharide-protein conjugate vaccine for all children aged 2–59 months and children aged 60–71 months with underlying medical conditions that increase their risk for pneumococcal disease or complications (10).

The findings in this report are subject to at least four limitations. First, the actual burden of influenza-associated pediatric mortality likely is underestimated because the current surveillance method will only detect those patients who are tested for influenza, who have a positive test, and who are reported to the surveillance system. Second, some data about medical conditions, vaccination status, clinical course, and treatment were missing; these data depend on the thoroughness and consistency of case reporting. Third, invasive bacterial testing is not performed systematically for all children and therefore depends on testing being part of clinical care or autopsy. Finally, determination of obesity as a high-risk medical condition did not use height and weight data, which might lead to underestimation of obesity among children.

This report emphasizes the importance of continued surveillance for influenza-associated pediatric mortality. State health departments should notify the Influenza Division at

CDC of laboratory-confirmed influenza-associated pediatric deaths that occur in their jurisdiction as soon as possible by submitting the web-based case report form. Surveillance provides information about risk factors associated with severe disease and death that can be used to monitor the impact of influenza on children, plan interventions, inform policy and resource allocation decisions, develop vaccination recommendations, and provide information to public health professionals, the media, and the general public regarding the severity of the influenza season. Health-care providers should be mindful of the potential for severe outcomes of influenza in children. Although antiviral medications are a valuable adjunct to preventing and reducing the impact of influenza, vaccination remains the primary prevention tool against influenza-associated complications.

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Immunization updates and challenges

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Purpose of review

Childhood vaccination recommendations in the United States have increased throughout the years. Many providers, patients, and families are overwhelmed and have concerns regarding the safety and efficacy of vaccines. Various barriers and challenges exist for healthcare providers to successfully implement the vaccination recommendations. This review will discuss the 2009 and newly released 2010 immunization recommendations, as well as challenges and strategies to improve vaccination in children and adolescents.

Recent findings

Seasonal influenza immunization continues to be promoted for all children, and recommendations for vaccination against novel influenza A have emerged as well. Concerns surrounding vaccine safety and necessity may cause increasing rates of vaccine refusal among some parents, but clear messages from providers and unbiased information about benefits and risks of immunization may counteract these doubts. Barriers to immunizing adolescents continue as access to healthcare in this age group changes.

Summary

Pediatric providers currently face numerous challenges in improving rates of immunization among children and adolescents. Promoting coverage through the influenza vaccines, counseling parents with clear information about the risks and benefits of vaccines, and taking advantage of nonpreventive visits for immunization are some strategies suggested to address these challenges.

Keywords

children, immunization, vaccine, vaccine refusal, vaccine safety

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Introduction

Childhood immunization recommendations in the United States have undergone major changes in the last few decades, including at least eight new vaccines and the emergence of several combination vaccines [1]. Table 1 summarizes the revisions included in the 2009 and 2010 recommended immunization schedules. In 2009, changes to the schedule were relatively minor but notably addressed the continued expansion of the influenza vaccine age range to 18 years [2^{••},3]. Significant revisions in the 2010 schedule include recommendations for the use of combination vaccines, revaccination with meningococcal conjugate vaccine (MCV4) for children at increased risk of meningococcal disease, and a recommendation for the use of the quadrivalent human papillomavirus (HPV) vaccine in high-risk boys aged 9 through 18 years [4^{••}]. In addition, because of the pandemic outbreak of novel influenza A (H1N1), recommendations for the vaccine made in late 2009 remain in place for children 6 months and above [5[•],6].

Although the prevalence of several infectious diseases has been greatly impacted through the implementation of the vaccination program in the United States [7], continuous additions and revisions to the immunization schedule may affect compliance by both providers and families. This article will briefly review some of the more notable updates to the immunization schedule for 2009 and 2010, as well as discussing the most recent challenges and strategies to improve vaccination rates in children and adolescents.

Influenza vaccination recommendations

Vaccine discussions in 2009 primarily revolved around influenza, both seasonal and H1N1. The American Academy of Pediatrics (AAP) Committee on Infectious Diseases recently issued a policy statement for the prevention and treatment of influenza in children for 2009–2010 [8^{••}]. Use of inactivated vaccine and live-attenuated influenza vaccine (LAIV) against both seasonal influenza and H1N1 in children is discussed, and the use of antiviral chemoprophylaxis is also addressed. In

Table 1 Summary of revisions in the 2009 and 2010 recommended immunization schedules

2009 revisions [2 ^{••} ,3]	
Rotavirus	Vaccine maximum starting age was changed from 12 weeks to 14 weeks 6 days, and maximum age for final dose was changed from 32 weeks to 8 months to synchronize with the newly approved two-dose rotavirus.
Hib	Indication for the vaccine was expanded to allow immunization of persons aged 5 years and older at risk for invasive Hib disease.
HPV	Vaccination catch-up interval is to be the same as routine dosing interval.
Tdap	Interval between tetanus–diphtheria and Tdap immunizations of less than 5 years is acceptable for those who require pertussis immunity.
Seasonal influenza	Vaccine recommended for annual administration to children 6 months through 18 years of age. Two doses 1 month apart of the vaccine are required for those under 9 years of age receiving the vaccine for the first time or for those who were vaccinated for the first time last season but only received one dose.
Other	Most of the footnotes for the individual vaccines have been revised to provide additional information and to clarify recommendations provided in the schedules.
2010 revisions [4 ^{••}]	
IPV	The fourth dose of the vaccine is now recommended on or after the fourth birthday. If four doses were administered before the age of 4 years, a fifth dose is recommended between 4 and 6 years of age.
HepA	Vaccine may now be given to children older than 23 months if immunity is desired.
MCV4	Revaccination is recommended for children at high risk of meningococcal disease, after 3 years if first dose was given through 6 years of age or after 5 years if the first dose was at 7 years or older.
HPV	Recommendations include use of the bivalent vaccine for girls, and the quadrivalent vaccine is now recommended for boys aged 9 through 18 years at high risk for acquiring genital warts.
H1N1 [5 [•] ,6]	Vaccine recommended for annual administration to children 6 months through 24 years of age. Two doses 1 month apart are required for those under 10 years of age.
Other	The use of combination vaccines is now addressed in the introductory paragraph. Combination vaccines are generally preferred over separate injections of their component vaccines as long as patient choice, provider assessment, and risk of adverse events have been considered.

H1N1, novel influenza A; HepA, hepatitis A; Hib, *Haemophilus influenzae* type b conjugate; HPV, human papillomavirus; IPV, inactivated poliovirus; MCV4, meningococcal conjugate; Tdap, tetanus and diphtheria toxoids and acellular pertussis.

addition, a brief review of the Centers for Disease Control and Prevention (CDC) estimates for the first several months of the H1N1 outbreak in the United States is presented.

Seasonal influenza

Recommendations continue to emphasize the importance of annual seasonal influenza immunization for children 6 months through 18 years of age [8^{••}]. Children at high risk for complications from the flu should be especially targeted, including the immunosuppressed or those with chronic illnesses. Particular attention is also encouraged among the school-aged population, as they currently bear the greatest influenza disease burden [8^{••},9]. Household members and caregivers of high-risk children and all children under the age of 5 years are also strongly encouraged to receive the vaccine [8^{••}].

The LAIV is administered intranasally and is licensed for use in individuals who are 2 years old and above, but only for healthy individuals and those living among healthy households [8^{••}]. Early studies [8^{••},10[•]] have shown increased levels of immunity for the LAIV in children, although more solid research is necessary. Children aged 9 years and older may continue to receive one dose of the trivalent inactivated vaccine, whereas children under 9 years of age should receive two doses in their first year receiving the vaccine and then one annual dose afterward [8^{••}]. If these children did not receive two doses in their first year of receiving it, they should have two doses in their second year and then continue with the annual single dose. Contraindications to all flu vaccines include

age under 6 months, severe allergy to egg, moderate-to-severe febrile illness, and history of serious adverse events with previous vaccines. In addition to the above, contraindications to the LAIV include age under 2 years, pregnancy, nasal congestion, and any chronic illness or disorder that may compromise respiratory or immune function. Thus, children with wheezing or asthma should not receive the LAIV. Living in a household with persons with the conditions mentioned above is also a contraindication to receiving LAIV.

Although influenza vaccination recommendations were expanded in the beginning of the 2008–2009 season to include all children, coverage remained low in the United States [11[•]]. According to data analyzed by the CDC from the Behavioral Risk Factor Surveillance System, total influenza vaccination coverage for children 6 months through 17 years was estimated at only 24%. Especially concerning was the low rate of vaccination among school-aged children of 5–17 years (20.8%). Greater efforts must be made to ensure that the new recommendations for this age group are promoted effectively, as this group may bear the greatest influenza disease burden [8^{••},9]. The AAP Policy Statement [8^{••}] contains a simple algorithm helpful for providers to capture those who need to be vaccinated.

Novel influenza A

In response to the H1N1 outbreak in 2009, recommendations soon appeared for its vaccine for children similar to those for seasonal influenza, with the exception of the upper age limit extended from 18 to 24 years [5[•],6].

Current studies do not show cross-reactive antibody to H1N1 in children who have received the seasonal influenza vaccine, and, therefore, receipt of both vaccines is recommended. It is permissible to immunize with both inactivated vaccines simultaneously, provided that different injection sites are used. Simultaneous administration of LAIV for both flu vaccines, however, is not recommended. A second dose of the H1N1 vaccine is recommended for children under 10 years [6]. This is in contrast to the seasonal influenza vaccine, wherein children under 9 years need two doses for the first time [8**].

Antiviral chemoprophylaxis recommendations have been issued by the CDC as adjunct therapy to influenza vaccination [8**,12*]. Unvaccinated children undergoing influenza treatment or chemoprophylaxis are also eligible and recommended to be immunized with the inactivated

vaccines [12*]. Up-to-date influenza decision-making and treatment algorithms for healthcare providers can be found on the CDC website (see Table 2).

In December 2009, the CDC released estimates of the prevalence of H1N1 influenza cases, hospitalizations, and deaths in the United States through 14 November 2009 [13]. According to this report, between April and mid-November, prevalence was estimated at between 34 and 67 million infected individuals. Approximately one-third of these were pediatric patients, with estimates between 12 and 23 million infected children 0 through 17 years of age. During this time period, there were an estimated 51 000–101 000 pediatric hospitalizations and 790–1550 pediatric deaths related to H1N1 in children 0 through 17 years of age. These numbers represented a dramatic 2.5 times increase from estimates reported in mid-October

Table 2 Online resources for pediatric providers about immunizations and related information

Website address	Organization	Description
www.cdc.gov/vaccines	CDC	General information about vaccines Access to current ACIP recommendations and immunization schedules Vaccine Information Statements and patient education materials Information regarding use of an IIS and local IIS contact information
www.immunize.org	IAC	Vaccine policy, licensing, and safety Free print education materials in 40 languages Summary grid of current recommendations, intervals, and contraindications IAC Express: weekly free e-mail notification with up-to-date information about vaccine approvals, new vaccine recommendations, new immunization resources and current events, and journal articles
www.aap.org/immunization	AAP: Childhood Support Immunization Program	Information for patients, parents, providers, and media on vaccines and vaccine-preventable diseases State level (AAP Chapter) immunization-related activities and initiatives
www.vaccineinformation.org	IAC	Information designed for patients, parents, providers, and media on vaccines and vaccine-preventable diseases (also available in Spanish)
http://kidshealth.org/teen/your_body/health_basics/immunizations.html www.nni.org	Nemour Foundation: Kids Health National Network for Immunization Information	Health and vaccine information directed towards adolescents Up-to-date information on immunization science and research including synopses of articles from peer-reviewed literature related to vaccines and immunization
www.vaccinesafety.edu	Johns Hopkins Institute for Vaccine Safety	Information on vaccines and safety to help guide and educate physicians, the public and the media about issues surrounding the safety of vaccines
www.who.int/immunization	WHO	Global policy, guidelines, and information about vaccines and related diseases
www.hhs.gov/nvpo	US Department of Health and Human Services National Vaccine Program Office	Publications and reports on vaccine-preventable diseases, vaccine safety, vaccine coverage, immunization laws, and immunization registries
www.cdc.gov/flu	CDC	Current information on seasonal flu activity and surveillance Vaccine and prevention information for providers and patients Algorithm for antiviral treatment and prevention of influenza
www.flu.gov	US Department of Health and Human Services	Comprehensive government-wide information on seasonal, H1N1 (swine), H5N1 (bird), and pandemic influenza for the public and professionals
www.preventchildhoodinfluenza.org	Childhood Influenza Immunization Coalition: National Foundation for Infectious Diseases	Information and resources for healthcare professionals, patients, families, and media regarding the influenza vaccine and related topics

AAP, American Academy of Pediatrics; ACIP, Advisory Committee on Immunization Practices; CDC, Centers for Disease Control and Prevention; H1N1, novel influenza A; H5N1, avian influenza A; IAC, Immunization Action Coalition; IIS, Immunization Information Systems.

2009, reflecting a surge of H1N1 activity in late October and early November. In light of this evidence, support continues to increase for significant prevention strategies against H1N1, such as vaccination.

Challenges in vaccine compliance

Recent studies have addressed increasing trends among parents who are refusing or delaying vaccination for their children. Issues thought to influence parental resistance to vaccines include both the increasing number of available vaccines and lack of perceived threat of the diseases they prevent [14[•]]. Provider attitudes towards surrounding vaccines may play a large role, as many parents rely heavily on provider counseling regarding vaccine decisions [14[•],15,16[•],17[•],18]. Finally, concerns about safety and risk for adverse events after vaccination continue to mount, as media exposure incites doubt throughout the community [19[•]].

Vaccine refusal

An increase in the number of parents refusing or delaying vaccines for their children has prompted studies to evaluate the characteristics of vaccine refusers. Gust *et al.* [16[•]] interviewed a random subset of parents ($n = 3924$) who completed the National Immunization Survey (NIS) by the CDC in 2003 and 2004 to explore just these factors. Approximately 28% of parents surveyed reported some level of doubt about vaccination (13% delayed vaccinations, 9% were unsure, and 6% completely refused vaccinations for their child). Factors associated with vaccine refusal included white race/ethnicity of the mother, age of child under 2 years, and general concern that vaccination may not be safe or may cause serious side effects. In another study [20] of parents who refused immunization for their children ($n = 1249$), investigators found that refusers were more likely to come from high-income and well educated communities, but continued to access the healthcare system.

Trust in vaccine information provided is important in the decision-making process for parents about immunizations. In a small qualitative study [15] of parents who refused vaccination for their children ($n = 25$), patients were again found to be mostly white and highly educated. Parents interviewed expressed distrust of the medical community, and were opposed to vaccine information offered at the time of vaccine administration rather than prior to administration. Many of these parents wished to discuss both risks and benefits with providers in order to address their concerns about vaccine safety. Similar themes were also addressed in a case-control intervention study of parental vaccine refusers, as patients in the case group ($n = 69$) tended to disagree or be neutral about their trust in providers or government agencies regarding vaccine information [17[•]]. Parents in this group suggested

that an informational brochure provided should include honest and balanced information about both risks and benefits of vaccines.

Provider recommendations have been shown to play a large role in parents' decisions on vaccination [14[•],15,16[•],17[•],18,21[•]], yet providers themselves are not always recommending vaccination [22]. A study [22] of pediatric providers ($n = 733$) found that 11% did not fully recommend vaccinations. These physicians were also more likely to report being neutral or agreeing that they have some concerns about immunizations. This raises the question of whether adequate immunization information is disseminated to pediatric providers. Another pilot study [23[•]] examined physicians' communication strategies in addressing vaccine refusal through the use of standardized patients. Although most of the physicians scored well on listening and spending sufficient time with the standardized patients, lower scores were obtained in validation of the standardized patients' concerns, using open-ended questions, and checking for knowledge or understanding. Additional training on communication for pediatric providers is essential in addressing vaccine refusal with patients.

Vaccine safety controversies

As mentioned above, safety concerns have greatly influenced vaccine acceptance rates among parents. Despite previous research in existence refuting the suggested relationship between measles or measles-mumps-rubella (MMR) vaccines and autism spectrum disorders (ASDs) [24], research continues to emerge in this area. In a case-control study [25] of over 200 vaccinated children in the UK, there was again found to be no difference between ASD patients and controls in measles antibody concentrations or altered immunological response following MMR vaccination. The proposed relationship between thimerosal preservatives in vaccines and ASDs has also been refuted yet again [19[•],24,26].

Combination vaccines offer advantages over separate vaccines, including fewer injections and thus better compliance, but their safety has come into question [27]. This past summer, the Advisory Committee on Immunization Practices (ACIP) revised the 1999 recommendations for the use of combination vaccines [28], and this revision is included in the latest 2010 recommended immunization schedule [4^{••}]. The ACIP states that combination vaccines are generally preferred over separate injections of their component vaccines as long as patient choice, provider assessment, and risk of adverse events have been considered. A recent exception to this came in 2008, when a higher incidence of febrile seizures following a MMR-varicella (MMRV) vaccine in the United States (Proquad, Merck & Co. Inc., Whitehouse Station, New Jersey, USA) led the ACIP to declare no preference

between use of the MMRV and the separate MMR and varicella vaccines [29]. In 2009, the ACIP issued further provisional recommendations encouraging providers to address the risks of febrile seizure with parents when considering the use of MMRV for a child's first dose at the age of 12–47 months [30]. For children receiving the first dose at 48 months or older, and for children of any age receiving the second dose, the MMRV vaccine is still considered preferred over its separate components.

Parental refusal of vaccines despite current evidence of their safety continues to show an impact on disease rates and outbreaks. Results of a case–control study [31] of pertussis vaccination and infection rates in Colorado children from 1996 to 2007 ($n = 156$ patients, 595 matched controls) showed that 11% of all pertussis patients were attributed to parental vaccine refusal. Although more research is needed on the epidemiology of disease related to vaccine refusal, it is obvious across the literature that comprehensive patient education by pediatric providers regarding the evidence and myths surrounding vaccine safety is vitally important to improving immunization rates.

Adolescent immunizations

Efforts continue toward bringing adolescents up-to-date for both routine and newly introduced vaccines. Barriers include infrequent preventive visits, incomplete records, lack of awareness about the risk of serious infectious diseases, and lack of coverage for adolescent vaccination [21[•],32,33[•],34–37]. Several studies over the last year have looked at the influences affecting poor adolescent immunization rates as well as the challenges in improving them.

Visits and venues

Although childhood immunizations occur during routine well child visits, a decrease in the number of preventive visits in adolescence creates a barrier to this process. This is problematic for those behind on childhood vaccines, as well as those who were older than 12 years when routine recommendations for the MCV4, HPV, and tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccines were released. According to the 2008 NIS-Teen of almost 18 000 US adolescents, coverage rates for these three vaccines had improved but still fell below 50% [38]. One method of addressing this problem is to vaccinate at acute visits whenever possible, although many practitioners currently miss these opportunities. In a large study of adolescents in Massachusetts ($n = 23\,987$), investigators found that missed opportunities for tetanus and diphtheria immunization occurred at 84% of all healthcare visits, mostly associated with nonpreventive visits [39].

Obtaining accurate immunization records for adolescents has also been identified as a barrier to vaccination at nonpreventive visits [21[•]]. The use of Immunization Information Systems (IIS), also known as immunization registries, has been promoted as a potential solution [21[•],33[•],34,39]. Current studies [40,41] show promise in the effectiveness of IIS to improve tracking and record keeping and more is sure to emerge in the coming years.

Adolescents may also use alternative sites for healthcare such as school-based health centers or family planning clinics. In a multistate qualitative study [33[•]] of participants with varying roles associated with adolescent immunization ($n = 49$), many patients discussed the lack of available vaccines in the sites where teens routinely seek care. Participants also raised the related issue of adolescents' ability to consent for vaccines, which is limited in many states. In this study as well as another qualitative interview of US pediatric providers, patients raised concerns that missed opportunities for vaccination increase when teens independently seek care without a parent and are unable to consent to their own immunization [21[•],33[•]].

Perceived risk of disease and safety

The HPV vaccine has particularly highlighted the low perceived threat of disease by adolescent girls and their parents, which studies show plays a role in the decision to be immunized [33[•],42–44]. In several international studies, attitudes towards the HPV vaccination revealed a low perceived threat of HPV infection and, therefore, an initial tendency to decline the vaccine. In adolescent girls, most demonstrated a low initial understanding of the threat of HPV but responded positively to vaccination once the risks of genital warts and cancer were explained [42,44,45]. For parents, the low perceived threat of HPV was associated with the belief that their daughters were not or would not soon be sexually active [33[•],43,46,47]. Given the most recent ACIP permissive recommendation for administration of quadrivalent HPV vaccine to boys aged 9 through 18 years to lower their risk for acquiring genital warts [48], we will undoubtedly see more research exploring attitudes and beliefs in adolescent boys and their parents on their perceived risk of disease. As administration of the HPV vaccine expands, the need for parent education by providers regarding the role of vaccines in disease prevention once again continues to grow.

Concerns regarding safety for adolescent vaccines have arisen recently as well, particularly with the HPV vaccine. A recent safety surveillance [49[•]] summarizes reports to the Vaccine Adverse Event Reporting System (VAERS) related to the more than 23 million doses of the quadrivalent HPV vaccine administered between June 2006 and December 2008. Results revealed 12 424 reports of adverse events following HPV immunization, 6% of

which were categorized as serious (although many appeared unrelated to vaccination after investigation). The most commonly reported adverse event was syncope (15%), which was not surprising given that postvaccination syncope reports to VAERS have increased significantly in adolescent girls following the addition of the MCV, Tdap, and HPV to the immunization schedule [50]. Most syncopal events related to vaccination were not serious (95%), although falls accompanied 15% of them, some with head injuries [49^{*}]. For this reason, providers are encouraged to monitor patients for 15 min after vaccination [48].

Financial barriers

The high cost of adolescent vaccines and concerns with reimbursement were also cited as barriers to improving teen immunization rates [33^{*},34,37]. In the United States, most insurance companies cover recommended adolescent vaccines, and the Vaccines for Children (VFC) program covers low-income and uninsured populations. However, in private practices that do not participate in the VFC program or for older teen patients ineligible for VFC, the cost of these expensive vaccines has become an added barrier [21^{*},33^{*},34,36].

Conclusion

As immunization recommendations expand and evolve, the public's perception of their safety and efficacy will also change. Pediatric healthcare providers have a responsibility to continue the efforts toward eliminating vaccine-preventable diseases and deaths by improving the rate of vaccination in children. Future research is needed to evaluate barriers and strategies for successful vaccination in children and adolescents.

Recommendations for improving vaccination efforts in the pediatric office are as follows (see Table 2 for helpful resources):

- (1) Stay up-to-date on the latest immunization recommendations and safety data.
 - (a) Consult online resources for most current information and post or distribute updates and revisions to other practice providers to ensure consistency.
 - (b) Sign up for e-mail alerts and updates for local disease patterns.
- (2) Improve patient–parent communication regarding vaccination.
 - (a) Allow time to explore and validate parents–patients' concerns regarding vaccines.
 - (b) Provide patient education materials and links to reliable websites.
 - (c) Discuss risks and benefits as well as vaccine safety prior to vaccine administration.

- (3) Avoid missed opportunities for vaccination.
 - (a) Consider joining an IIS to consolidate and keep track of patients' immunization records as well as identifying overdue vaccinations.
 - (b) Administer vaccinations during any visit (including nonpreventive) when appropriate.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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TECHNICAL REPORT

Immunizing Parents and Other Close Family Contacts in the Pediatric Office Setting

Herschel R. Lessin, MD, Kathryn M. Edwards, MD, and the COMMITTEE ON PRACTICE AND AMBULATORY MEDICINE AND THE COMMITTEE ON INFECTIOUS DISEASES

KEY WORDS

parental immunization, adults, vaccines, Tdap, cocooning

ABBREVIATIONS

CDC—Centers for Disease Control and Prevention

Tdap—tetanus toxoid, reduced diphtheria toxoid, and reduced-content acellular pertussis vaccine

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abstract

FREE

Additional strategies are needed to protect children from vaccine-preventable diseases. In particular, very young infants, as well as children who are immunocompromised, are at especially high risk for developing the serious consequences of vaccine-preventable diseases and cannot be immunized completely. There is some evidence that children who become infected with these diseases are exposed to pathogens through household contacts, particularly from parents or other close family contacts. Such infections likely are attributable to adults who are not fully protected from these diseases, either because their immunity to vaccine-preventable diseases has waned over time or because they have not received a vaccine. There are many challenges that have added to low adult immunization rates in the United States. One option to increase immunization coverage for parents and close family contacts of infants and vulnerable children is to provide alternative locations for these adults to be immunized, such as the pediatric office setting. Ideally, adults should receive immunizations in their medical homes; however, to provide greater protection to these adults and reduce the exposure of children to pathogens, immunizing parents or other adult family contacts in the pediatric office setting could increase immunization coverage for this population to protect themselves as well as children to whom they provide care. *Pediatrics* 2012;129:e247–e253

INTRODUCTION

Prevention of infectious diseases through administration of vaccines according to recommended childhood and adolescent immunization schedules is an effective strategy to improve child health. Childhood immunizations are one of the greatest advances in modern medicine, markedly reducing morbidity and mortality. Data from the Centers for Disease Control and Prevention (CDC)'s 2009 National Immunization Survey of more than 17 000 households revealed that immunization rates against most vaccine-preventable diseases in children 19 to 35 months of age were >90%; <1% of children received no vaccines.¹ Despite widespread adherence to childhood immunization schedules, some children remain unprotected.² This includes infants who are too young to be vaccinated, children who do not receive all scheduled immunizations at appropriate times, young infants who have not received a full primary series and are not yet fully immune, and vaccine recipients who experience vaccine failure or waning immunity in

adolescence or adulthood.³ Children who receive immunosuppressive agents as a result of cancer, organ transplantation, autoimmune diseases, and other primary and secondary immune deficiencies may be incapable of mounting an adequate immune response to any vaccine, and certain live-attenuated vaccines (eg, measles-mumps-rubella and varicella vaccines) may be contraindicated for medical reasons.

Thus, additional strategies are needed to protect children from vaccine-preventable diseases, such as immunizing household contacts of children to reduce their exposure to vaccine-preventable pathogens. This can be facilitated by immunizing parents and other close family contacts in the pediatric office setting. With this in mind, the goals of this technical report are as follows:

1. review the literature to determine how immunization of close family contacts could be used to protect vulnerable children;
2. explore potential issues surrounding implementation of this practice in the pediatric office setting; and
3. develop objectives and a research plan to advance this concept.

BACKGROUND

The objective of providing immunizations for parents and other close family contacts of children in pediatric practice is to decrease infections in the family member, with subsequent reduction in exposure to the children. This strategy is referred to as “cocooning.”^{4–6} Exposure to infected parents or family members is a risk factor for many infections. For example, infants with pertussis are often infected in their home by family members or other close contacts.^{7–10} Bisgard et al⁹ examined 774 cases of infant pertussis from 4 states and determined the source of contagion in

these infants through family interviews. An infectious source was identified in 43% of the case infants; of these, mothers were the source in 32% of cases, and another family member was the source in 43% of cases. The specific ages of the infectious source persons were described in 36% of reports; of these, 38 (17%) were 0 to 4 years of age, 16 (7%) were 5 to 9 years of age, 43 (20%) were 10 to 19 years of age, 45 (21%) were 20 to 29 years of age, and 77 (35%) were 30 years of age or older. Thus, more than half of the infectious sources were adults. Similarly, a prospective study conducted between 2006 and 2008 concluded that if parental immunity to pertussis was maintained, 35% to 55% of infant pertussis cases could have been prevented.¹⁰

Several studies have documented that vaccination of pregnant women against influenza reduces the incidence of influenza in their offspring.^{11,12} Although research has documented a benefit of influenza vaccination of pregnant women for their babies, no studies have been conducted to determine whether postpartum vaccination or vaccination of other close family contacts with influenza vaccine reduces the incidence of influenza in their children. A 2010 report by Rekhtman et al¹³ found that 69% of infants younger than 2 months of age hospitalized with influenza A had a history of exposure to a family member with upper respiratory tract infection symptoms. The ages and immunization status of the contacts, however, were not reported.

Several parental immunization programs have been conducted to reduce the burden of disease in their children. Healy et al¹⁴ provided tetanus toxoid, reduced diphtheria toxoid, and reduced-content acellular pertussis vaccine (Tdap) to medically underserved, uninsured women postpartum in Houston through a standing order

protocol. Nearly all (96%) of the women without self-reported contraindications to vaccination received Tdap before hospital discharge. Shah and colleagues^{15,16} conducted several immunization campaigns of parents whose infants were hospitalized in NICUs. During one influenza season, all parents of infants admitted to the NICU were offered trivalent inactivated influenza vaccine at their infant's bedside. Of the 158 infants admitted to the NICU, 95% of the parents were immunized. Remarkably, 23% of the parent population had never received trivalent inactivated influenza vaccine previously, despite having indications for personal influenza immunization.¹⁵ The same group offered Tdap to all parents of infants admitted to the NICU. During the 4-month study period, 352 children were admitted to the NICU, and 87% of their parents received Tdap. However, 11% of parents refused vaccination, citing that pertussis was not a significant health threat or that they did not believe that vaccinations were protective.¹⁶ Overall, these programs highlight the observation that most parents are likely to agree to immunizations for the purpose of protecting their infants.

In addition to the hospital setting, the practice of offering Tdap to all parents of infants during the first month of life was evaluated in a pediatric office setting. Two hundred parents were approached for immunization. Of eligible parents, more than 50% (82/160) received the vaccine. Interestingly, 60% of these parents opting for immunization received the vaccine the first time they were approached, and 40% received the vaccine at a subsequent office visit during the baby's first month of life.⁴

In summary, there is considerable evidence that children are exposed to infections in their home environment from parents and other family members

and that parents are willing to be immunized to protect their infants from vaccine-preventable diseases.

BARRIERS TO IMMUNIZATION OF ADULTS

Data from the CDC in 2010 reported that Tdap coverage among adults who have contact with an infant was only 5%.¹⁷ Another study conducted in 2004–2005 reported that 74% of insured adults did not receive influenza vaccine.¹⁸ With evidence to support the benefits of immunization of parents and other close family contacts for the protection of children, several barriers to adult immunization remain. First, there are patient factors, such as a reluctance of healthy adults to seek preventive health care. Many adults see little need for a visit to a health care provider in the absence of an acute or chronic illness. Even among insured adults, influenza vaccination represented the least frequently received preventative health service among routine recommended services (26%) during a 2-year study period.¹⁸ Second, lack of insurance coverage for vaccine-eligible adults and potential loss of income (because of the need to take time from work for preventive care) add to the challenges. Third, many healthy adults are unaware of the continuing need for immunization and the risks to themselves or others when their immunizations are not current.^{19,20} Therefore, many adults do not receive recommended adult immunizations.

Physician and health care system factors contribute to low immunization rates in adults. Physicians may not have enough time during health maintenance visits to address immunizations, given the multiple chronic conditions or acute illnesses they are frequently managing^{21,22}; thus, patients may not become aware of the importance of immunization for their own health or

the health of their children. Physicians also face financial barriers in providing immunizations to adults. Pediatricians, for whom immunization is part of their core mission and business, report that economic concerns are a problem. Freed et al²³ reported in 2009 that 49% of pediatricians had delayed purchasing immunizations because of financial concerns. This study also reported that 5% of pediatricians and 21% of family practitioners were considering discontinuing immunization services. Presumably, practices in these disciplines have far more experience and expertise in the vaccine-purchasing realm than do practices that focus solely on adult patient populations. A survey of internists and family physicians published in 2011²⁴ found that although 96% of such practices stocked at least 1 adult immunization, only 27% stocked all recommended adult immunizations. Nearly three-quarters of respondents listed payment and coverage issues as a barrier. In addition, many adults seek specialty care and do not have a medical home where a primary care provider who routinely reviews the immunization status of patients. The adult health care system is often more focused on either treating disease or the secondary and tertiary levels of health prevention than on primary prevention associated with immunizations.^{19,20}

IMMUNIZATION VENUES FOR ADULTS

In addition to the traditional medical home, there are a number of venues for immunizing adults.²⁵ At the start of the influenza season each year, “flu clinics” in pharmacies, supermarkets, department stores, workplace settings, and even airports are common. Many local and state health departments provide annual seasonal influenza vaccine clinics. Hospitals have been implementing standing orders for pneumococcal

and influenza immunization before patient discharge for many years. Additionally, greater numbers of women have been immunized in obstetric offices, given the increased appreciation of the burden of influenza in this population. Recent immunization coverage rates among pregnant women during the 2009–2010 influenza season, according to the CDC, were 51% for seasonal influenza and 47% for 2009 H1N1. In addition, women for whom vaccination was recommended by their health care provider were three- to 10-fold more likely to receive vaccine than were women whose health care provider did not encourage vaccination. A 50% coverage rate is encouraging, but because it is recommended that all pregnant women receive influenza vaccine, much work remains to ensure that the Healthy People 2020 goal of 80% influenza vaccine coverage is achieved.^{26,27}

The American College of Obstetricians and Gynecologists, American Academy of Pediatrics, American Academy of Family Physicians, and CDC recommend that when possible, postpartum women should receive Tdap before being discharged from the hospital to protect them and their infants from pertussis and that immunization should be confirmed during the 6-week follow-up visit.^{28,29} Additionally, in June 2011, the Advisory Council on Immunization Practices voted to recommend Tdap immunization to pregnant women in the late second or third trimester.³⁰ A recent provider survey of members of the American College of Obstetricians and Gynecologists, however, found that only 78.7% routinely stock and administer vaccines.³¹ Among that group, 91% stocked human papillomavirus vaccine, 66.8% stocked influenza vaccine, and 30% stocked Tdap. The overwhelming majority reported financial issues as the major barrier to providing immunization services. Of

respondents who provide primary care, 61% reported that they administer influenza vaccine, and only 30% reported that they administer Tdap. Respondent obstetrician-gynecologists also reported that immunization training during medical school and residency was not adequate (40% and 35%, respectively). Because obstetrician-gynecologists are the primary care providers for many women of childbearing age, the lack of immunization opportunities in that setting is concerning.³¹

POTENTIAL BENEFITS AND CONCERNS OF IMMUNIZING PARENTS IN THE PEDIATRIC OFFICE SETTING

There are many potential benefits of adding the pediatric office as another venue for adult immunization. Probably the most compelling is convenience for parents who must balance parenting responsibilities with work demands. Limited access to immunizations has been identified as one of the primary barriers to adult immunization.³² One study reported that alternative locations for immunization, such as the workplace, can successfully address the issue of inconvenience in the vaccination decision.³³ Parents visit the pediatric office frequently with their infants and young children, where most vaccines needed for immunization of both children and adults are available. These visits represent an opportunity to immunize parents or other adult caregivers with minimal disruption for both the adults and the practice. Immunizations represent a major focus for pediatric care, and many educational opportunities exist for the pediatrician to explain the benefits of immunization for the child and for close family contacts. Thus, convenience, physician vaccine knowledge and encouragement, and vaccine availability are strong factors for immunizing parents and close family contacts in the pediatric office.

However, there are a number of concerns. First, most parents and close family contacts would be older than the usual patients seen by pediatricians. Pediatricians may be comfortable immunizing this population but are not likely to deliver other types of preventive health care. It is possible that adults who receive immunizations in the pediatric office may defer other preventive services usually delivered by family physicians, internists, and obstetrician-gynecologists.³⁴ Effort should be made to avoid compromising the adult medical home, and attempts should be made to ensure this does not happen. Parents and close family contacts should be encouraged to receive other primary care services in their medical homes.

Pediatricians may have concerns about safety, including whether they can obtain complete medical information to evaluate for contraindications and whether they have adequate facilities for dealing with adverse events in adults in a pediatric practice setting. Pediatricians may be concerned about liability if an adverse event occurs during adult immunization.³⁴ However, physicians are protected by the National Childhood Vaccine Injury Act of 1986 (Public Law No. 99-660), which limits the liability for vaccine manufacturers and established the Vaccine Injury Compensation Program. The act both protects and requires physicians to report suspected adverse events, and the Vaccine Injury Compensation Program covers all vaccines recommended for routine use in children, regardless of the age of the person being vaccinated. Claims arising from covered vaccines must be adjudicated through the program before civil litigation can be pursued.³⁵ Therefore, because both Tdap and influenza vaccines are recommended for children, this act would protect pediatricians when administering these vaccines to

adults.³⁵ In addition, pediatricians would need to provide the adult being immunized the required Vaccine Information Statement^{32,36} prior to vaccination.

There also are a number of medical record issues. Vaccination of parents and close family contacts of pediatric patients, including any required consent for treatment, would need to be documented by the pediatric office. Thus, close family contacts would likely need their own brief medical record documenting the vaccines administered and any required consent. The vaccinated close family contacts could be provided with a vaccine card listing the names and dates of vaccines received. The type of communication between pediatric offices and adult primary care offices or state immunization registries regarding the immunization status of the adults would need to be determined.

Logistical and financial issues will need to be addressed. Obtaining adequate supplies of vaccine for both children and close family contacts will be critical. Although supplies of influenza vaccine have been plentiful in the past few years, there have been years of shortages and occasional rationing of various vaccines. Because nearly all privately supplied influenza vaccine is preordered months in advance, there is a risk of using the ordered supply too quickly when immunizing both close family contacts and children. This is less likely, given that increasing numbers of manufacturers are producing influenza vaccine annually. Alternatively, too much vaccine might be ordered if the pediatrician were planning on immunizing both adults and children. Influenza vaccine may not be returnable to the manufacturer, leaving practices at economic risk of unused doses. This is a significant concern, given the narrow financial margins for immunizations.^{34,37}

Immunizing parents and close family contacts must be financially viable for

pediatric practices, and the practices must determine whether they are able or willing to submit vaccine charges to adult insurers or simply require payment at the time of service. Many practices that currently provide this service as a convenience for the close family contacts require payment at the time of service or before administration of vaccines. Issues of source of supply must also be considered. In universal purchase states, practices may be legally enjoined from charging parents for doses supplied by the state, although administration fees might be charged. Pediatricians in such states may not be able to provide immunizations for adults and should check with their state vaccine purchase programs regarding use of these vaccines for this purpose. In most states, vaccines supplied to pediatricians by the Vaccines for Children Program may not be used for adults and certainly cannot be billed. If a practice chooses to involve itself in the insurance coverage of parents and close family contacts, it will produce a significantly increased burden that may make the provision of such services nonviable. If parents wish to submit to insurance, they should be informed that receiving vaccines at a location outside of their primary provider's practice may not be reimbursed and, therefore, it may be financially beneficial for them to obtain the vaccine through their primary health care provider. Ultimately, financial arrangements will be up to the individual practice and the individual adult involved. Payment details must be carefully evaluated before the provision of this service and communicated clearly to the family contacts seeking immunization. Additional logistic concerns exist. For example, pediatric offices may need additional staff to immunize parents and close family contacts. However, it would seem logical that the same nurse providing care for the child

could also administer vaccine to the adult. In addition, pediatricians must decide whether to vaccinate only parents or also immunize grandparents, child care providers, and other household contacts, because the reasons for immunizing parents also apply to other care providers.⁶ Finally, the spectrum of vaccinations available for close family contacts in the practice must be determined.

Despite the challenges, pediatricians already are immunizing parents and other adults. One recent study quantified influenza vaccination of parents and guardians in pediatric offices and found that over the course of 2 influenza seasons, 43 (51%) of the 84 offices surveyed administered 2033 seasonal influenza vaccinations to parents or guardians.³⁸ The authors concluded that many pediatricians offered influenza vaccine to parents and other care providers, but that the actual number of doses administered was small. In addition, a 2006 survey of nonretired fellows of the American Academy of Pediatrics reported that 30% of respondent pediatricians usually offer influenza vaccination to parents of at-risk children.³⁹ No similar studies have evaluated the administration of Tdap by pediatric practices.

RESEARCH NEEDS

Further studies are needed to investigate the extent of this practice; the level of family contact satisfaction with the practice; how practices handle the logistic, liability, legal, and financial barriers that limit or complicate this service; and most importantly, how this practice will affect disease rates in children and adults.

SUMMARY

Although additional data are needed to assess the effects of pediatricians providing immunizations for parents

and close family contacts on the burden of infectious diseases in children, the following reasonable statements can be made at this time for pediatricians considering vaccinating parents and other adult care providers.

1. Pediatric offices may choose to serve as an alternate venue for adult care provider vaccination if the practice is acceptable to both pediatricians and the adults who are to be vaccinated. However, the practice's decision of whether to offer vaccinations to adult care providers is not a deviation from the pediatric standard of care.
2. Pediatric practices choosing to offer immunizations to parents and close family contacts may avoid compromising the adult medical home by inquiring about the availability and likelihood of the family contact obtaining vaccines in that setting and notifying their medical homes if vaccines are administered. Offering immunizations in the pediatric practice setting would not be intended to undermine the adult medical home model but could serve as an additional venue for adult care providers to receive vaccinations. Pediatricians may actively encourage all parents and close family contacts to have their own medical home for their health care needs.
3. As part of their anticipatory guidance, pediatricians can actively support educating adults about the value of immunizations and emphasize that such medical care is not just for children.
4. If choosing to vaccinate parents and close family contacts, appropriate indications, contraindications, and precautions to vaccination of adults would need to be assessed and documented in a medical record. A Vaccine Information Statement would need to be provided,

and necessary consent to treatment would need to be documented.

5. Parents and close family contacts immunized in the pediatric office would need to receive a record of administered immunizations. In addition, if adults are included in vaccine registries, the immunizations provided in the pediatric practice would need to be recorded in the registry.
6. At the present time, if a practice chooses to provide such services, the focus of parent and close family contact immunization in the pediatric practice would be centered on influenza (either inactivated or live-attenuated vaccine) and Tdap. Decisions about other vaccines can be made on an individual basis.
7. Liability issues surrounding parent and close family contact immunizations in the pediatric office may be discussed with the malpractice insurance carriers for the pediatric practice, with the knowledge that policies may vary on a state-by-state basis. Pediatricians providing the aforementioned vaccinations would be protected by the Vaccine Injury Compensation Program.
8. Pediatricians may investigate insurance regulations within their states. Expectations for method of payment for parents and close family contact immunizations would need to be clearly outlined with the adult seeking vaccination. Pediatricians also may need to be aware of any state funds available to provide vaccines to adults at no cost.
9. Further research is needed to address the clinical implications of

immunizing parents and close family contacts in the pediatric office, patient satisfaction, public health benefit, effects on adult medical homes, and cost-effectiveness.

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Immunizing Parents and Other Close Family Contacts in the Pediatric Office Setting

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Research article

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A survey of pediatricians' attitudes regarding influenza immunization in children

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Abstract

Background: The Advisory Committee on Immunization Practices advocates that influenza immunization is the most effective method for prevention of illness due to influenza. Recommendations for vaccination of children against influenza have been revised several times since 2002, and as of 2008 include all children 6 months to 18 years of age. Nevertheless, influenza immunization rates have remained low.

Methods: We surveyed practicing pediatricians in Maryland in the spring of 2007 to determine their attitudes and practices toward childhood influenza immunization.

Results: The overall response to the survey was 21%. A total of 61% of respondents reported that immunization either is cost neutral or produces a loss, and 36.6% noted it was minimally profitable. Eighty-six percent of respondents were receptive to supporting school-based immunization programs, and 61% indicated that they would participate in such programs. Respondents reported higher rates of immunization of select patient groups than those noted by the Centers for Disease Control and Prevention

Conclusion: Vaccination was reported to occur at multiple types of patient encounters, as recommended. Survey respondents stated that practice-based immunization was not a profitable service. Pediatricians were supportive of school-based immunization programs, and more than half stated they would be actively involved in such programs. School-based programs may be critical to achieving high vaccination coverage in the school-aged population.

Background

Influenza causes annual epidemics and affects all segments of the population. Children experience the highest rates of infection, shed the greatest quantities of influenza virus for extended periods of time, and have long been recognized as vectors for spread of disease [1-4]. Young children are also at increased risk of complications from

influenza. Because of high rates of influenza-related hospitalizations in children younger than 24 months of age, the Advisory Committee on Immunization Practices (ACIP) encouraged universal vaccination of children aged 6 to 23 months in 2002 [5]. In 2004, the ACIP made a formal recommendation for universal vaccination among children 6 to 23 months [6]. Later, this recommendation

was expanded to children 6 to \leq 59 months of age [7]. Recommendations by the ACIP for children were subsequently further expanded and as of 2008 included the following groups: all children 6 months to 18 years of age, children with certain medical conditions, children who are contacts of persons at higher risk for complications due to influenza [4]. In addition, ACIP recommends vaccination for all persons, including school-aged children, who want to reduce the risk of becoming ill with influenza or of transmitting influenza to others [4].

Despite these recommendations, estimates of influenza vaccination levels reported by the US Centers for Disease Control and Prevention (CDC) fall below targets proposed in the Healthy People 2010 initiative [4,8,9]. Possible reasons for low rates of influenza vaccination may be limited practitioner recognition of the severity of influenza in young children, difficulty in identifying appropriate high-risk candidates, confusion about which provider is responsible for immunization when multiple providers are involved in patient care, and underutilization of strategies known to improve vaccination rates [10,11].

This study was designed to determine the attitudes and practices of pediatricians regarding immunizing children against influenza.

Methods

The Maryland Chapter of the American Academy of Pediatrics consists of 1100 members, of which 900 maintain a current practice. The 900 practicing pediatricians in the state were issued a survey by mail during the spring of 2007 to determine their attitudes and practices regarding childhood influenza vaccination, based on their own opinions and personal recollections. Thirteen questions were selected for inclusion in the questionnaire [see additional file 1] and were divided into 4 major categories: size and location of practice (questions 1, 2, 5); influenza immunization practices regarding patient selection and specific type of vaccine administered (questions 3, 3a, 4, 12, 13); profitability of immunization (questions 6, 7); and participation in school-based influenza immunization programs (questions 8–11).

Questions were free response, multiple choice, or simple yes or no; more than 1 answer could be selected for some multiple-choice questions. Data were tabulated based on the number of responses for each choice per individual question divided by the total number of responses for that question. Free text responses to question 7 were subjectively categorized and the percentage of responses in each category was calculated. Clinicians were provided with a return envelope, were sent weekly e-mail reminders to prompt them to return the survey by a specified cutoff date, and were compensated \$10 for completing the sur-

vey. The survey was coordinated by the Maryland Chapter of the American Academy of Pediatrics, and all results were tabulated and analyzed by the sponsor (MedImmune, Gaithersburg, MD).

Results

Response rate

Of the 900 pediatricians who were surveyed, a total of 190 questionnaires were returned and analyzed, for an overall response rate of 21.1%. Some of those who replied did not provide responses to all questions. Responses were balanced by sex and practitioners spanned a 66-year range in age, with the median age being younger than 50 years (Table 1).

Size and location of practice

A little more than one third of practices were located in urban areas, approximately one half were situated in suburbs, 6% were based in rural areas, and <3% were in a combination of areas. The median practice was 6000 patients, of which fewer than one third, on average, was eligible for the Vaccines for Children (VFC) program (Table 1).

Influenza immunization practices

For all age groups and specified at-risk candidates, the percentage of patients reportedly immunized by respondents exceeded national averages reported by the CDC [4]. With respect to the setting for immunization, nearly all practitioners reported immunizing patients during regular visits, and approximately three quarters also reported vaccinating during sick visits and at special influenza vaccine clinics. Fewer than half of all practices had any form of callback system to contact at-risk candidates who had not yet been immunized (Table 1).

Various influenza vaccines are marketed, including inactivated preservative-free formulations in single-dose pre-filled syringes; inactivated thimerosal-containing formulations in multidose vials; and a live attenuated, preservative-free, single-dose nasal spray. Concerning the specific types of vaccine administered, those who responded noted that inactivated influenza vaccines were administered more frequently than the nasal spray. Use of inactivated vaccines was evenly split between the thimerosal-free and thimerosal-containing formulations. Providers with more VFC-eligible children were more likely to administer thimerosal-free vaccine, and those with fewer VFC-eligible children were more likely to administer thimerosal-containing inactivated vaccine (Table 1).

Pediatricians were queried to determine how burdensome it would be to ask, in addition to other standard vaccination screening questions, whether the parent or healthcare provider had ever noted asthma or wheezing in individual

Table 1: Responses by Pediatricians Surveyed in Maryland to a Questionnaire Regarding Attitudes Regarding Influenza Immunization Practices

Demographics of respondents	
Median age of practitioners, y (range)	48 (25–91)
Sex, %	
Men	50.3
Women	49.7
Size and location of practice	
Location, %	
Suburban	54.1
Urban	37.2
Rural	6.0
Combination	2.7
Practice size, n	
Median (range)	6000 (30–80,000)
Mean	8797
VFC-eligible children in practices, %	
Median (range)	20 (0–100)
Mean	32
Influenza immunization practices	
Patients in at-risk categories immunized with influenza vaccine, %	
Children aged 6–23 mo	75
Children aged 24–59 mo	50
Children at high risk	80
Household contacts of at-risk individuals	45
When and where immunization occurs, %	
Regular visits	98.8
Sick visits	74.6
Special influenza immunization clinics	72.2
Availability of callback system, %	39.8
Vaccine types used, %	
Thimerosal-free inactivated, median (range)	50 (0–100)
Thimerosal-containing inactivated, median (range)	50 (0–100)
Live attenuated nasal spray, median (range)	5 (0–100)
How much more burdensome would it be to ask if the parent or a provider ever noted wheezing or asthma in the child (5-point scale; 1 = not at all and 5 = very), %	
1	54.2
2	26.0
3	11.3
4	5.1
5	3.4
Profitability of influenza immunization	
How profitable is influenza immunization of children?, %	
Cost neutral	46.5
Produces a loss	14.5
Minimally profitable	36.6
What would improve profitability?, %	
Better reimbursement	56.5
Better payment for vaccine administration	13.7
Less costly vaccine	8.7
All other responses	21.1
Participation in school-based immunization programs	
Would you support a school-based immunization program?, %	85.7
Would you participate in a school immunization program?, %	60.8
What would persuade you to participate?, %	
Financial remuneration	57.5
Civic involvement	53.1
Source of new patients	22.9
Nothing	22.3
How might you participate?, %	
Off-site consultation	69.5
On-site supervision	52.5
Both on-site and off-site	38.4

children, conditions which are potential warnings/precautions for the administration of the live attenuated nasal spray influenza vaccine. Based on a 5-point scale with 1 being "not at all" and 5 being "very," approximately 80% of those who replied noted that it would not be a burden at all, or only a very slight burden, whereas 3.4% specified that it would be very burdensome to ask this additional question (Table 1).

Profitability of immunization

Overall, pediatricians reported that influenza immunization is not a profitable service. A total of 61% of respondents reported that it either is cost neutral or produces a loss; 36.6% noted it was minimally profitable. As noted by two thirds of responses, the most significant barrier to profits is poor reimbursement for costs of the vaccine and administration. Acquisition price of the vaccines was not seen as a major obstacle (Table 1).

Participation in school-based immunization programs

Eighty-six percent of respondents were receptive to supporting school-based immunization programs, 61% indicated that they would participate in such programs. Of those who would participate, about 70% noted that they would provide off-site consultation, half were receptive to being available on-site in a supervisory role, and approximately one third would be willing to provide both on-site and off-site services. Primary incentives for participation were financial remuneration and civic involvement. Providers with high VFC-eligible populations were more likely to state that they would participate in school-based programs (76% of providers with $\geq 50\%$ VFC-eligible populations would participate compared with 53% of those $<50\%$ VFC-eligible); however, providers with high and low VFC-eligible populations expressed similar overall support of such programs (Table 1).

Discussion

Various provider groups have been surveyed regarding their knowledge of recommendations for influenza immunization [10-12]. Not surprisingly, pediatricians tend to be the most knowledgeable with respect to current recommendations for children, and this is the group that was targeted in the present study.

Current recommendations state that influenza vaccination should be offered during routine healthcare visits, sick visits, and influenza vaccine clinics, among other venues [4]. The survey results support that regular visits, sick visits, and special clinics are regularly used by pediatricians. Pediatricians noted that they administer an injectable form of influenza vaccine more frequently than the nasal spray. In Maryland, the 2 largest medical insurers did not reimburse for the nasal spray at the time of the survey and this likely influenced vaccine choice. Despite

controversy over the safety of thimerosal-containing vaccines, preservative-containing and preservative-free injectable vaccines were equally used; VFC participation appeared to increase utilization of thimerosal-free formulations. Similar to previous reports [11], the majority of practices did not have any callback system in place to notify patients about immunization opportunities. Respondents reported that they immunize children at rates in excess of those reported by the CDC from national surveys [13], likely due to overestimation of their actual vaccination rates [11].

Overall, pediatricians do not believe the practice of administering influenza vaccine to children is profitable for their practice. Increased reimbursement for influenza vaccine and its administration would likely increase vaccination coverage in the future.

Almost 90% of respondents noted they would support school-based immunization programs, the value of which has been previously demonstrated [14-17]; approximately 60% stated they would participate in such programs. Given the logistical obstacles to vaccinating large numbers of school-aged children, school-based vaccination programs may be essential for achieving high rates of vaccination coverage in children 5 to 18 years of age, who are recommended to be vaccinated beginning in the 2008-2009 influenza season [4].

There are several inherent limitations to the survey findings. Results of previous surveys of immunization practices among various physician groups indicate that pediatricians are fairly diligent in providing feedback, and response rates of 50% to 60% are common [10,11,18]. It is unclear why the response rate was less than 25% in the present study. There is potential for bias given this response rate; responders may have disproportionate interest in influenza vaccination. Because only pediatricians in the state of Maryland were surveyed, extrapolations to broader populations are problematic. In particular, findings regarding school-based programs may have been influenced by past school-based influenza vaccination programs conducted in Maryland [14,15,17]. Nevertheless, several of the findings pertaining to immunization practices are consistent with survey results from other investigators [11].

Conclusion

Vaccination was reported to occur at multiple types of patient encounters, as recommended. Survey respondents stated that practice-based immunization was not a profitable service. Pediatricians were supportive of school-based immunization programs, and more than half stated they would be actively involved in such programs. School-

based programs may be critical to achieving high vaccination coverage in the school-aged population.

Competing interests

Dr. Levy has served on an advisory panel for MedImmune; Drs. Ambrose, Oleka, and Lewin were employees of MedImmune at the time of the study. Drs. Ambrose and Oleka are current employees of MedImmune.

Authors' contributions

DJL helped design the survey, conducted the study, and aided in the analysis of the study results. CSA aided in the analysis of the study results and helped draft the manuscript. NA helped design the survey and tabulated and analyzed the survey results. EBL designed the survey and aided in the analysis of study results. All authors read and approved the final submitted manuscript.

Additional material

Additional file 1

Levy Supplementary File. Pediatrician Survey – The survey distributed to practicing pediatricians in Maryland is presented.

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and Susan D. Goold, MD, MHSA¹

Abstract

Background: Parents consult other child health information sources in addition to the pediatrician. There are little data describing which of these sources parents are likely to follow. **Methods:** The authors surveyed 543 parents of patients in 6 pediatric practices in southeast Michigan shortly after an office visit to determine the degree to which parents report following advice from 7 common child health sources on a scale from 1 (*don't follow at all*) to 7 (*follow completely*). **Results:** Pediatrician advice was more completely followed than other sources with mothers a distant second. Although 96% of parents used the Internet to find child health information, few followed most of the advice found there. White parents were 3 times more likely than African Americans to follow advice from television and newspapers. **Conclusion:** Parents rely on child health advice from the pediatrician and their mother. Other sources are consulted but not widely followed.

Keywords

parents, adherence, health information seeking

Introduction

Prior studies have examined which sources parents consult when seeking child health information,^{1–5} but few have directly compared the degree to which parents report actually following advice from other sources. Although the pediatrician is the source of child health information most often consulted by parents,^{2,3,6,7} there are few data describing the degree to which parents rely on child health advice from other sources.

Parents have a wide variety of sources to consult when searching for child health information. According to a recent survey, 94% of those with incomes greater than \$75 000, and 94% of college graduates have access to the Internet, with the vast majority having high-speed Internet access.⁸ Of adults with Internet access, 61% go online to find health information.⁹ Child health information is easily found on the Internet from many reputable sources, such as the National Institutes of Health, WebMD, and the websites of various children's hospitals. However, a broad assortment of information about child health is also available whose reliability is uncertain. Some of this information likely conflicts with physician-provided advice.¹⁰

In addition to the Internet, there are a myriad of magazines and books devoted to parenting. Some promote

alternative practices along with standard pediatric recommendations.^{11–13} Knowing which sources of child health advice parents rely on in addition to the pediatrician can inform the design of educational materials to reinforce important health messages. Our study was designed to determine which common sources of child health advice parents' report following most closely and whether there were significant racial and demographic differences in these sources.

Methods

Participants

As part of a larger study designed to validate instruments measuring various aspects of the parent–physician relationship, parents who were accompanying their child to a primary care doctor's visit were approached for participation by a research assistant in the reception area

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prior to the child's appointment. Parents were recruited consecutively from 6 community-based, university-affiliated pediatric primary care clinics in southeast Michigan between January and April 2006. Parents were not approached if their child appeared to require undivided parental attention because of behavior or illness. Parents were eligible if they had a child ≤ 18 years old and could speak and read English easily.

Survey Administration

Parents completed a brief demographic questionnaire prior to seeing the doctor, including the reason for the visit (well-child exam, sick visit, or other). They were interviewed by phone by a member of the research team not affiliated with the physician's practice within 2 weeks of that visit. Parents were asked the following question about each of 7 common sources of child health information, "When you have a question or concern about your child's health, how much do you follow the advice of . . .?" Listed information sources were the respondent's mother, other family members, friends, the child's physician, books on parenting, television or newspapers (the media), and the Internet. Parents rated each individual information source on a 7-point scale from 1 (*don't follow at all*) to 7 (*follow completely*).

Variables

Our outcome variable was the parent's rating of how closely they followed the advice received from each information source. Demographic variables included parents' self-reported race (using US Census categories), parental educational attainment, marital status, and age of youngest child. The child's health insurance status (public, private, or none) was used as a rough proxy for family income since a child's eligibility for Medicaid or State Children's Health Insurance Program (SCHIP) eligibility is based almost exclusively on family income.

Data Analysis

We consolidated parental ratings into 3 categories, "Follows Completely" (ranking of 6 or 7), "Follows Somewhat" (ratings of 5 to 3), and "Does Not Follow" (ratings of 1 and 2). Results were calculated only for parents who reported using the listed source for child health information. We created a dichotomous variable, "Follows Completely," for use in the logistic models to further examine the characteristics of those parents who follow advice from sources other than the child's pediatrician.

Parental race was categorized as white, African American, and other. Parents who selected more than

one racial group and those who selected a race other than white or African American were classified as "other." We included Hispanic parents in this category because of their small numbers and diversity of racial group selections.

Four categories were used to describe parental educational attainment: "High school graduate or less," "Some college," "4-year college graduate," and "Any postgraduate education." Child health insurance status was categorized as only private, any public, or none. We categorized parental marital status as married/living with a partner, divorced/widowed/separated, or never married.

Because younger children generally have more visits with their physician than do older children, their parents may have more exposure and opportunity to obtain physician counseling and possibly be less inclined to follow advice from alternative sources, regardless of the age of their other children. To examine this association we compared the responses of parents whose youngest child < 3 years with those of parents with only older children (any child < 3 years old vs no child < 3 years).

We generated descriptive statistics for the demographic variables of the entire sample. For each information source we calculated the percentage of parents in each rating category. To determine whether the degree to which parents follow information from each source is associated with any demographic characteristic, we used logistic regression to create separate models for each of the 7 sources of information adjusted for all demographic variables. All analyses were conducted using SAS, version 9.1. This study was approved by the Institutional Review Board of the University of Michigan Medical School.

Results

We approached 998 parents for participation, of whom 806 were eligible, enrolling 669 (83% of those eligible). Phone interviews were completed at 2 weeks by 543 parents (81% response). Participating parents were predominantly non-Hispanic white, married or living with a partner, and had education beyond high school. Less than a third (29%) of the children had any form of public health insurance, though this varied by race. Just more than a third of the parents were bringing their child to a well-child visit at the time of enrollment (Table 1).

Information Sources Consulted

More than 90% of parents reported consulting each of the listed information sources for child health advice with near universal use of television, newspapers, books, and the Internet (Table 2). Equally high proportions of

Table 1. Demographic Characteristics (n = 543)

	Percentage (n)			
	All	White (n = 432)	African American (n = 46)	Other (n = 64)
Age (years)				
Mean (range)	35 (18-63)	35 (18-63)	34 (19-58)	33 (18-53)
Marital status				
Married/living with partner	81 (441)	84 (363)	61 (28)	77 (49)
Divorced/widowed/separated	9 (47)	8 (34)	11 (5)	13 (8)
Never married	10 (55)	8 (35)	28 (13)	11 (7)
Child's health insurance				
Private only	70 (377)	74 (319)	49 (22)	55 (35)
Any public	29 (159)	25 (109)	49 (22)	44 (28)
None	1 (5)	1 (3)	2 (1)	2 (1)
Parent education				
High school graduate or less	21 (113)	21 (92)	20 (9)	19 (12)
Some college	34 (184)	32 (138)	48 (22)	38 (24)
College graduate	23 (123)	23 (99)	17 (8)	23 (15)
Postgraduate	22 (121)	24 (101)	15 (7)	20 (13)
Age of youngest child (years)				
<3	46 (250)	44 (189)	52 (24)	56 (36)
≥3	54 (292)	56 (242)	48 (22)	44 (28)
Physician visit type				
Sick	47 (253)	48 (206)	46 (21)	39 (25)
Well-child exam	38 (205)	37 (208)	37 (17)	47 (30)

Table 2. Percentage of Participants Using Source for Child Health Information

	Percentage (n)			
	All (n = 543)	African American (n = 46)	White (n = 432)	(n = 64)
Seeks advice from mother	94 (507)	91 (42)	94 (405)	98 (63)
Seeks advice from family	98 (530)	93 (43)	98 (424)	97 (62)
Seeks advice from friends	98 (531)	98 (45)	98 (423)	98 (63)
Seeks advice from doctor	98 (536)	98 (45)	99 (427)	98 (63)
Seeks advice from TV and newspapers	98 (534)	98 (45)	99 (426)	97 (62)
Seeks advice from parenting books	98 (531)	98 (45)	98 (422)	98 (63)
Seeks advice from the Internet	96 (521)	96 (44)	96 (416)	94 (60)

African American and white parents reported using the Internet to find child health advice (96%).

Though African American parents were significantly less likely than white parents to have asked their mother for child health advice, the actual difference was slight (91% vs 94%; $P = .04$). There were no racial differences in use of the other sources.

Ratings of Sources

Advice from the child's pediatrician was completely followed by 94% of parents, whereas less than 10% reported

completely following advice from the Internet, television, or newspapers. Though other sources were followed more closely than the media or the Internet, no source approached the degree to which parents endorsed following the pediatrician's advice (Figure 1). Mothers were a distant second.

Certain parental characteristics were associated with the degree to which parents reported following advice (Table 3). For example, 96% of white parents reported completely following physician advice, whereas only 87% of African American parents reported that degree of adherence. Conversely, African American parents were

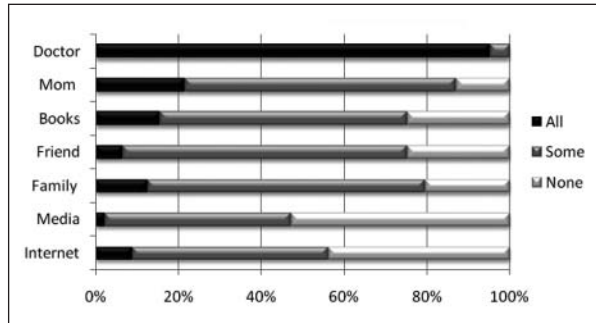


Figure 1. Amount of advice followed by parents

more likely than white parents to completely follow all of their mother's advice. Single parents were twice as likely than other parents to completely follow their mother's advice, even after controlling for race (Table 3).

Although African American and white parents reported consulting the media and the Internet for child health advice in similar numbers, no African American parent reported completely following the child health advice found on television, in newspapers, or on the Internet. For white and other race parents, education was an important factor in influencing whether they followed Internet advice. White and other race parents with postcollege education were much more likely than less educated parents to completely follow Internet-provided health advice (Table 4). Parental demographic characteristics were not significantly associated with the degree to which parents completely followed child health advice from family, friends, and books.

Discussion and Conclusion

Discussion

Parents seek information about their child's health from a variety of sources other than the pediatrician. Nevertheless, it is still the pediatrician's advice that parents follow most closely. Even highly educated parents, who are more likely to completely follow advice from the Internet than other groups of parents, still follow more of the pediatrician's advice.

Whereas prior studies have asked participants to identify where they look for child health information or to note the trustworthiness of specific health information sources, our study is unique in that we asked parents to report how closely they actually followed the advice received from the each source.^{4,5,14-16} Though many sources may be consulted or even perceived as trustworthy, the most important metric is which advice parents

ultimately follow, especially when recommendations may be conflicting.

We sampled from a general population of parents seeking care for their children for a wide variety of common childhood illnesses and conditions in primary care pediatricians' offices. Advice for managing these problems is readily available from many sources and advice that conflicts with standard medical recommendations is easily found. Prior studies of parent health information seeking surveyed parents whose children had specific diseases or conditions where information outside of the medical context may be less available, or less understandable.^{4,5,16-19}

There were significant differences in income between the African American and white parents in our sample. Nearly half (49%) of African American parents had a household income that qualified their children for some form of public health insurance. For 2006, that level was at or below 200% of the federal poverty guidelines. Only 25% of white parents in our sample had a similar level of income. Despite this income difference, the proportion of African American and White parents who reported using the Internet to find child health information was equally high at 96%. This is a higher rate of African American Internet usage for health information than in previous reports.⁸

Our findings also suggest that African American parents are less receptive to physician advice and more likely to follow their mother's child care advice than white or other race parents. Our prior work has also shown that African Americans have lower levels of trust in their child's physician than white parents.²⁰ The difference we found in the degree to which white and African American parents follow the pediatrician's advice may be the result of distrust of the child's pediatrician, conflicts between maternal and pediatrician-provided advice, or some combination of the two. Further research is needed to clarify this issue.

Limitations

Like all studies that rely on self-report, our results may be biased by social desirability. On enrollment, parents were assured that their responses were confidential and would not be revealed to their child's physician. This assurance was repeated a few weeks later when a research team member not affiliated with the pediatrician contacted the parent for the follow-up interview. Nevertheless, some parents may have believed that the interviewers were associated with their pediatrician. This may have led some parents to overreport the extent to which they follow physician advice. We believe that this effect is likely minimal. The interview took place a few weeks after the office visit

Table 3. Adjusted Odds of Completely Following Advice From Child's Physician or Respondent's Mother^a

	Percentage (n)	Odds Ratio (95% Confidence Interval)
Completely follows doctor's advice		
White	96 (411)	Reference
African American	87 (39)	0.2 (0.07, 0.62)
Other	94 (59)	0.5 (0.16, 1.61)
Married/living with partner	94 (415)	Reference
Divorced/widowed/separated	94 (44)	1.2 (0.26, 6.01)
Never married	93 (51)	1.1 (0.25, 4.86)
Public insurance	94 (148)	Reference
Private insurance	95 (355)	1.4 (0.4, 3.27)
≤High school graduate	96 (107)	Reference
Some college	95 (174)	0.72 (0.22, 2.40)
4-year college	95 (115)	0.72 (0.20, 2.61)
Postcollege education	95 (113)	0.70 (0.19, 2.56)
Child <3 years old	94 (235)	Reference
Child ≥3 years old	94 (274)	0.8 (0.33, 1.80)
Completely follows mother's advice		
White	19 (76)	Reference
African American	38 (16)	2.5 (1.18, 5.28)
Other	29 (18)	1.7 (0.95, 3.16)
Married/living with partner	18 (80)	Reference
Divorced/widowed/separated	17 (8)	1.06 (0.43, 2.6)
Never married	40 (22)	2.2 (1.06, 4.51)
Public insurance	28 (43)	Reference
Private insurance	18 (65)	0.69 (0.39, 1.22)
≤High school graduate	26 (28)	Reference
Some college	22 (38)	0.81 (0.46, 1.41)
4-year college	26 (31)	0.99 (0.55, 1.80)
Postcollege education	11 (12)	0.33 (0.16, 0.71)
Child <3 years old	22 (55)	Reference
Child ≤3 years old	19 (55)	1.1 (0.66, 1.67)

^aAdjusted for all demographic variables.

and was conducted by phone to create both spatial and temporal distance from the physician's office. Nearly all the parents in our sample reported using alternative information sources to find information about their child's health and were not reluctant to admit that fact. Nevertheless, even if some overreporting occurred, the magnitude of the difference we found between the degree to which parents reported following physician advice compared with advice from other sources makes it unlikely that this difference is because of social desirability alone.

We asked parents about following a source's advice when they had a question about their child's health, without reference to any specific issue, to obtain a broad assessment of parental ratings of each information source. It is possible that our results may have been different had we asked about specific topics. For example, parents who refuse to immunize their children for nonmedical

reasons have been shown to be less trusting of their child's physician and rely more on information from alternative child health sources.⁶ We also cannot know the degree to which parents actually follow the advice from any source.

Our findings may not be applicable to the small, but significant minority of parents whose children's health care is more fragmented, do not use a physician's office as their child's regular source of health care, or those who shun traditional medicine. In addition, we did not include parents who could not speak English or were recent immigrants. Therefore, we were unable to identify preferred sources of child health information for these populations, which should be a priority for future research.

Demonstrating that parents preferentially follow physician advice over the advice of other sources could well be considered research that proves the obvious.

Table 4. Adjusted Odds of Completely Following Advice From the Media or the Internet^a

	Percentage (n)	Odds Ratio (95% Confidence Interval)
Does not follow media advice		
White	98 (417)	Reference
African American	100 (45)	3.1 (1.47, 6.55)
Other	95 (5)	0.7 (0.42, 1.23)
Married/living with partner	98 (427)	Reference
Divorced/widowed/separated	96 (44)	1.1 (0.56, 2.1)
Never married	94 (3)	1.1 (0.59, 2.19)
Public insurance	96 (150)	Reference
Private insurance	98 (365)	0.9 (0.58, 1.44)
≤High school graduate	99 (110)	Reference
Some college	97 (176)	0.27 (0.03, 2.25)
4-year college	98 (117)	0.36 (0.04, 3.46)
Postcollege education	98 (117)	0.53 (0.05, 5.95)
Child <3 years old	98 (241)	Reference
Child ≥3 years old	98 (281)	1.3 (0.88, 1.80)
Completely follows Internet advice		
Married/living with partner	8 (36)	Reference
Divorced/widowed/separated	7 (3)	0.4 (0.10, 1.77)
Never married	14 (7)	0.6 (0.24, 1.36)
Public insurance	8 (12)	Reference
Private insurance	9 (34)	0.9 (0.43, 1.70)
≤High school graduate	4 (4)	Reference
Some college	10 (17)	2.7 (0.89, 8.31)
4-year college	10 (12)	2.9 (0.91, 9.33)
Postcollege education	11 (13)	3.3 (1.03, 10.30)
Child <3 years old	8 (18)	Reference
Child ≥3 years old	10 (28)	1.4 (0.72, 2.51)

^aAdjusted for all demographic variables.

However, pediatricians may be appropriately concerned about whose advice parents actually follow. Physician advice competes with continual media exposure of celebrities and others who criticize standard child health advice and/or promote nontraditional alternatives and the easy availability of inaccurate child health information. Our study attempted to answer the question of whether the pediatrician's advice will still be followed after the family leaves the office and talks to friends and family, watches television, and searches the internet for more information. Our study suggests physician advice retains a privileged status among all groups of parents. However, more work needs to be done to examine the dynamics of the parent-pediatrician relationship for African Americans to better understand why they are less likely to follow their child's pediatrician's advice.

Authors' Note

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SPECIAL ARTICLE

Vaccine Refusal, Mandatory Immunization, and the Risks of Vaccine-Preventable Diseases

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ABSTRACT

Vaccines are among the most effective prevention tools available to clinicians. However, the success of an immunization program depends on high rates of acceptance and coverage. There is evidence of an increase in vaccine refusal in the United States and of geographic clustering of refusals that results in outbreaks. Children with exemptions from school immunization requirements (a measure of vaccine refusal) are at increased risk for measles and pertussis and can infect others who are too young to be vaccinated, cannot be vaccinated for medical reasons, or were vaccinated but did not have a sufficient immunologic response. Clinicians can play a crucial role in parental decision making. Health care providers are cited as the most frequent source of immunization information by parents, including parents of unvaccinated children. Although some clinicians have discontinued or have considered discontinuing their provider relationship with patients who refuse vaccines, the American Academy of Pediatrics Committee on Bioethics advises against this and recommends that clinicians address vaccine refusal by respectfully listening to parental concerns and discussing the risks of nonvaccination.

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VACCINES ARE AMONG THE MOST EFFECTIVE TOOLS AVAILABLE FOR PREVENTING infectious diseases and their complications and sequelae. High immunization coverage has resulted in drastic declines in vaccine-preventable diseases, particularly in many high- and middle-income countries. A reduction in the incidence of a vaccine-preventable disease often leads to the public perception that the severity of the disease and susceptibility to it have decreased.¹ At the same time, public concern about real or perceived adverse events associated with vaccines has increased. This heightened level of concern often results in an increase in the number of people refusing vaccines.^{1,2}

In the United States, policy interventions, such as immunization requirements for school entry, have contributed to high vaccine coverage and record or near-record lows in the levels of vaccine-preventable diseases. Herd immunity, induced by high vaccination rates, has played an important role in greatly reducing or eliminating continual endemic transmission of a number of diseases, thereby benefiting the community overall in addition to the individual vaccinated person.

Recent parental concerns about perceived vaccine safety issues, such as a purported association between vaccines and autism, though not supported by a credible body of scientific evidence,³⁻⁸ have led increasing numbers of parents to refuse or delay vaccination for their children.^{9,10} The primary measure of vaccine refusal in the United States is the proportion of children who are exempted from school immunization requirements for nonmedical reasons. There has been an increase in state-level rates of nonmedical exemptions from immunization requirements.¹¹ In this article, we review

the evidentiary basis for school immunization requirements, explore the determinants of vaccine refusal, and discuss the individual and community risks of vaccine-preventable diseases associated with vaccine refusal.

EVOLUTION OF U.S. IMMUNIZATION REQUIREMENTS

Vaccination was introduced in the United States at the turn of the 19th century. The first U.S. law to require smallpox vaccination was passed soon afterward, in 1809 in Massachusetts, to prevent and control frequent smallpox outbreaks that had substantial health and economic consequences.¹²⁻¹⁴ Subsequently, other states enacted similar legislation.¹³ Despite the challenges inherent in establishing a reliable and safe vaccine delivery system, vaccination became widely accepted as an effective tool for preventing smallpox through the middle of the 19th century, and the incidence of smallpox declined between 1802 and 1840.¹⁵ In the 1850s, “irregular physicians, the advocates of unorthodox medical theories,”¹⁶ led challenges to vaccination. Vaccine use decreased, and smallpox made a major reappearance in the 1870s.¹⁵ Many states passed new vaccination laws, whereas other states started enforcing existing laws. Increased enforcement of the laws often resulted in increased opposition to vaccination. Several states, including California, Illinois, Indiana, Minnesota, Utah, West Virginia, and Wisconsin, repealed compulsory vaccination laws.¹⁵ Many other states retained them.

In a 1905 landmark case, *Jacobson v. Massachusetts*, which has since served as the foundation for public health laws, the U.S. Supreme Court endorsed the rights of states to pass and enforce compulsory vaccination laws.¹⁷ In 1922, deciding a case filed by a girl excluded from a public school (and later a private school) in San Antonio, Texas, the Supreme Court found school immunization requirements to be constitutional.¹⁸ Since then, courts have been generally supportive of the states’ power to enact and implement immunization requirements.

Difficulties with efforts to control measles in the 1960s and 1970s ushered in the modern era of immunization laws in the United States.¹² In 1969, a total of 17 states had laws that required children to be vaccinated against measles before entering school, and 12 states had legally man-

dated requirements for vaccination against all six diseases for which routine immunization was carried out at the time.¹³ During the 1970s, efforts were made to strengthen and strictly enforce immunization laws.^{12,13} During measles outbreaks, some state and local health officials excluded from school those students who did not comply with immunization requirements, resulting in minimal backlash, quick improvement in local coverage, and control of outbreaks.¹⁹⁻²² Efforts by the public health community and other immunization advocates to increase measles vaccine coverage among school-age children resulted in enforcement of immunization requirements for all vaccines and the introduction of such requirements in states that did not already have them. By the beginning of the 1980s, all 50 states had school immunization requirements.

RECENT SCHOOL IMMUNIZATION REQUIREMENTS

Because laws concerning immunization are state-based, there are substantial differences in requirements across the country. The requirements from state to state differ in terms of the school grades covered, the vaccines included, the processes and authority used to introduce new vaccines, reasons for exemptions (medical reasons, religious reasons, philosophical or personal beliefs), and the procedures for granting exemptions.²³

State immunization laws contain provisions for certain exemptions. As of March 2008, all states permitted medical exemptions from school immunization requirements, 48 states allowed religious exemptions, and 21 states allowed exemptions based on philosophical or personal beliefs.²³ Several states (New York, Arkansas, and Texas) have recently expanded eligibility for exemptions.

SECULAR AND GEOGRAPHIC TRENDS IN IMMUNIZATION REFUSAL

Between 1991 and 2004, the mean state-level rate of nonmedical exemptions increased from 0.98 to 1.48%. The increase in exemption rates was not uniform.¹¹ Exemption rates for states that allowed only religious exemptions remained at approximately 1% between 1991 and 2004; however, in states that allowed exemptions for philosophical or personal beliefs, the mean exemption rate increased from 0.99 to 2.54%.¹¹

Like any average, the mean exemption rate presents only part of the picture, since geographic clustering of nonmedical exemptions can result in local accumulation of a critical mass of susceptible children that increases the risk of outbreaks. There is evidence of substantial geographic heterogeneity in nonmedical-exemption rates between and within states.²⁴ For example, in the period from 2006 through 2007, the state-level nonmedical-exemption rate in Washington was 6%; however, the county-level rate ranged from 1.2 to 26.9% (Fig. 1).²⁵ In a spatial analysis of Michigan's exemption data according to census tracts, 23 statistically significant clusters of increased exemptions were identified.²⁶ Similar heterogeneity in exemption rates has been identified in Oregon²⁷ and California (unpublished data).

The reasons for the geographic clustering of exemptions from school vaccination requirements are not fully understood, but they may include characteristics of the local population (e.g., cultural issues, socioeconomic status, or educational level), the beliefs of local health care providers and opinion leaders (e.g., clergy and politicians), and local media coverage. The factors known to be associated with exemption rates are heterogeneity in school policies²⁸ and the beliefs of school personnel who are responsible for compliance with the immunization requirements.²⁹

Instead of refusing vaccines, some parents delay vaccination of their children.³⁰⁻³² Many parents follow novel vaccine schedules proposed by individual physicians (rather than those developed by expert committees with members representing multiple disciplines).^{32,33} Most novel schedules involve administering vaccines over a longer period than that recommended by the Advisory Committee on Immunization Practices and the American Academy of Pediatrics or skipping the administration of some vaccines.

INDIVIDUAL RISK AND VACCINE REFUSAL

Children with nonmedical exemptions are at increased risk for acquiring and transmitting vaccine-preventable diseases.^{34,35} In a retrospective cohort study based on nationwide surveillance data from 1985 through 1992, children with exemptions were 35 times as likely to contract measles as nonexempt children (relative risk, 35; 95% confidence interval [CI], 34 to 37).³⁴ In a retro-

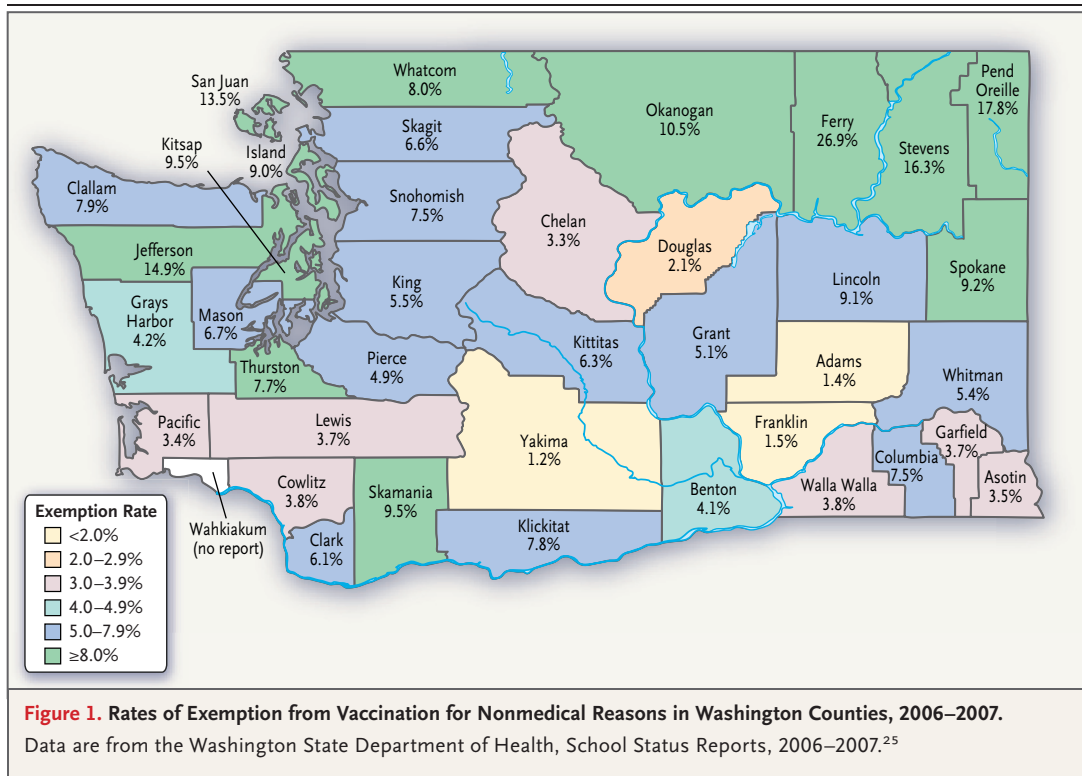
spective cohort study in Colorado based on data for the years 1987 through 1998, children with exemptions, as compared with unvaccinated children, were 22 times as likely to have had measles (relative risk, 22.2; 95% CI, 15.9 to 31.1) and almost six times as likely to have had pertussis (relative risk, 5.9; 95% CI, 4.2 to 8.2).³⁵ Earlier data showed that lower incidences of measles and mumps were associated with the existence and enforcement of immunization requirements for school entry.^{12,36-38}

The consequences of delayed vaccination, as compared with vaccine refusal, have not been studied in detail. However, it is known that the risk of vaccine-preventable diseases and the risk of sequelae from vaccine-preventable diseases are not constant throughout childhood. Young children are often at increased risk for illness and death related to infectious diseases, and vaccine delays may leave them vulnerable at ages with a high risk of contracting several vaccine-preventable diseases. Moreover, novel vaccine schedules that recommend administering vaccines over a longer period may exacerbate health inequities, since parents with high socioeconomic status are more likely to make the extra visits required under the alternative schedules than parents with low socioeconomic status.³⁹

CLUSTERING OF VACCINE REFUSALS AND COMMUNITY RISK

Multiple studies have shown an increase in the local risk of vaccine-preventable diseases when there is geographic aggregation of persons refusing vaccination. In Michigan, significant overlap between geographic clusters of nonmedical exemptions and pertussis clusters was documented.²⁶ The odds ratio for the likelihood that a census tract included in a pertussis cluster would also be included in an exemptions cluster was 2.7 (95% CI, 2.5 to 3.6) after adjustment for demographic factors.

In Colorado, the county-level incidence of measles and pertussis in vaccinated children from 1987 through 1998 was associated with the frequency of exemptions in that county.³⁵ At least 11% of the nonexempt children who acquired measles were infected through contact with an exempt child.³⁵ Moreover, school-based outbreaks in Colorado have been associated with increased exemption rates; the mean exemption rate among



schools with outbreaks was 4.3%, as compared with 1.5% for the schools that did not have an outbreak ($P=0.001$).³⁵

High vaccine coverage, particularly at the community level, is extremely important for children who cannot be vaccinated, including children who have medical contraindications to vaccination and those who are too young to be vaccinated. These groups are often more susceptible to the complications of infectious diseases than the general population of children and depend on the protection provided by the vaccination of children in their environs.^{40–42}

VACCINE REFUSAL AND THE RECENT INCREASE IN MEASLES CASES

Measles vaccination has been extremely successful in controlling a disease that previously contributed to considerable morbidity and mortality. In the United States, the reported number of cases dropped from an average of 500,000 annually in the era before vaccination (with reported cases considered to be a fraction of the estimated total, which was more than 2 million) to a mean of 62

cases per year from 2000 through 2007.^{43–45} Between January 1, 2008, and April 25, 2008, there were five measles outbreaks and a total of 64 cases reported.⁴⁵ All but one of the persons with measles were either unvaccinated or did not have evidence of immunization. Of the 21 cases among children and adolescents in the vaccine-eligible age group (16 months to 19 years) with a known reason for nonvaccination, 14, or 67%, had obtained a nonmedical exemption and all of the 10 school-age children had obtained a nonmedical exemption.⁴⁵ Thirteen cases occurred in children too young to be vaccinated, and in more than a third of the cases (18 of 44) occurring in a known transmission setting the disease was acquired in a health care facility.⁴⁵

Outbreaks of vaccine-preventable disease often start among persons who refused vaccination, spread rapidly within unvaccinated populations, and also spread to other subpopulations. For example, of the four outbreaks with discrete index cases (one outbreak occurred by means of multiple importations) reported January through April 2008, three out of four index cases occurred in people who had refused vaccination due to per-

sonal beliefs; vaccination status could not be verified for the remaining cases.^{45,46} In Washington State, a recent outbreak of measles occurred between April 12, 2008, and May 30, 2008, involving 19 cases. All of the persons with measles were unimmunized with the exception of the last case, a person who had been vaccinated. Of the other 18 cases, 1 was an infant who was too young to be vaccinated, 2 were younger than 4 years of age, and the remaining 15 were of school age (unpublished data).

WHO REFUSES VACCINES AND WHY

Using data from the National Immunization Survey for the period from 1995 through 2001, Smith et al. compared the characteristics of children between the ages of 19 and 35 months who did not receive any vaccine (unvaccinated) with the characteristics of those who were partially vaccinated (undervaccinated).⁴⁷ As compared with the undervaccinated children, the unvaccinated children were more likely to be male, to be white, to belong to households with higher income, to have a married mother with a college education, and to live with four or more children.⁴⁷ Other studies have shown that children who are unvaccinated are likely to belong to families that intentionally refuse vaccines, whereas children who are undervaccinated are likely to have missed some vaccinations because of factors related to the health care system or sociodemographic characteristics.⁴⁸⁻⁵¹

In a case-control study of the knowledge, attitudes, and beliefs of parents of exempt children as compared with parents of vaccinated children, respondents rated their views of their children's vulnerability to specific diseases, the severity of these diseases, and the efficacy and safety of the specific vaccines available for them. Composite scores were created on the basis of these vaccine-specific responses. As compared with parents of vaccinated children, significantly more parents of exempt children thought their children had a low susceptibility to the diseases (58% vs. 15%, $P < 0.05$), that the severity of the diseases was low (51% vs. 18%, $P < 0.05$), and that the efficacy and safety of the vaccines was low (54% vs. 17% for efficacy and 60% vs. 15% for safety, $P < 0.05$ for both comparisons).⁵² Moreover, parents of exempt children were more likely than parents of vaccinated children both to have

providers who offered complementary or alternative health care and to obtain information from the Internet and groups opposed to aspects of immunization.⁵² The most frequent reason for nonvaccination, stated by 69% of the parents, was concern that the vaccine might cause harm.⁵²

Other studies have also reported the importance of parents' concerns about vaccine safety when they decide against vaccination.⁵³⁻⁵⁶ A national survey of parents from 2001 through 2002 showed that although only 1% of respondents thought vaccines were unsafe, the children of these parents were almost three times as likely to not be up to date on recommended vaccinations as the children of parents who thought that vaccines were safe.⁵⁴ In a separate case-control study with a national sample, underimmunization was associated with negative perceptions of vaccine safety (odds ratio, 2.0; 95% CI, 1.2 to 3.4).⁵⁵ And in another case-control study, Bardenheier et al. found that although concerns regarding general vaccine safety did not differ between the parents of vaccinated children and the parents of undervaccinated or unvaccinated children, more than half of the case and control parents did express concerns about vaccine safety to their child's health care provider.⁵⁷ Moreover, parents of undervaccinated or unvaccinated children were more likely to believe that children receive too many vaccines.⁵⁷

THE ROLE OF HEALTH CARE PROVIDERS

Clinicians and other health care providers play a crucial role in parental decision making with regard to immunization. Health care providers are cited by parents, including parents of unvaccinated children, as the most frequent source of information about vaccination.⁵²

In a study of the knowledge, attitudes, and practices of primary care providers, a high proportion of those providing care for children whose parents have refused vaccination and those providing care for appropriately vaccinated children were both found to have favorable opinions of vaccines.⁵⁸ However, those providing care for unvaccinated children were less likely to have confidence in vaccine safety (odds ratio, 0.37; 95% CI, 0.19 to 0.72) and less likely to perceive vaccines as benefitting individuals and communities.⁵⁸ Moreover, there was overlap between clinicians' unfa-

avorable opinions of vaccines and the likelihood that they had unvaccinated children in their practice.⁵⁸

There is evidence that health care providers have a positive overall effect on parents' decision making with regard to vaccination of their children. In a study by Smith et al., parents who reported that their immunization decisions were influenced by their child's health care provider were almost twice as likely to consider vaccines safe as parents who said their decisions were not influenced by the provider.⁵⁹

In focus-group discussions, several parents who were not certain about vaccinating their child were willing to discuss their immunization concerns with a health care provider and wanted the provider to offer information relevant to their specific concerns.⁵⁶ These findings highlight the critical role that clinicians can play in explaining the benefits of immunization and addressing parental concerns about its risks.

CLINICIANS' RESPONSE TO VACCINE REFUSAL

Some clinicians have discontinued or have considered discontinuing their provider relationship with families that refuse vaccines.^{60,61} In a national survey of members of the American Academy of Pediatrics, almost 40% of respondents said they would not provide care to a family that refused all vaccines, and 28% said they would not provide care to a family that refused some vaccines.⁶¹

The academy's Committee on Bioethics advises against discontinuing care for families that decline vaccines and has recommended that pediatricians "share honestly what is and is not known about the risks and benefits of the vaccine in question."⁶² The committee also recommends that clinicians address vaccine refusal by respectfully listening to parental concerns, explaining the risk of nonimmunization, and discussing the specific vaccines that are of most concern to parents.⁶² The committee advises against more serious action in a majority of cases: "Continued refusal after adequate discussion should be respected unless the child is put at significant risk of serious harm (e.g., as might be the case during an epidemic). Only then should state agencies be involved to override parental discretion on the basis of medical neglect."⁶²

POLICY-LEVEL DETERMINANTS OF VACCINE REFUSAL

Immunization requirements and the policies that ensure compliance with the requirements vary considerably among the states; these variations have been associated with state-level exemption rates.^{11,63} For example, the complexity of procedures for obtaining exemption has been shown to be inversely associated with rates of exemption.⁶³ Moreover, between 1991 and 2004, the mean annual incidence of pertussis was almost twice as high in states with administrative procedures that made it easy to obtain exemptions as in states that made it difficult.¹¹

One possible way to balance individual rights and the greater public good with respect to vaccination would be to institute and broaden administrative controls. For example, a model law proposed for Arkansas suggested that parents seeking nonmedical exemptions be provided with counseling on the hazards of refusing vaccination.⁶⁴

States also differ in terms of meeting the recommendations for age-appropriate coverage for children younger than 2 years of age.⁶⁵ School immunization requirements ensure completion by the time of school entry, but they do not directly influence the timeliness of vaccination among preschoolers. However, there is some evidence that school immunization laws have an indirect effect on preschool vaccine coverage. For example, varicella vaccine was introduced in the United States in 1995 and has played an important role in reducing the incidence of chickenpox.⁶⁶ In 2000, states that had implemented mandatory immunization for varicella by the time of school entry had coverage among children 19 to 35 months old that was higher than the average for all states. Having an immunization requirement could be an indicator of the effectiveness of a state's immunization program, but the effect of school-based requirements on coverage among preschoolers cannot be completely discounted.

CONCLUSIONS

Vaccine refusal not only increases the individual risk of disease but also increases the risk for the whole community. As a result of substantial gains in reducing vaccine-preventable diseases, the memory of several infectious diseases has faded from

the public consciousness and the risk–benefit calculus seems to have shifted in favor of the perceived risks of vaccination in some parents' minds. Major reasons for vaccine refusal in the United States are parental perceptions and concerns about vaccine safety and a low level of concern about the risk of many vaccine-preventable diseases. If the enormous benefits to society from vaccination are to be maintained, increased efforts will be needed to educate the public about those benefits and to increase public confidence in the systems we use to monitor and ensure vaccine safety. Since clinicians have an influence on parental decision making, it is important that they understand the benefits and risks of vaccines and anticipate questions that parents may have about safety. There are a number of sources of information on vaccines that should be useful to both

clinicians and parents (e.g., Appendix 1 in the fifth edition of *Vaccines*, edited by Plotkin et al.; the list of Web sites on vaccine safety posted on the World Health Organization's Web site; and the Web site of the National Center for Immunization and Respiratory Diseases).⁶⁷⁻⁶⁹

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Trivalent Live Attenuated Intranasal Influenza Vaccine Administered During the 2003–2004 Influenza Type A (H3N2) Outbreak Provided Immediate, Direct, and Indirect Protection in Children

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ABSTRACT

OBJECTIVE. Live attenuated influenza vaccine may protect against wild-type influenza illness shortly after vaccine administration by innate immunity. The 2003–2004 influenza A (H3N2) outbreak arrived early, and the circulating strain was antigenically distinct from the vaccine strain. The objective of this study was to determine the effectiveness of influenza vaccines for healthy school-aged children when administered during the influenza outbreak.

DESIGN/METHODS. An open-labeled, nonrandomized, community-based influenza vaccine trial was conducted in children 5 to 18 years old. Age-eligible healthy children received trivalent live attenuated influenza vaccine. Trivalent inactivated influenza vaccine was given to children with underlying health conditions. Influenza-positive illness was compared between vaccinated and nonvaccinated children. Medically attended acute respiratory illness and pneumonia and influenza rates for Scott and White Health Plan vaccinees were compared with age-eligible Scott and White Health Plan nonparticipants in the intervention communities. Herd protection was assessed by comparing age-specific medically attended acute respiratory illness rates in Scott and White Health Plan members in the intervention and comparison communities.

RESULTS. We administered 1 dose of trivalent live attenuated influenza vaccine or trivalent inactivated influenza vaccine to 6569 and 1040 children, respectively (31.5% vaccination coverage), from October 10 to December 30, 2003. The influenza outbreak occurred from October 12 to December 20, 2003. Significant protection against influenza-positive illness (37.3%) and pneumonia and influenza events (50%) was detected in children who received trivalent live attenuated influenza vaccine but not trivalent inactivated influenza vaccine. Trivalent live attenuated influenza vaccine recipients had similar protection against influenza-positive illness within 14 days compared with >14 days (10 of 25 vs 9 of 30) after vaccination. Indirect effectiveness against medically attended acute respiratory illness was detected in children 5 to 11 and adults 35 to 44 years of age.

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Key Words

influenza, direct effectiveness, indirect effectiveness, herd protection, live attenuated influenza vaccine-trivalent, inactivated influenza vaccine-trivalent, medically attended acute respiratory illness

Abbreviations

IIV-T—trivalent inactivated influenza vaccine
 LAIV-T—trivalent live attenuated influenza vaccine
 MAARI—medically attended acute respiratory illness
 FDA—Food and Drug Administration
 T-B—Temple and Belton
 SWC—Scott and White Clinic
 SWHP—Scott and White Health Plan
 ICD-9-CM—*International Classification of Diseases, Ninth Revision, Clinical Modification*
 P&I—pneumonia and influenza
 CI—confidence interval
 RR—rate ratio

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CONCLUSION. One dose of trivalent live attenuated influenza vaccine was efficacious in children even when administered during an influenza outbreak and when the dominant circulating influenza virus was antigenically distinct from the vaccine strain. We hypothesize that trivalent live attenuated influenza vaccine provides protection against influenza by both innate and adaptive immune mechanisms.

THE CURRENT INFLUENZA vaccine recommendations (2006–2007) by the Advisory Committee on Immunization Prevention of the Centers for Disease Control and Prevention are prioritized on the basis of risk for serious influenza-associated complications.¹ High-priority groups include individuals who are at risk for serious complications from influenza, health care workers with direct patient contact, and household contacts of infants who are younger than 6 months. This strategy has resulted in modest reduction in influenza-associated mortality and morbidity, but it has not controlled annual influenza epidemics. From 1979 to 2001, an annual average of 41 000 deaths were attributed to influenza.² In the past 20 years (1976–1999), a significant increase has occurred in influenza-associated all-cause excess deaths.³ From 1990 to 1999, the annual number of influenza-associated all-cause deaths exceeded 50 000,³ and influenza-associated respiratory and circulation hospitalizations exceeded 380 000.⁴ Improved vaccination coverage for groups at risk for influenza complications has not resulted in a corresponding reduction in influenza-associated all-cause deaths and influenza-associated hospitalizations.^{1–4}

Universal influenza vaccination of school-aged children is being considered as a complementary strategy to that currently advocated by the Advisory Committee on Immunization Prevention.^{5–7} Children have high rates of infection, medically attended illness, and hospitalization from influenza.^{8–16} Children play an important role in the transmission of influenza within families, schools, and communities.^{5,8,15} Intensity of respiratory illnesses in children early in the influenza season may be a harbinger of influenza-associated mortality in elderly adults.¹⁷ Vaccination with trivalent inactivated influenza vaccine (IIV-T) of ~80% of schoolchildren in a community has decreased respiratory illnesses in adults¹⁸ and excess deaths in the elderly.¹⁹ Vaccinating children in a child care facility reduced influenza-related morbidity among household members.²⁰ In Russia, a mass vaccination campaign in children 3 to 17 years of age reduced significantly influenza-like illness in children and in unvaccinated elderly adults who lived in the home.²¹ In an ongoing study in central Texas, vaccination coverage of ~20% to 25% with trivalent live attenuated influenza vaccine (LAIV-T) in children 18 months to 18 years of age resulted in an 8% to 18% reduction against medi-

cally attended acute respiratory illness (MAARI) in adults ≥ 35 years of age.²² These observations are consistent with mathematical models for the control of influenza epidemics, which have illustrated that the greatest reduction in morbidity and mortality occurs through vaccination of school-aged children.²³

Since 1998, we have been conducting an open-label, nonrandomized, community-based trial with the goal of controlling epidemic influenza through active immunization of school-aged children.^{22,24–26} LAIV-T and IIV-T are safe and efficacious in children.^{26–31} LAIV-T was approved by the Food and Drug Administration (FDA) in the summer of 2003 for use in healthy individuals 5 to 49 years of age. Our study reports on the efficacy of LAIV-T in its first year of licensure in the United States, which coincided with the unusually early arrival of the 2003–2004 influenza outbreak with a drifted variant, A/Fujian/411/2002 (H3N2). The early arrival of influenza coincided with our community vaccination campaign and provided the opportunity to determine the direct and indirect effectiveness (herd protection) of influenza vaccination of school-aged children through the influenza outbreak.

METHODS

Study Design

An open-label, nonrandomized, community-based trial with FDA-approved influenza vaccines was conducted in children 5 to 18 years of age. Age-eligible children who resided in the intervention communities were offered influenza vaccines. LAIV-T was offered to age-eligible, healthy children, and IIV-T was offered to age-eligible children with high risk conditions for influenza. During the enrollment period, age-eligible children in the intervention communities were vaccinated 7 days a week in the Scott and White Clinic (SWC), the mall, churches, and public and private schools. The intervention communities (T-B) comprise the adjacent cities of Temple and Belton in central Texas and their surrounding towns. Age-eligible children in the comparison communities, Waco, Bryan, and College Station, were not offered an influenza vaccine through our community-based study. Waco is ~40 miles north of Temple; Bryan and College Station, adjacent cities, are ~90 miles southeast of Temple. Community physicians in both the intervention and comparison communities were able to provide LAIV-T and IIV-T to children who were not enrolled in our community-based trial.

The intervention and comparison communities in central Texas were chosen because of the similarities between their demographics, the relative proximity between the communities that helps to ensure similar influenza outbreak periods and circulating influenza strains, and all of the communities are served by large multispecialty clinics of Scott and White Clinic (SWC),

which is a major health care provider for those communities. A subset of SWC patients who were members of the Scott and White Health Plan (SWHP) provided defined populations for analysis. Age-specific rates for MAARI in the periods before, after, and during the influenza outbreak (2003–2004) were calculated for the intervention and comparison communities. The institutional review boards of Baylor College of Medicine and SWC approved this study. Informed consent was obtained from the legal guardians of enrolled participants.

Participant Population

Age-eligible healthy children received LAIV-T when they were 5 to 18 years of age, had residence in T-B, and had signed informed consent by the legal guardian or adult participant. Participants who were using nasal steroids were not excluded from receiving LAIV-T. Age-eligible children who had underlying risk conditions for influenza or who resided with immunocompromised household contact were offered IIV-T.

Immunization

At enrollment, all participants received a single dose of an FDA-approved influenza vaccine: 0.5 mL of LAIV-T by nasal spray or 0.5 mL of IIV-T by intramuscular injection. A second vaccine dose was offered 4 to 6 weeks after the first dose to children who were younger than 9 years and received the vaccine for the first time. The composition of both vaccines was A/New Caledonia/20/99 (H1N1)-like, A/Panama/2007/99 (H3N2)-like, and B/Hong Kong/330/2001-like.

Community Demographics

Demographic characteristics of the intervention and comparison communities have been previously described using US Census Bureau, Census 2000 data.²² The populations' ethnic and racial distributions were comparable. Approximately 30% of the populations for the intervention and comparison communities were ≤ 19 years of age. The intervention communities had a higher proportion of individuals who were ≥ 65 years of age (14.7% vs 9.8%), and the comparison communities had a higher proportion of young adults who were 20 to 34 years of age (21.0% vs 32.4%). The average household size was larger in the comparison communities (2.63 vs 2.73). Population size using the US Census 2000 data were also determined using zip codes to define the intervention (76501, 76502, 76504, 76513, 76554, 76534, 76569, 76571, and 76579) and comparison (77801, 77802, 77803, 77840, 77845, 76701, 76704, 76705, 76706, 76707, 76708, 76710, 76711, 76712, 76633, 76643, and 76557) communities.

Database

Demographic information of LAIV-T and IIV-T recipients were entered and tracked in a computerized immuniza-

tion registry as previously described.³² The SWC and SWHP clinical records were retrievable electronically for all of the SWCs of Central Texas. Demographic information and *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes for MAARI were extracted electronically from the SWHP administrative database.

MAARI and Pneumonia and Influenza (P&I) Diagnosis Codes

The ICD-9-CM codes for MAARI visits included those for otitis media and sinusitis (381–383, 461.x), upper respiratory tract illness (79.x, 460, 462–463, 465, 487.1), and lower respiratory tract illness (464.x, 466.x, 480.x–487.0, 490.x–496.x, 510.x–513.x, 515.x–516.x, 518.x, and 786.1). The ICD-9-CM codes for the Centers for Disease Control and Prevention defined P&I included those for lower respiratory tract illness and influenza (480.x–487.0). Each medical encounter had up to 6 ICD-9-CM codes. Medical encounters included those in clinics, emergency departments, and hospitals. Multiple entries on a single day were counted as 1 encounter. MAARI is a nonspecific case definition for influenza; P&I is a more specific clinical case definition for influenza.

Influenza Surveillance

Central Texas surveillance was performed as previously described.^{22,24–26} In brief, children and adults who presented to an SWC facility with a history of a febrile respiratory illness were candidates for a throat culture for virus isolation. Throat cultures that were obtained from the SWC surveillance sites were processed at the viral diagnostic laboratory of Scott and White Hospital in Temple, Texas. The outbreak or epidemic period was defined as the weeks with the most intense influenza activity accounting for 80% to 85% of all positive influenza cultures.^{22,24–26}

Statistical Analysis

SWHP membership status and census were determined from the SWHP database on December 31, 2003. Primary outcomes were direct and indirect effectiveness. Direct effectiveness of the influenza vaccines was evaluated in the intervention communities. It compared MAARI and P&I rates during the influenza epidemic outbreak in LAIV-T and IIV-T SWHP vaccinees compared with MAARI and P&I rates in age-eligible SWHP nonparticipants who had never received LAIV-T or had not received IIV-T in 2003. Indirect effectiveness compared age-specific MAARI rates during the influenza outbreak for SWHP members in the intervention and comparison communities. For assessment of effectiveness, point estimates and 95% confidence intervals (CIs) for the incidence rate ratios (RRs) were calculated. Effectiveness of the influenza vaccine was equal to $(1 - RR) \times 100\%$.^{22,24} Age-specific MAARI rates in the preepidemic and postepidemic periods were also com-

pared between SWHP members in the intervention and comparison communities to check for potential health care use bias.

RESULTS

LAIV-T and IIV-T Immunization of Children 5 to 18 Years of Age

The influenza immunization campaign started on October 10, 2003, and ended on December 30, 2003. We vaccinated 7609 children with an influenza vaccine; 6569 children received LAIV-T, and 1040 received IIV-T. Approximately 24% of the children whom we vaccinated (1608 LAIV-T and 193 IIV-T vaccinees) lived in areas outside the intervention communities. An additional 1097 children who were 5 to 18 years of age and living in the intervention communities received IIV-T from the SWC. Thus 4961 and 1944 children who were 5 to 18 years of age and resided within the zip code-defined intervention communities received LAIV-T and IIV-T vaccines, respectively.

A total of 897 (35%) of 2564 LAIV-T vaccinees who were 5 to <9 years of age were eligible for a second dose because of not having received a previous influenza vaccine. A total of 163 (18.2%) of the 897 LAIV-T vaccinees received a second vaccine dose. Seventy-five children received the second dose on December 20, 2003 (end of the influenza outbreak), or later. A total of 737 IIV-T vaccinees were 5 to <9 years of age. The number of IIV-T vaccinees who were eligible for a second dose was not known. Thirty-six IIV-T vaccinees received a second vaccine dose; 8 children received the second dose of IIV-T on December 20, 2003, or later.

A total of 52.4% of LAIV-T recipients were female, and 32.9% were of minority ethnicity or race (Hispanic: 20.1%; black: 6.9%; other: 5.9%). A total of 45.3% of IIV-T recipients were female, and 37.3% were of minority ethnicity or race (Hispanic: 20.4%; black: 11.5%;

other: 5.4%). The racial/ethnic distribution in the intervention communities was 65.1% white, 18.8% Hispanic, 13.9% black, and 2.1% other. In the previous year, 2002–2003, LAIV-T was not available in the intervention or comparison communities; however, 3242 current LAIV-T vaccinees received LAIV-T as study participants 1 or more of the study years from 1998–1999 to 2001–2002.²⁶

LAIV-T and IIV-T Coverage in Children 5 to 18 Years of Age in the Intervention Communities

In our previous report, we had estimated vaccination coverage on the basis of population data extracted from the US census 2000 for the T-B intervention communities.²⁰ The true vaccination coverage may have been overestimated. We therefore estimated vaccination coverage for the 2003–2004 season on the basis of 3 methods: (1) population data from the US census 2000 for the T-B intervention communities, (2) population data from the US census 2000 using zip codes to define the T-B intervention communities, and (3) age-eligible children who attended public schools in the independent school districts of the T-B intervention communities (Table 1). Influenza vaccination coverage in school-age children using defined populations on the basis of either zip codes or school attendance in the independent school districts (public schools) gave comparable estimates (31.5% and 30.7%). In contrast, influenza vaccination coverage on the basis of the census of the cities in the intervention communities underestimated the population, thereby inflating the influenza vaccination coverage to 40.6%.

IIV-T Coverage in Individuals Who Attended SWCs in the Intervention and Comparison Communities

The SWC population was used as a surrogate to estimate the age-specific influenza vaccination coverage in the

TABLE 1 Influenza Vaccination Coverage of Children Who Were 5 to 18 Years of Age and Living in the T-B Intervention Communities

Parameter	T-B Intervention Communities		
	Census Defined by City Population ^a	Census Defined by Zip Code ^a	Independent School Districts Census
Population	80 843	103 719	NA
No. of children	16 975 ^b	21 937 ^b	19 807 ^b
LAIV-T vaccinees ^c	4956	4961	4362
IIV-T vaccinees ^c	1930	1944	1717
Total vaccinees	6886 (40.6%)	6905 (31.5%)	6079 (30.7%)

NA indicates not applicable.

^a US Census 2000 data define by city (Temple, Belton, Holland, Academy, Rogers, Salado, and Troy are the T-B intervention communities) or zip code (76501, 76502, 76503, 76504, 76505, 76508, 76513, 76534, 76554, 76569, 76571, and 76579) for the T-B intervention communities.

^b Number of children in city and zip code is for children aged 5 to <19 years. Number of children who attended schools in the independent school districts is based on the census in the first 6 weeks for elementary, middle, and high school students in the T-B intervention communities.

^c We vaccinated 7609 children 5 to 18 years of age with an influenza vaccine; 6569 children received LAIV-T, and 1040 received IIV-T. Approximately 24% of these children (1608 LAIV-T and 193 IIV-T vaccinees) lived in areas outside the intervention communities. An additional 1097 children who were 5 to 18 years of age and living in the intervention communities received IIV-T from the SWC. Thus, 4961 and 1944 children who were 5 to 18 years of age and resided within the zip code-defined intervention communities received LAIV-T and IIV-T vaccines, respectively.

intervention and comparison communities. The current procedural terminology, which is a uniform language for medical services and procedures used for administrative management purposes such as processing claims, was used to identify influenza vaccine administration in the SWC population. The SWC administrative data files were used to determine age-specific denominators, which consisted of individuals who had received medical service in the SWC clinic, emergency department, or hospital during the study year (July 1, 2003, to June 30, 2004).

To determine the penetration of IIV-T use in the intervention and comparison communities, we used age-specific rates for IIV-T in the SWC population during the 2003 study year (Table 2). Overall rates for IIV-T use among the SWC population were similar in the intervention and comparison communities (18 263 [27.5%] of 66 509 vs 14 570 [28.8%] of 50 565). The rate of IIV-T vaccine use was significantly greater in children who were younger than 5 years (28.5% vs 23.6%; $P < .01$) and adults who were ≥ 65 years (61.4% vs 57.6%; $P < .01$) and residing in the intervention communities. The IIV-T vaccination rates were significantly greater ($P < .01$) among the other age-specific groups who were living in the comparison communities (5 to <10 years: 14.7% vs 18.1%; 10 to <19 years: 14.4% vs 17%; 19 to <35 years: 9.9% vs 15.8%; and 35 to <65 years: 27.1% vs 32.2%). It is important to note that at least 64.1% of the population in the intervention communities received medical care at the SWC in contrast to 16.2% of the population in the comparison communities (Table 2). Few ($n = 154$) age-eligible children in the comparison communities received LAIV-T through the SWC.

Influenza Viral Surveillance

The 2003–2004 influenza epidemic occurred early throughout the United States. Influenza virus surveillance defined the influenza outbreak in Central Texas, from October 12, 2003 (week 42), to December 20, 2003 (week 51), with peak activity occurring in week 47, the

week of Thanksgiving (Fig 1B). A total of 1077 (46.4%) of 2320 specimens that were obtained in our viral surveillance network were positive for influenza; 1076 were type A and 1 was type B. All influenza A isolates that were subtyped were H3N2. A total of 74.5% and 25.5% of our isolates that were characterized by the Centers for Disease Control and Prevention were A/Fujian/411/2002-like and A/Panama/2007/99-like, respectively. A/Fujian/411/2002 (H3N2)-like was also the dominant influenza virus in the United States. A/Fujian/411/2002 (H3N2) was a significant antigenic variant that was distinct from the vaccine virus A/Panama/2007/99 (H3N2). Vaccination of children in our study paralleled the influenza outbreak (Fig 1); this greatly limited the administration of the second dose of influenza vaccine to children who were younger than 9 years and received the vaccine for the first time. Approximately 58% of the first vaccine doses had been administered by the beginning of the peak week (November 16, 2003) for influenza activity.

Protection Against Influenza-Positive, Medically Attended Acute Febrile Respiratory Illness

We established an influenza virus surveillance network in the intervention and comparison communities. People who sought medical care for an acute febrile respiratory illness were cultured for influenza. During the influenza outbreak, 450 (44.8%) of 1003 people in the intervention communities and 280 (51.2%) of 547 people in the comparison communities had an influenza culture-positive acute febrile respiratory illness.

The impact of influenza vaccination status on influenza-positive acute febrile illness was determined in children who were 5 to 18 years of age and resided in the intervention communities during the influenza outbreak (Table 3). All influenza-positive acute febrile respiratory illnesses after influenza vaccine administration were included in the analysis. Children who were vaccinated with LAIV-T in 2003 had significant protection against influenza-positive acute respiratory illness. Children

TABLE 2 IIV-T Coverage in SWC Population in the Intervention and Comparison Communities

Age, y	No. (%) in Intervention Communities			No. (%) in Comparison Communities		
	Population ^a	SWC	SWC-IIV-T	Population ^a	SWC	SWC-IIV-T
<5	7483	5523	1572 (28.5)	21 284	3329	785 (23.6) ^b
5 to <10	7635	5004	736 (14.7)	20 652	3264	590 (18.1) ^b
10 to <19	14 302	8388	1204 (14.4)	40 376	5706	968 (17) ^b
19 to <35	22 052	12 428	1232 (9.9)	107 698	11 853	1873 (15.8) ^b
35 to <65	37 864	23 550	6387 (27.1)	90 689	19 112	6146 (32.2) ^b
≥ 65	14 383	11 616	7132 (61.4)	31 377	7301	4208 (57.6) ^b
Total	103 719	66 509	18 263 (27.5)	312 076	50 565	14 570 (28.8)

The SWC administrative data files were used to determine age-specific denominators, which consisted of individuals who had receive medical service in the SWC, emergency department, or hospital during the study year (July 1, 2003, to June 30, 2004). Current procedural terminology data were used to estimate the usage of IIV-T in the SWC population in the intervention and comparison communities.

^a Population extracted from the US Census Bureau, Census 2000 defined by zip codes.

^b Significant differences (z test for comparison of proportions; $P < .001$) were observed in the use of IIV-T by age-specific SWC patients in the intervention communities compared with age-specific SWC patients in the comparison communities.

FIGURE 1

Influenza vaccination during the 2003–2004 influenza virus season with biweekly MAARI rates for children 5 to 17 years of age in the intervention and comparison communities. A, The 2003–2004 influenza epidemic occurred early throughout the United States. Our influenza virus surveillance defined the influenza outbreak in Central Texas, in the intervention (□) and comparison (■) communities from October 12, 2003, to December 20, 2003, with peak activity occurring in week 47, the week of Thanksgiving. The influenza vaccination campaign enrolled children (▲) in the intervention communities to receive LAIV-T or IIV-T from October 10, 2003, to December 30, 2003. B, Biweekly MAARI rates for children 5 to 17 years of age were determined among SWHP members who resided in the intervention (○) and comparison communities (●) during the 2003–2004 study year. The preepidemic period was defined from June 29 to October 11, 2003; the influenza outbreak occurred from October 12 to December 20, 2003; and the postepidemic period was from December 21, 2003, to July 3, 2004.

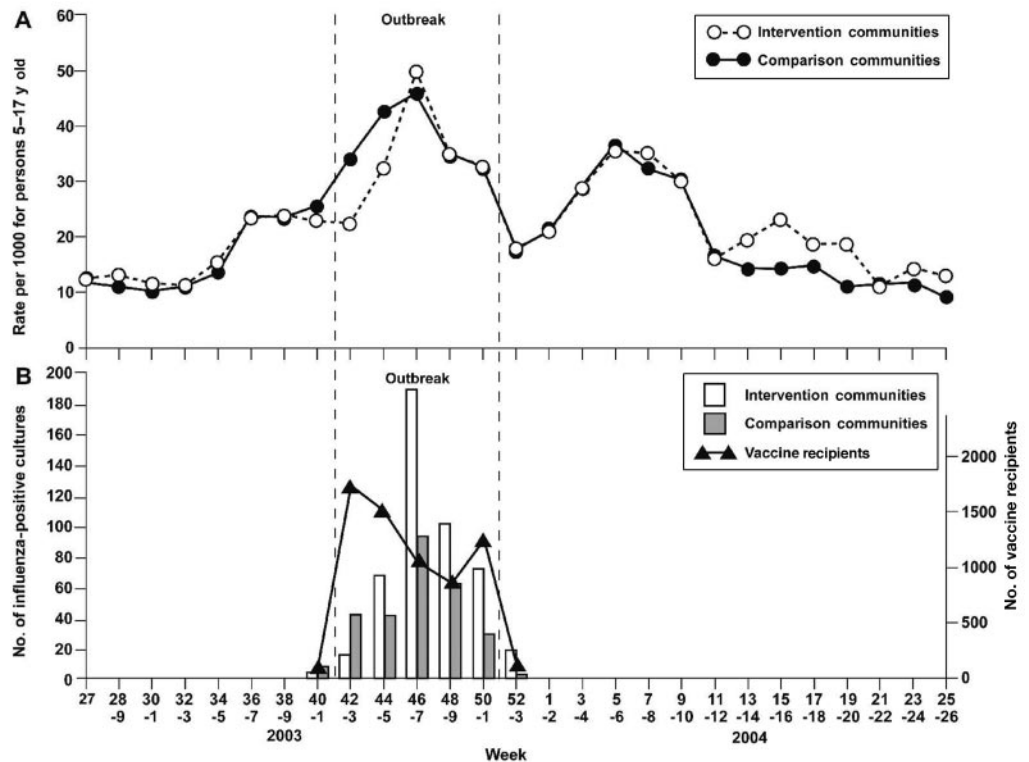


TABLE 3 Influenza-Positive Acute Febrile Respiratory Illness in Children Who Were 5 to 18 Years of Age and Resided in the Intervention Communities During the 2003 Influenza Outbreak

Influenza Vaccination Status	Influenza Positive, n/N (%)	P ^a	Efficacy, % ^b
Never vaccinated	127/231 (55)	Reference	Reference
LAIV-T in 2003	19/55 (34.5)	.006	37.3
LAIV-T in 1998–2001 ^c	34/79 (43)	.07	21.8
IIV-T in 2003	14/24 (58.3)	NS	0

Influenza outbreak period was from October 12 to December 20, 2003.

^a χ^2 test was used to determine for differences between the group that was never vaccinated and the group that was vaccinated. $P \leq .05$ was considered significant.

^b Efficacy = $(1 - \text{vaccine group}/\text{never vaccinated}) \times 100$.

^c Age-eligible children who had received LAIV-T in ≥ 1 year from 1998 to 2001 but not in 2003.

who received LAIV-T in ≥ 1 year from 1998 to 2001 but not in 2003 approached protection against influenza-positive acute febrile respiratory illness. No reduction in influenza-positive acute febrile respiratory illness was among IIV-T recipients.

To determine the onset of protection that was provided by LAIV-T in children who were enrolled in this community trial, we evaluated the date when an influenza-positive acute febrile respiratory illness occurred in relation to influenza vaccine administration in the intervention communities (Table 4). Children who received LAIV-T in 2003 had similar frequencies of influenza-positive acute febrile respiratory illnesses (25%–45.5%) in weeks 1, 2, 3, 4, or >4 after vaccine administration. In

TABLE 4 Influenza-Positive Acute Febrile Respiratory Illness After Influenza Vaccine Administration in Children Who Were 5 to 18 Years of Age and Resided in the Intervention Communities During the 2003 Influenza Outbreak

Vaccine	Influenza-Positive Acute Respiratory Illness, n/N (%)				
	Week 1 (0–6 d)	Week 2 (7–13 d)	Week 3 (14–20 d)	Week 4 (21–27 d)	>Week 4 (≥ 28 d)
LAIV-T	5/14 (35.7)	5/11 (45.5)	2/6 (33.3)	2/8 (25)	5/16 (31.3)
IIV-T	6/8 (75)	1/1 (100)	0/0 (0)	0/0 (0)	7/15 (46.7)

Influenza outbreak period was from October 12 to December 20, 2003.

contrast, the IIV-T recipients had 7 of 9 acute febrile respiratory illness episodes positive for influenza within the first 2 weeks of vaccine administration. No acute febrile respiratory illnesses were cultured in weeks 3 and 4 after IIV-T administration, and after week 4, influenza-positive acute respiratory illness was detected in 46.7% (7 of 15) of the cultured episodes.

Direct Effectiveness Measures

The influenza immunization campaign started on October 10, 2003, and ended on December 30, 2003, encompassing the influenza outbreak (October 12 to December 20). Direct effectiveness of the influenza vaccines was calculated from day 1 after vaccination to the end of the influenza outbreak (week 51). MAARI and P&I incidence rates during the influenza outbreak in LAIV-T and IIV-T SWHP vaccinees was compared with age-eligible SWHP nonparticipants who had never received an in-

influenza vaccine in the intervention communities. Also included were children who had previously received LAIV-T in ≥ 1 year from 1998 to 2001 but not in the study year (2003). Point estimates and 95% CIs for the incidence RRs were calculated. Children who were 5 to 9, 10 to 18, and 5 to 18 years and received LAIV-T or IIV-T did not have a significant reduction in MAARI during the influenza outbreak compared with age-eligible children who never received an influenza vaccine (Table 5). Using a more specific case definition for influenza disease (P&I), LAIV-T vaccinees who were 5 to 9 (RR: 0.2; 95% CI: 0.04–0.60) and 5 to 18 (RR: 0.5; 95% CI: 0.2–0.9) years of age experienced a significant reduction in P&I events compared with age-eligible participants who were never vaccinated. No significant reduction against P&I was observed in the IIV-T group.

Indirect Effectiveness Measure

Age-specific MAARI rates were compared between SWHP members who resided in the intervention and comparison communities during the 2003 influenza outbreak (October 12 to December 20, 2003; Table 6). Because of the potential for differences in the incidence rates between intervention and comparison communities, age-specific MAARI rates were also compared during the preepidemic period (June 29 to October 11, 2003) and postepidemic period (December 21, 2005, to July 3, 2004). Children who were 5 to 11 years of age in the intervention communities had significantly lower MAARI incidence rates during the influenza outbreak compared with those in the comparison communities (RR: 0.87; 95% CI: 0.80–0.95). The MAARI rates before and after the epidemic were comparable between children who were 5 to 11 years in the intervention and comparison communities, suggesting that the observed decrease in MAARI rate during the epidemic period in the intervention communities was attributed to protection that was provided by the influenza vaccines that

were delivered during the community influenza immunization campaign. Adults who were 35 to 44 years of age in the intervention communities during the epidemic period also had lower MAARI rates (RR: 0.91; 95% CI: 0.83–1.00). The intervention communities generally had lower MAARI incidence rates in adults who were ≥ 45 of age during the preepidemic, epidemic, and postepidemic influenza periods (Table 6). Therefore, this decrease in MAARI rates during the influenza outbreak in adults who were ≥ 45 years of age could not be attributed to the community influenza immunization campaign in school-aged children.

Age-specific biweekly MAARI rates for the intervention and comparison communities are illustrated in Figs 1A and 2. The biweekly MAARI rates during the preepidemic and postepidemic periods in children who were 5 to 17 years of age were similar between the intervention and comparison communities. In this age group a substantial reduction in the biweekly MAARI rates occurred during the first half of the influenza outbreak in the intervention communities (Fig 1A). A similar pattern of lower biweekly MAARI rates during the first half of the influenza outbreak was observed in the other age groups in the intervention communities (Fig 2).

DISCUSSION

The 2003–2004 influenza epidemic was notable in that it arrived unusually early in the United States; it was considered a moderately severe epidemic with a large number of pediatric deaths; the epidemic influenza virus, A/Fujian/411/2002 (H3N2), was a drift variant from the vaccine virus A/Panama/2007/99 (H3N2)-like, and it was the first year that LAIV-T was licensed for use in healthy individuals 5 to 49 years of age.^{33,34} Our ongoing community-based influenza vaccination program in children to control epidemic influenza provided us the opportunity to assess the effectiveness of LAIV-T and IIV-T when they were administered during an influenza

TABLE 5 Direct Effectiveness Against MAARI in Children Who Were 5 to 18 Years of Age, Were Members of SWHP, and Resided in the Intervention Communities During the 2003 Influenza Outbreak

Vaccine	Age, y	No. of Children	No. of MAARI Events	Child-Days	Rate per 10 000	RR (95% CI)
Never vaccinated	5–9	645	140	45 150	31.0	Reference
	10–18	2208	362	154 560	23.4	Reference
	5–18	2853	502	199 710	25.1	Reference
LAIV-T in 2003	5–9	667	81	29 731	27.2	0.9 (0.7–1.2)
	10–18	877	90	37 079	24.3	1.0 (0.8–1.3)
	5–18	1544	171	66 810	25.6	1.0 (0.9–1.2)
LAIV-T in 1998–2001 ^a	5–9	194	49	13 580	36.1	1.2 (0.8–1.6)
	10–18	709	148	49 630	29.8	1.3 (1.0–1.5)
	5–18	903	197	63 210	31.2	1.2 (1.0–1.5)
IIV-T in 2003	5–9	195	41	8676	47.3	1.5 (1.0–2.2)
	10–18	295	36	12 331	29.2	1.2 (0.9–1.8)
	5–18	490	77	21 007	36.7	1.5 (1.1–1.9)

Influenza outbreak period was from October 12 to December 20, 2003. Point estimates and 95% CIs for the incidence RRs were calculated.

^a Age-eligible children who had received LAIV-T in ≥ 1 year from 1998 to 2001 but not in 2003.

TABLE 6 Indirect Effectiveness: Age-Specific Incidence Rates of MAARI of SWHP Members in the Intervention and Comparison Communities Before, During, and After the 2003 Influenza Outbreak

Age, y	MAARI Rates per 1000 Person-Weeks								
	Intervention Communities			Comparison Communities			RR		
	Before	During	After	Before	During	After	Before	During	After
<5	33.1	57.7	42.5	33.2	60.6	42.9	1	0.95	0.99
5–11	11.2	18.8	14.4	10.1	21.6	13.6	1.12	0.87 ^a	1.06
12–17	6.0	15.8	8.2	6.3	16.0	7.7	0.96	0.99	1.06
18–24	5.3	10.3	6.8	5.6	10.1	6.7	0.94	1.02	1.02
25–34	6.1	11.4	7.8	6.3	10.6	7.2	0.96	1.08	1.08
35–44	5.2	9.6	7.1	5.5	10.6	7.4	0.94	0.91 ^a	0.96
45–54	4.1	8.4	6.5	5.0	9.9	7.8	0.81 ^a	0.85 ^a	0.84 ^a
55–64	4.0	8.4	6.3	4.6	9.3	7.9	0.87 ^a	0.90	0.79 ^a
≥65	3.7	8.3	6.6	4.5	9.8	7.9	0.83 ^a	0.85 ^a	0.84 ^a

The preepidemic period was from June 29 to October 11, 2003; the epidemic period was from October 12 to December 20, 2003; the postepidemic period was from December 21, 2003, to July 3, 2004. Difference in incidence rates between intervention and comparison were calculated using Mantel-Haenszel estimates. The point estimates of incidence rates and their 95% CIs were used to determine statistical differences between populations.

^a The 95% upper bound CI does not cross 1.

outbreak. Most children who were younger than 9 years and had never previously received an influenza vaccine were able to receive only 1 dose of an influenza vaccine because of the time constraint imposed by the influenza outbreak. Despite this limitation, children who were 5 to 18 years of age and received LAIV-T had a significant reduction in influenza-positive medically attended febrile respiratory illness (Table 3) and P&I medically attended illness during the influenza outbreak. The vaccine effectiveness [% = (1 - RR) × 100] was most apparent in children who were 5 to 9 years of age, with 80% effectiveness against P&I medically attended illness (95% CI: 40%–96%).

The 2003 Advisory Committee on Immunization Practices and the package inserts recommend that 2 doses 4 weeks apart for IIV-T and at least 6 weeks apart for LAIV-T (FluMist; MedImmune Inc, Gaithersburg, MD) be administered to children who are younger than 9 years if they have never received an influenza vaccine.^{34,35} There are ample data for the necessity of 2 doses of IIV-T given at least 4 weeks apart in previously unvaccinated young children for induction of protective levels of serum antibodies and protection against influenza-associated morbidity.^{35–44} This is because priming (first challenge) with either natural infection or IIV is required for induction of a protective immune response when a booster dose (second dose) with the inactivated influenza vaccine is administered.^{36–38} The 2003 IIV-T immunogenicity in young children who were administered 2 doses at least 4 weeks apart were comparable to that observed in other studies except that the response to the influenza B component was low.⁴⁴ The antibody response to the epidemic influenza virus A/Fujian/411/2002 (H3N2) was not reported.⁴⁴ Vaccine effectiveness of 49% against P&I was observed in a retrospective cohort study among children who were 6 to 23 months of age

and had received 2 doses of IIV-T (beginning 2 weeks after the second dose).^{45–47} No significant protection against P&I was observed in partially vaccinated children (children with only 1 dose and no previous influenza vaccination or children with 2 doses but sought medical attention <14 days after the second dose).^{45–47} In a study of health care workers, the 2003–2004 influenza vaccine was not effective against influenza-like illness,⁴⁶ but when a more specific case definition was used (laboratory-confirmed influenza), vaccine effectiveness was estimated at 52% in healthy adults 50 to 64 years of age.^{45,46} In our study, a single dose of IIV-T was not associated with a significant reduction in culture-positive medically attended influenza illness (Table 3) or P&I medically attended illness during the influenza outbreak. The lack of protection with IIV-T in our study may be because (1) most children who were younger than 9 years and had not previously received an influenza vaccine were able to receive only 1 dose of IIV-T during the outbreak, (2) IIV-T was associated with modest heterotypic protective antibody response to the variant A/Fujian/411/2002 (H3N2) epidemic virus, (3) MAARI and P&I during the outbreak were not sufficiently specific definitions for influenza, or (4) the reference group (children who never received an influenza vaccine) in the intervention communities was an inadequate comparison group for those who had received IIV-T. The reference group may not have been adequate for comparison with the IIV-T group because many of the IIV-T recipients had asthma or other chronic medical conditions compared with our reference group, who were mostly healthy children. Higher MAARI rates have been reported in IIV-T–vaccinated children with asthma compared with unvaccinated children with asthma, probably because of severity of underlying disease.³²

In our study, LAIV-T in children 5 to 18 years of age

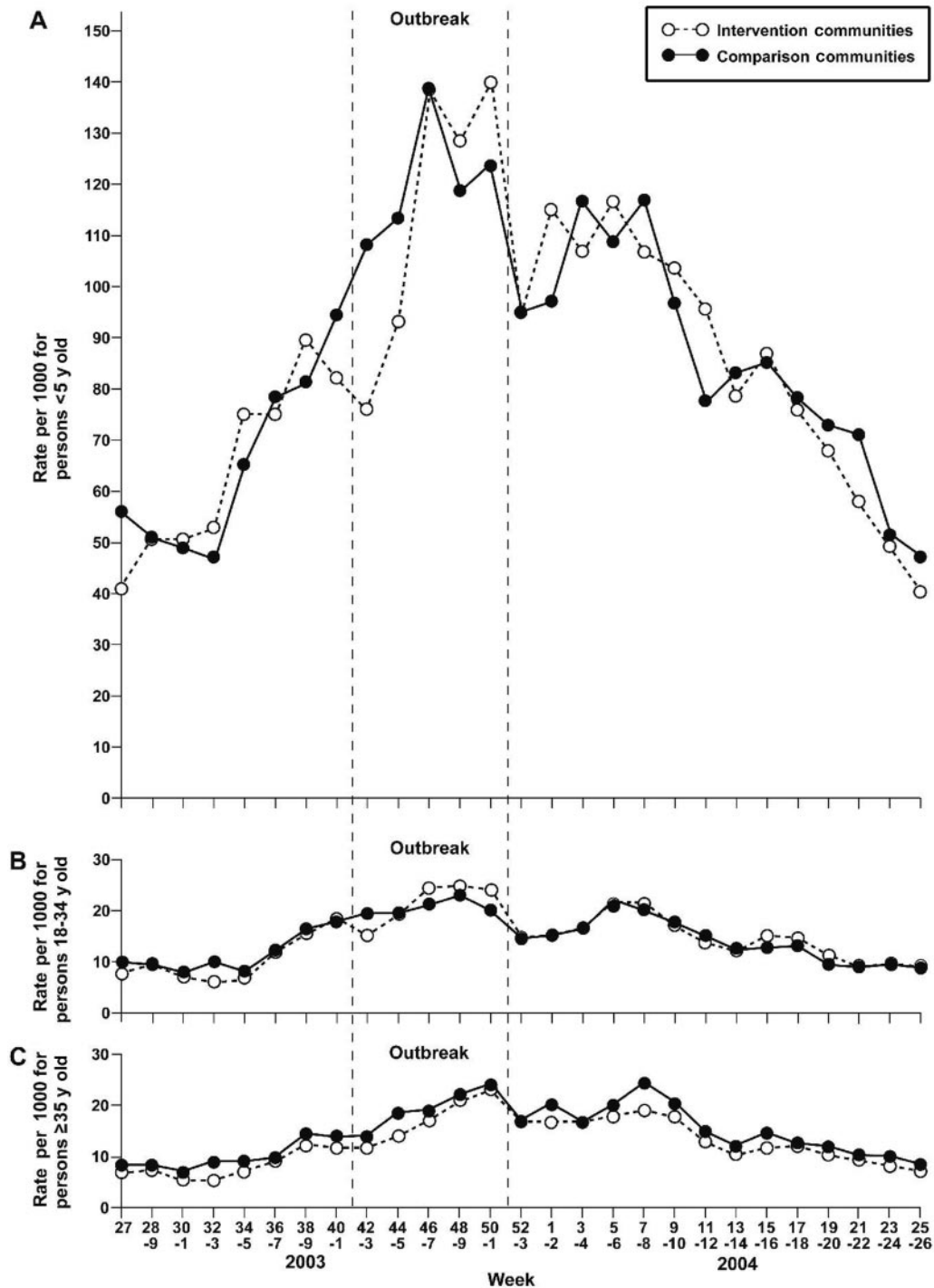


FIGURE 2

Biweekly MAARI rates in the intervention and comparison communities. Biweekly MAARI rates were determined for adults who were ≥ 35 years of age (A), adults who were 18 to 34 years of age (B), and children who were younger than 5 years of age (C) among SWHP members who resided in the intervention (\circ) and comparison communities (\bullet) during the 2003–2004 study year. The preepidemic period was defined from June 29 to October 11, 2003; the influenza outbreak occurred from October 12 to December 20, 2003; and the postepidemic period was from December 21, 2003, to July 3, 2004.

was associated with a vaccine effectiveness of 37.3% ($P < .05$) against influenza-positive medically attended febrile respiratory illness and of 50% (95% CI: 10%–80%) against P&I medically attended illness during the influenza outbreak. The LAIV-T effectiveness in children 5 to

9 years of age was 80% (95% CI: 40%–96%) against P&I medically attended illness despite that most of these children received only 1 dose of LAIV-T. In the initial phase III trial of LAIV-T in children who were 15 to 71 months of age and had never been vaccinated against

influenza, 1 dose of LAIV-T achieved an efficacy of 89% (95% CI: 65%–96%) for the prevention of culture-confirmed influenza compared with 94% (95% CI: 88%–97%) with 2 doses given ~60 days apart.²⁷ Before licensure of LAIV-T in the United States, we implemented a 1-dose annual regimen of LAIV-T in children 18 months to 18 years of age and showed it to be safe and effective against influenza-associated medically attended illnesses.^{24–26} It is not surprising that 1 dose of LAIV-T protected children against influenza. Other attenuated live virus vaccines, such as measles-mumps-rubella and varicella zoster, are administered once at 12 to 15 months of age for protection against infection. A subsequent booster later in life is required for waning of immunity. Live virus vaccines in general require fewer doses compared with inactive virus vaccines in children and generate a protective immune response similar to that of natural infection.⁴⁸

LAIV-T vaccinees had significant protection against influenza-positive acute febrile respiratory illness (Table 3). The percentage of LAIV-T vaccinees who were protected against influenza-positive acute febrile respiratory illness was similar for those who were infected within 1, 2, 3, or ≥ 4 weeks after vaccine administration, although the findings are limited by small numbers (Table 4). We speculate that LAIV-T may provide protection against influenza infection by both innate and adaptive immunity. LAIV-T induces influenza-specific serum and respiratory mucosal antibodies that are good correlates of immune protection.^{49,50} LAIV-T may interfere with wild-type influenza infection shortly after vaccine administration by eliciting an innate antiviral state for 1 to 2 weeks after vaccination. Influenza virus replication in the nasal mucosa produces proinflammatory cytokines such as interferons and tumor necrosis factor- α , which may be the first line of defense against influenza infection.^{51,52} The innate antiviral state that is produced by replication of LAIV-T in the upper respiratory tract may protect children from illnesses that are associated with influenza and other circulating respiratory viruses within the first weeks of vaccination. Protection against disease with wild-type influenza has been observed in the ferret model with co-administration of LAIV and wild-type influenza virus.⁵³ Results from an influenza challenge study performed in human volunteers suggested that LAIV induced an antiviral effect that protected against illness from an experimental challenge with wild-type influenza virus.⁵⁴ In an earlier study, we reported on the significant reduction in MAARI, otitis media/sinusitis, upper respiratory tract illness, and lower respiratory tract illness that sometimes occurred within the first 2 weeks after LAIV-T administration in children and before the onset of the influenza season.²⁶ Taken together, there is a growing body of evidence that supports that LAIV-T protects against influenza illness

shortly after administration possibly through stimulation of the innate antiviral immune response.

Several studies have documented the direct and indirect (herd protection) benefit against influenza by implementing an influenza vaccination program in preschool and school-aged children.^{18–22} We recently reported that vaccination coverage of 20% to 25% of age-eligible children was associated with an 8% to 18% reduction in MAARI rates in adults who were ≥ 35 years of age during the influenza season.²⁰ Our estimation of vaccination coverage was based on the US Census 2000 city population data. If we had used US Census data based on zip codes that defined the intervention communities, then the influenza vaccination coverage (LAIV-T and IIV-T) in the original report would have been reduced to 15.3% to 17.6%. In this report, we demonstrate that vaccination coverage of school-aged children based on US Census 2000 city population data overestimated the influenza vaccination coverage. A more accurate estimate was obtained using either US Census 2000 zip code data or 2003 Census data of school children who attended public schools in the intervention communities. Census defined by zip code increased the population by ~5000 children who were 5 to 18 years of age and reduced the influenza vaccination coverage from 40.6% to 31.5%. The influenza vaccination coverage of children who attended public schools in the intervention communities was 30.7% (vaccination coverage for children 5 to <9 years was 40.6% and for 10 to <19 years was 26.4%). Therefore, it seems that in this study, we achieved influenza vaccination coverage of ~31% in children 5 to 18 years of age. MAARI rates were available through administrative data sets for SWHP members who lived in the intervention and comparison communities. These data were used to estimate indirect effectiveness (herd protection) in the intervention communities attributed to our community-based influenza vaccination program in children 5 to 18 years of age. A 13% reduction in MAARI events during the influenza outbreak was detected in SWHP children who were 5 to 11 years of age and living in the intervention communities compared with SWHP children who were 5 to 11 years of age and residing in the comparison communities (Table 6). Herd protection was also observed in SWHP adults who were 35 to 44 years of age. LAIV-T was not provided by our program or through SWC in the comparison communities. Age-specific IIV-T coverage rates were comparable among individuals who used SWC in the intervention and comparison communities (Table 2), suggesting that IIV-T alone did not account for the herd protection that was observed in the intervention communities. Significantly lower MAARI rates were detected in adults who were ≥ 45 years of age before and after the influenza outbreak in the intervention communities. This may bias the significant reduction in MAARI that was experienced by adults who were

≥45 years of age during the 2003–2004 influenza outbreak in the intervention communities (Table 6). The reduction of MAARI risk noted before and after the 2003–2004 influenza outbreak may be consistent with a healthier SWHP adult population in the intervention communities. In future years, we will need to continue to evaluate for bias in estimates of indirect protection against influenza as it was recently demonstrated in observational studies conducted in elderly adults.^{55,56} However, it should be noted that herd protection was demonstrated for adults who were 35 to 44 years of age, who may have had most contact with children in the elementary schools who had the highest vaccine uptake.

CONCLUSIONS

Our community-based influenza vaccination program in children 5 to 18 years of age improved the influenza vaccination coverage in the intervention communities. One dose of LAIV-T administered to children 5 to 18 years of age during the influenza outbreak was well tolerated and associated with protection against influenza-positive febrile respiratory illness, direct effectiveness against P&I medically attended illness, and indirect effectiveness against MAARI. Protection provided by LAIV-T may have been attributed to a combination of both innate and adaptive immunity.

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Trivalent Live Attenuated Intranasal Influenza Vaccine Administered During the 2003 2004 Influenza Type A (H3N2) Outbreak Provided Immediate, Direct, and Indirect Protection in Children

Pedro A. Piedra, Manjusha J. Gaglani, Claudia A. Kozinetz, Gayla B. Herschler, Charles Fewlass, Dianne Harvey, Nadine Zimmerman and W. Paul Glezen
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Impact of maternal immunization on influenza hospitalizations in infants

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In the United States, influenza vaccination is universally recommended for all children 6 months-18 years of age due to the large burden of influenza hospitalizations and outpatient visits in this age group.¹ Infants <6 months of age have the highest rates of pediatric influenza hospitalizations,²⁻⁶ but none of the influenza vaccines are licensed for this age group.⁷⁻⁹ Hence, influenza vaccine is recommended for all close contacts of infants to reduce the likelihood of transmission.¹⁰ It is also recommended for pregnant women since they have an increased risk of influenza-related complications and hospitalizations, with the highest risk during the third trimester.¹¹⁻¹⁶ National data indicate that the proportion of pregnant women who received influenza vaccine has increased from a low of 9% in 2002 through 2003 to a high of 51% in 2009 through 2010 during the H1N1 influenza pandemic.^{1,17,18}

Influenza vaccination during pregnancy is primarily recommended to pro-

We sought to determine whether maternal vaccination during pregnancy was associated with a reduced risk of laboratory-confirmed influenza hospitalizations in infants <6 months old. Active population-based, laboratory-confirmed influenza surveillance was conducted in children hospitalized with fever and/or respiratory symptoms in 3 US counties from November through April during the 2002 through 2009 influenza seasons. The exposure, influenza vaccination during pregnancy, and the outcome, positive/negative influenza testing among their hospitalized infants, were compared using logistic regression analyses. Among 1510 hospitalized infants <6 months old, 151 (10%) had laboratory-confirmed influenza and 294 (19%) mothers reported receiving influenza vaccine during pregnancy. Eighteen (12%) mothers of influenza-positive infants and 276 (20%) mothers of influenza-negative infants were vaccinated (unadjusted odds ratio, 0.53; 95% confidence interval, 0.32–0.88 and adjusted odds ratio, 0.52; 95% confidence interval, 0.30–0.91). Infants of vaccinated mothers were 45-48% less likely to have influenza hospitalizations than infants of unvaccinated mothers. Our results support the current influenza vaccination recommendation for pregnant women.

Key words: infants, influenza hospitalization, influenza vaccine, maternal vaccination, vaccine effectiveness

tect pregnant women themselves. However, a recent randomized controlled trial from Bangladesh and an observational study among Native American

populations reported benefits of influenza vaccine both for mothers and their young infants.^{19,20} Influenza antibodies are efficiently transferred across the pla-

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Contents are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention.

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centa and have been observed to provide indirect protection to infants for the first 2-3 months of life, when infants are too young to receive influenza vaccine.^{20,21} We sought to determine whether maternal vaccination during pregnancy was associated with a reduced risk of laboratory-confirmed influenza hospitalizations in infants <6 months of age living in 3 geographically diverse US counties over 7 consecutive influenza seasons. We focused on influenza hospitalizations because they are associated with the highest costs and because most childhood deaths occur among hospitalized patients.^{22,23}

Materials and methods

The New Vaccine Surveillance Network, funded by the Centers for Disease Control and Prevention, conducted active, population-based, laboratory-confirmed influenza surveillance among children hospitalized with influenza in 3 US counties: Davidson County, Tennessee (Nashville); Hamilton County, Ohio (Cincinnati); and Monroe County, New York (Rochester).² Children were eligible for enrollment if they were hospitalized with fever and/or acute respiratory symptoms during the winter from November through April and resided within these 3 counties. Seven consecutive influenza seasons were included: 2002-2003 through 2008-2009 in Nashville, TN, and Rochester, NY, and 2003-2004 through 2008-2009 in Cincinnati, OH. In 2008 through 2009, the seasonal influenza season ended in April 2009, which was prior to the detection of H1N1 in this network.

All enrolled children had nasal and throat swabs obtained for viral culture and/or reverse transcription polymerase chain reaction for influenza A or B as previously described.²⁴ Parents of enrolled children had a standardized questionnaire administered to ascertain presenting symptoms and their duration, birth and medical history, history of maternal influenza vaccination during pregnancy with the enrolled child, and social history. The medical record was reviewed after discharge.

The study population comprised inpatients <6 months of age enrolled

through hospital surveillance with fever and/or acute respiratory symptoms during 1 of the 7 consecutive influenza seasons. Most infants were enrolled as inpatients although some were enrolled as outpatients and subsequently hospitalized. For infants with multiple hospitalizations during an influenza season, only the first hospitalization during the study period was included. Each influenza season was defined as the period spanning the first to last influenza-positive nasal/throat swab among all study infants. Since the opportunity for the mother to receive the influenza vaccine varied by birth month, we divided each influenza season into early, middle, and late season tertiles, based on the day of enrollment of influenza-positive infants. A control group of hospitalized infants without laboratory-confirmed influenza were assigned to early, middle, and late tertiles by comparing their dates of enrollment with the influenza-positive cases.

The primary exposure variable was maternal influenza vaccination status during pregnancy, and the primary outcome variable was the presence or absence of laboratory-confirmed influenza among their hospitalized infants. Categorical variables that can influence hospitalizations in general and thus could potentially influence influenza-related hospitalizations in infants were compared by χ^2 analysis. For adjusted analyses, we created 3 multivariate logistic regression model analyses a priori based on demographic, medical, and social risk factors previously shown to be associated with increased risk of influenza or respiratory hospitalizations.^{2,3,5,25-29} The core demographic model included the following covariates: age, sex, race/ethnicity, site, study year, and tertile of the influenza season. The second model evaluated the core demographic model and 2 medical covariates: prematurity and presence of any high-risk medical conditions in the infant for which influenza vaccine was recommended in persons ≥ 6 months of age.¹⁶ The third model included the core demographic model and 5 additional variables: smoke exposure at home, number of siblings (0 to ≥ 3), day care attendance, insurance status (public/private/none), and whether the in-

fant was ever breast-fed. All model covariates were treated as categorical variables. Confidence intervals (CI) were calculated at the 95% level; P values $\leq .05$ were considered statistically significant. All analyses were computed using STATA software 10.0 (StataCorp, College Station, TX).

From 2005-2006 through 2008-2009, we asked mothers of young infants if they had an influenza-like illness during pregnancy because an influenza illness during pregnancy could lead to the development of protective antibodies for that influenza serotype in the infant. Hence, we performed a subanalysis of the unadjusted and the 3 adjusted models described above to determine the protective effect of either maternal vaccination for all years or influenza-like illness during pregnancy from the last 4 years of the study period.

Human and nonhuman experimentation

The study was approved with informed consent from the parent or guardian by the institutional review boards at each site and the Centers for Disease Control and Prevention.

Results

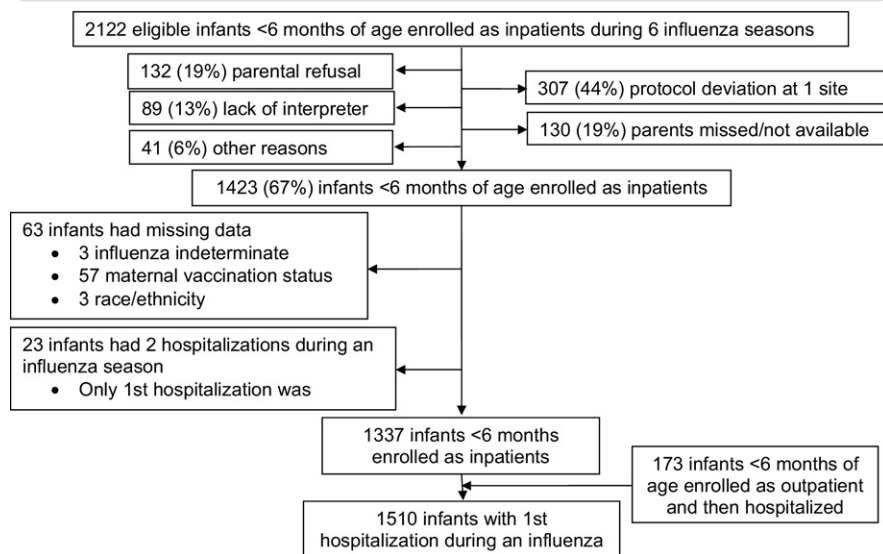
Over 7 influenza seasons, 2122 hospitalized infants were eligible for enrollment in the 3 New Vaccine Surveillance Network sites and 1423 (67%) of the eligible infants were included from the inpatient setting (Figure 1). Reasons for exclusion were 307 (44%) protocol deviations at Cincinnati, OH, 132 (19%) parental refusal, 130 (19%) parents missed or not available, 89 (13%) lack of language translator, 38 (5%) discharged prior to being approached, and 3 (<1%) physician refusal. Of these 1423 hospitalized and enrolled infants, 57 (4%) had unknown or missing maternal influenza vaccination status, 3 (0.2%) had indeterminate influenza status (ie, negative RNA control), 3 (0.2%) had unknown race/ethnicity, and 23 (2%) represented a second study hospitalization during the influenza season and were excluded from analysis. The overall study population comprised these 1337 eligible infants enrolled solely from the inpatient setting and an additional 173 eligible in-

infants who were hospitalized following enrollment in the emergency department and fulfilled all inpatient enrollment criteria. Among these 1510 infants hospitalized with fever and/or respiratory symptoms during the influenza season (Table 1), 151 (10%) had laboratory-confirmed influenza—with 136 (90%) influenza A and 15 (10%) influenza B. Among all hospitalized infants, a higher proportion of infants <2 months than those 2 to <6 months of age were influenza positive. The proportion of infants who were influenza positive varied significantly across study years, ranging from 3% in 2006 through 2007 to 15% in 2003 through 2004.

A total of 294 (19%) mothers reported that they had received the influenza vaccine during that pregnancy (Table 2). This proportion varied by influenza season, ranging from 10% in 2003 through 2004 to 38% in 2008 through 2009, and by age of the infant at the time of enrollment during the influenza season, ranging from 24% for neonates <1 month of age to 9% for infants 4–5 months of age. The proportion of infants whose mothers were vaccinated varied from only 13–15% at the Cincinnati, OH, and Nashville, TN, sites up to 33% at the Rochester, NY, site. The proportion of infants whose mothers were vaccinated was 15% for blacks, 21% for whites, and 22% for Hispanics. Infants with private insurance were more likely to have a vaccinated mother than those with public or no insurance. Breast-fed infants were more likely to have mothers who reported being vaccinated than infants of mothers who never breast-fed. Non-smoking households had a higher proportion of infants whose mothers were vaccinated than households with a smoker.

Among influenza-positive infants during all study years, 12% of their mothers reported influenza vaccination during pregnancy, while among influenza-negative infants, 20% of their mothers reported influenza vaccination, yielding an unadjusted odds ratio (OR) of 0.53 (95% confidence interval [CI], 0.32–0.88). Similar results were obtained in the 3 multivariate models shown in Figure 2. Since a significant proportion of data from Cincinnati,

FIGURE 1
Study population



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OH, was excluded for protocol violations, a sensitivity analysis that included only Rochester, NY, and Nashville, TN, data was performed and yielded similar results to the combined data. In the core demographic model, adjusting for age, sex, race/ethnicity, site, study year, and early, middle, or late influenza season, the OR for having an influenza-positive, hospitalized infant among vaccinated mothers was 0.55 (95% CI, 0.32–0.95). Model 2 included the core demographic model plus prematurity and high-risk conditions and had an OR of 0.55 (95% CI, 0.32–0.94). These medical covariates did not impact the estimate and were not included in the third model. Model 3 included the core demographic model, exposure to smoke, siblings, day care, insurance, and presence of breastfeeding and had an OR of 0.52 (95% CI, 0.30–0.91). As shown, adjustments for covariates did not affect the results substantially. Overall, results of the multivariate modeling suggest that maternal vaccination reduced the risk of influenza by 45–48%.

A total of 110 mothers from 2005–2006 through 2008–2009 reported a history of influenza-like illness during pregnancy, of which 81 (74%) had not received the influenza vaccine during that pregnancy. In a subanalysis combining both maternal influenza vaccination for all 7 years and a his-

tory of an influenza-like illness during pregnancy for 4 years, we found that the unadjusted and adjusted estimates were similar with a 45–49% reduced risk of influenza in the infant.

Comment

Our results indicate that hospitalized infants whose mothers received influenza vaccine during pregnancy were 45–48% less likely to have laboratory-confirmed influenza during their first influenza season compared with infants of unvaccinated mothers. Adding history of influenza-like illness during pregnancy to the analyses had little impact on the OR for having an influenza-positive, hospitalized infant. Given that infants <6 months of age have the highest hospitalization rate among all children^{2–6} and that the vaccine is not licensed for that age group,¹⁶ these data support that infants born to vaccinated mothers benefit from the transfer of maternally derived antibodies.

Four previously published studies support our conclusions. First, a prospective, observational study among Native Americans from 2002 through 2005 found that infants of vaccinated mothers had a 41% reduction of the risk of laboratory-confirmed influenza infection in the inpatient and outpatient settings as

TABLE 1
Characteristics of infants <6 months of age hospitalized with and without laboratory confirmed influenza

Characteristic	Total n = 1510	(row %)		P value
		Influenza + n = 151	Influenza - n = 1359	
Maternal influenza vaccine				
No	1216	133 (11%)	1083 (89%)	.01
Yes	294	18 (6%)	276 (94%)	
Influenza season				
Early	572	51 (9%)	521 (91%)	.51
Middle	485	50 (10%)	435 (89%)	
Late	453	50 (11%)	403 (89%)	
Age group, mo				
0	399	49 (12%)	350 (87%)	< .001
1	507	66 (13%)	441 (87%)	
2-3	411	24 (6%)	387 (94%)	
4-5	193	12 (6%)	181 (94%)	
Sex				
Female	664	68 (10%)	596 (90%)	.78
Male	846	83 (10%)	763 (90%)	
Study site				
Nashville, TN	554	60 (11%)	494 (89%)	.53
Rochester, NY	425	44 (10%)	381 (90%)	
Cincinnati, OH	531	47 (9%)	484 (91%)	
Study year				
2002-2003	99	9 (9%)	90 (91%)	< .001
2003-2004	251	38 (15%)	213 (84%)	
2004-2005	322	40 (12%)	282 (88%)	
2005-2006	176	16 (9%)	160 (91%)	
2006-2007	230	8 (3%)	222 (97%)	
2007-2008	232	29 (13%)	203 (88%)	
2008-2009	200	11 (6%)	189 (95%)	
Race/ethnicity				
White	706	59 (8%)	647 (92%)	.11
Black	439	53 (12%)	386 (88%)	
Hispanic	365	39 (11%)	326 (89%)	
Medical covariates				
Premature				
Yes	178	13 (7%)	165 (93%)	.20
No	1325	138 (10%)	1187 (90%)	
High-risk condition				
Yes	119	7 (6%)	112 (94%)	.12
No	1391	144 (10%)	1247 (90%)	

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determined by viral culture or antibody titers (relative risk, 0.59; 95% CI, 0.37–0.93).²⁰ A second study, a randomized controlled trial of maternal influenza vaccination during pregnancy, was conducted in Bangladesh in 2004 through 2005. In this tropical country with year-round influenza circulation, investigators reported fewer rapid test–confirmed influenza cases among infants of mothers who received influenza vaccine compared with infants of unvaccinated mothers (6 vs 16 infants, respectively) for a vaccine effectiveness estimate of 63% (95% CI, 5–85%). Among 110 infants in the influenza vaccine group and 153 infants in the control group, vaccine effectiveness against unspecified respiratory illness with fever was 29% (95% CI, 7–46%).¹⁹ Third, a matched case-control study compared hospitalized infants with physician-ordered direct fluorescent antibody for seasonal influenza from 2000 through 2009. Cases with a positive influenza test result and controls with a negative test result were matched by date of birth and date of hospitalization. Maternal vaccinations were included only if they were confirmed and given at least 14 days prior to delivery. Effectiveness of maternal vaccination among infants <6 months of age was reported to be 91.5% (95% CI, 62–98%).³⁰ Fourth, a Northern California Kaiser Permanente database study over 5 influenza seasons (1997 through 2002), found that maternal vaccination was associated with a decreased risk of pneumonia or influenza hospitalization in their infants with an adjusted hazard ratio of 0.63 (95% CI, 0.30–1.29), translating into 37% protection.³¹ Our 95% CIs for protection of maternal vaccination from influenza hospitalizations among infants <6 months of age overlap those from each of these studies.

Our study differs from the previously published studies in several ways. First, we included 7 consecutive influenza seasons and used prospective, population-based and laboratory-confirmed surveillance to identify eligible infants. By systematically testing all eligible infants using culture and molecular methods to define influenza infections, we utilized sensitive and specific methods and

avoided the biases associated with physician-ordered testing; the study utilizing physician-ordered testing to identify eligible infants had a much higher proportion of infants with high-risk conditions than our study population. Second, we focused on hospitalizations whereas 2 previous studies included more outpatient visits than hospitalizations. Third, we included 3 diverse geographic regions of the United States whereas all previous studies reported data from 1 geographic region.

Our study has several limitations. Although we enrolled a large proportion of eligible infants, a number of them had to be excluded because of protocol violations, and infants who were and were not included in the study population could have systematically differed. Neither confirmed influenza vaccination status nor documented influenza disease status was available from mothers, and serologic assays were not performed on either infants or mothers. Since the study focused on hospitalized infants and not those seen only in the outpatient clinic or emergency departments, the generalizability of these results to outpatient settings is unknown. However, admission criteria for infants with fever and respiratory symptoms change over the first few weeks of life, so limiting the study population to solely inpatients allowed us to focus on severe outcomes.

Our estimates of maternal vaccination are consistent with national estimates¹⁷ and lower than estimates from one health care system that implemented interventions to increase their maternal vaccination rates.³² We have previously reported higher influenza vaccine coverage among children 6-59 months of age in Rochester, NY, than in Nashville, TN, or Cincinnati, OH.³³ Because of this consistent pattern, these differences seem to reflect geographical differences in influenza vaccination patterns. We found higher rates of maternal vaccination when the infant had private insurance compared with public or no insurance. This differs from the seasonal influenza vaccine coverage reported by the Rhode Island Pregnancy Risk Assessment Monitoring System, which found similar coverage between women with

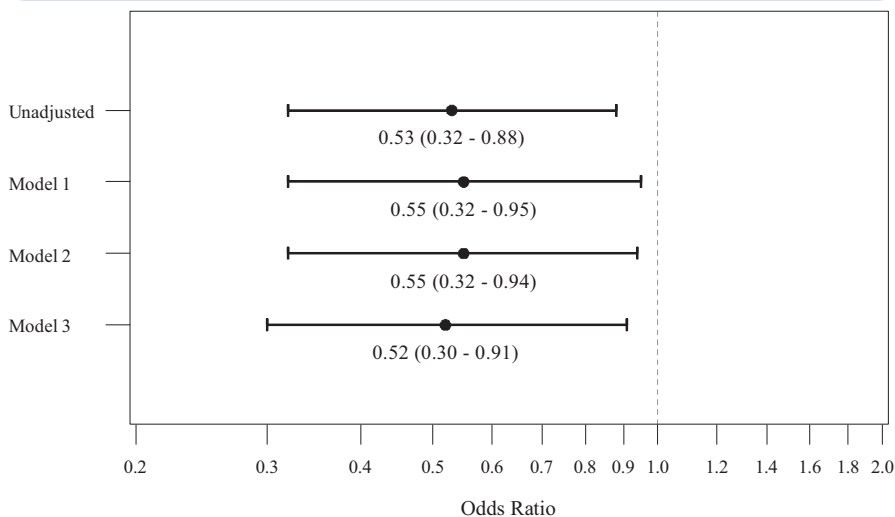
TABLE 1
Characteristics of infants <6 months of age hospitalized with and without laboratory confirmed influenza (continued)

Characteristic	Total n = 1510	(row %)		P value
		Influenza + n = 151	Influenza - n = 1359	
Social covariates				
Exposed to smoke				
Yes	613	62 (10%)	551 (90%)	.85
No	896	88 (10%)	808 (90%)	
No. of siblings				
0	341	33 (10%)	308 (90%)	.10
1	539	42 (8%)	497 (92%)	
2	341	43 (13%)	298 (87%)	
≥3	289	33 (11%)	256 (89%)	
Day care				
Yes	152	7 (5%)	145 (95%)	.02
No	1356	144 (11%)	1212 (89%)	
Insurance				
Public	891	94 (11%)	797 (89%)	.67
Private	507	46 (9%)	461 (91%)	
None	105	10 (10%)	95 (90%)	
Ever breast-fed				
Yes	916	97 (11%)	819 (89%)	.34
No	594	54 (9%)	540 (91%)	

Percentages may not sum to 100% due to rounding.

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FIGURE 2
Infant protection from maternal vaccination



Odds ratio and 95% confidence interval for protection provided by influenza vaccination during pregnancy on laboratory-confirmed influenza hospitalizations among infants for unadjusted and adjusted models.

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TABLE 2
Characteristics of hospitalized infants <6 months of age by maternal influenza vaccination status

Characteristic	Total n = 1510	(row %)		P value
		Vaccinated n = 294	Not vaccinated n = 1216	
Influenza-positive				
No	1359	276 (20%)	1083 (80%)	.01
Yes	151	18 (12%)	133 (88%)	
Influenza season				
Early	572	98 (17%)	474 (83%)	.06
Middle	485	92 (19%)	393 (81%)	
Late	453	104 (23%)	349 (77%)	
Age group, mo				
0	399	96 (24%)	303 (76%)	< .001
1	507	92 (18%)	415 (82%)	
2-3	411	88 (21%)	323 (79%)	
4-5	193	18 (9%)	175 (91%)	
Sex				
Female	664	123 (19%)	541 (81%)	.41
Male	846	171 (20%)	675 (80%)	
Study site				
Nashville, TN	554	84 (15%)	470 (85%)	< .001
Rochester, NY	425	142 (33%)	283 (67%)	
Cincinnati, OH	531	68 (13%)	463 (87%)	
Study year				
2002-2003	99	18 (18%)	81 (82%)	< .001
2003-2004	251	25 (10%)	226 (90%)	
2004-2005	322	43 (13%)	279 (87%)	
2005-2006	176	31 (18%)	145 (82%)	
2006-2007	230	45 (20%)	185 (80%)	
2007-2008	232	57 (25%)	175 (75%)	
2008-2009	200	75 (38%)	125 (63%)	
Race/ethnicity				
White	698	147 (21%)	551 (79%)	.005
Black	430	63 (15%)	367 (85%)	
Hispanic	363	80 (22%)	283 (78%)	
Medical covariates				
Premature				
Yes	178	33 (19%)	145 (81%)	.73
No	1325	260 (20%)	1065 (80%)	
High-risk condition				
Yes	119	22 (18%)	97 (82%)	.78
No	1391	272 (20%)	1119 (80%)	

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public and private insurance. Given that obstetrician-gynecologists have consistently identified financial costs as a major barrier to influenza vaccination of pregnant women,³⁴⁻³⁶ it is possible that differences in vaccine coverage between public and private insurance vary geographically.

Maternal vaccination during pregnancy is recommended since pregnant women have an increased risk of influenza-associated morbidity and mortality.¹¹⁻¹⁵ However, despite this recommendation, pregnant women have traditionally had the lowest influenza vaccine coverage of any group for whom influenza vaccine is specifically recommended.¹⁷ Although most (84.5%) obstetricians support influenza vaccination of all pregnant women,³⁴ few mothers (20%) report being offered influenza vaccination during pregnancy.³⁷ Obstetricians play a critical role in the influenza vaccination coverage of pregnant women. For first pregnancies, obstetricians are often the only medical professional seeing the pregnant women; for subsequent pregnancies, pregnant women may see the pediatrician, however, pediatricians do not tend to vaccinate pregnant women since they are not their patients. Half of all pregnant women who received the monovalent H1N1 vaccine in 2009 through 2010 reported receiving it in the obstetrician-gynecologist office and none reported receiving it in a pediatric office.¹⁸

Because numerous studies have demonstrated comparable or increased influenza antibody titers in the cord blood when compared with maternal levels,^{3,38-43} maternal vaccination should afford some protection of newborn infants against influenza and is supported by our study. Similar to other studies, we found between 45% and 48% protection against laboratory-confirmed influenza hospitalizations among infants whose mothers reported receiving influenza vaccine during pregnancy. Using data from our earlier studies of 4.5 influenza-attributable hospitalizations among 1000 infants <6 months of age² and census data of 4,251,095 live-births in the United States in 2008,⁴⁴ we project that there are an average of 19,130 influenza-attributable hospitalizations among infants <6 months of age per year. A 45-48% reduction in this burden would yield an estimated 8600-9200

TABLE 2
Characteristics of hospitalized infants <6 months of age by maternal influenza vaccination status (continued)

Characteristic	Total n = 1510	(row %)		P value
		Vaccinated n = 294	Not vaccinated n = 1216	
Social covariates				
Exposed to smoke				
Yes	613	83 (14%)	530 (86%)	< .001
No	896	211 (24%)	685 (76%)	
No. of siblings				
0	341	75 (22%)	266 (78%)	.32
1	539	108 (20%)	431 (80%)	
2	341	64 (19%)	277 (81%)	
≥3	289	47 (16%)	242 (84%)	
Day care				
Yes	152	29 (19%)	123 (81%)	.89
No	1356	265 (20%)	1091 (80%)	
Insurance				
Public	891	146 (16%)	745 (84%)	< .001
Private	507	137 (27%)	370 (73%)	
None	105	8 (8%)	97 (92%)	
Ever breast-fed				
Yes	916	207 (22%)	709 (77%)	< .001
No	594	87 (15%)	507 (85%)	

Percentages may not sum to 100% due to rounding.

Poehling. Maternal influenza immunization and their infants. *Am J Obstet Gynecol* 2011.

fewer influenza-attributable hospitalizations among young infants each year. Thus, our findings suggest that influenza vaccination of pregnant women may reduce the risk of influenza-attributable hospitalization among infants in the first 5 months of life, further supporting the current influenza vaccination recommendations for pregnant women. ■

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Influenza Vaccination of Healthcare Personnel

CME EDUCATIONAL OBJECTIVES

1. Review the evidence supporting recommendations for annual influenza vaccination in all healthcare providers.
2. Discuss the current vaccination coverage rates in healthcare providers and identify barriers to achieving better coverage.
3. Identify strategies to improve influenza vaccination coverage rates among healthcare providers.

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The U.S. Centers for Disease Control and Prevention (CDC) has recommended influenza vaccination for all healthcare providers (HCPs) since 1981. Since then, healthcare organizations across the

country have established voluntary programs to provide influenza vaccine to HCPs in an effort to protect the lives and health of the staff and their patients. Between 1989 and 2003, HCP vaccination coverage lev-

els in the U.S. increased from 10% to ~40%; however, coverage levels have remained relatively constant since 1997. Despite compelling reasons for universal influenza immunization of all HCPs, only 45% received influen-

Christy M. Tabarani, MD; and Joseph B. Domachowske, MD

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SIDEBAR.

Dr. Poland's Seven Truths

1. Influenza is a serious illness adversely affecting the public health on an annual basis.
2. Healthcare providers can transmit influenza to their patients.
3. Influenza vaccination of healthcare providers saves money for employees and prevents workplace disruption.
4. Influenza vaccination of HCP is the standard of care.
5. Immunization requirements are effective in increasing vaccination rates.
6. HCP and the healthcare system in general have an ethical duty to protect patients from transmissible diseases.
7. The healthcare system with either lead or be lambasted.

Modified from Poland GA, Tosh P, and Jacobson RM. *Vaccine*. 2005;23:2251-2255.²

za vaccination in 2007.¹ To frame the problem and its potential solutions, several questions must be considered. First, why is annual influenza immunization recommended for this group of individuals? When the vaccine is accepted, why do HCPs receive it? When providers "opt out" of receiving the vaccine, why have they chosen to do so? What influenza vaccines are available, and which ones can be given to healthcare providers? What are the current influenza vaccine coverage rates in HCPs? And finally, how can we improve our immunization coverage rates in this population? Each of these questions will be considered.

WHY IS ANNUAL INFLUENZA IMMUNIZATION RECOMMENDED FOR ALL HEALTHCARE PROVIDERS?

Physicians and nurses are usually the focus of attention when considering the topic of influenza vaccination in HCPs; however, a HCP is much less strictly defined and includes anyone who may interact with patients during

the work day. As such, HCPs might include (but are not limited to) physicians, nurses, nursing assistants, therapists, technicians, emergency medical service personnel, dental personnel, pharmacists, laboratory personnel, autopsy personnel, students and trainees, contractual staff not employed by the healthcare facility, and those such as administrators, office assistants, dieticians, housekeeping and catering staff, maintenance workers, and volunteers not directly involved in patient care but potentially exposed to influenza in their work environment. The definition of a "healthcare facility" is also quite broad, including hospitals, long-term care facilities, off-site clinics, and private offices.

The reasons that all HCPs should receive annual seasonal influenza vaccine are both complex and compelling. In 2005, Drs. Greg Poland, Prithish Tosh, and Robert Jacobson published an article in the journal *Vaccine*, "Requiring influenza vaccination for health care workers: seven truths we must accept."² The seven truths, paraphrased in the Sidebar, build a compelling argument for mandatory influenza vaccination for all HCPs. Although we are still far from a healthcare environment in which "no vaccine" translates to "no job," the seven points discussed by Dr. Poland and colleagues ring true because they outline our collective failure to optimize influenza vaccine coverage rates in HCPs and provide some serious suggestions on how to move forward.

Most medical providers understand that influenza can be transmitted to patients and other employees by both symptomatic and asymptomatic individuals. Staying home from work when ill is an important message to convey to each other and to our coworkers. However, it is an insufficient strategy for preventing nosocomial transmission of influenza because an individual can transmit infection to

susceptible contacts for at least 24 hours before the acute onset of fever, headache, and chills.^{3,4} Studies also reveal that many HCPs continue to work despite being ill with influenza, increasing the potential of exposing patients and coworkers.⁵⁻⁷ Complications of nosocomial influenza are particularly burdensome on the elderly, the immunocompromised, the critically ill, and young children — the very populations most likely to be found in hospitals and medical clinics. Infection in these populations can result in severe, prolonged illness, increased length of hospital stay, and death.^{3,8,9}

For example, during an influenza A outbreak in a neonatal intensive care unit in 1998, 19 of the 54 patients on the ward tested positive for influenza A. Of these 19, six were symptomatic, and one died. Only 15% of the HCPs had received the influenza vaccine, including 67% of the physicians and 9% of the nurses. Only 29% of staff with symptomatic influenza took time off from work.¹⁰

The problem is mirrored in adult medicine. A Scottish study compared patient mortality rates between long-term care hospitals that offered influenza vaccination to HCPs, in which 51% were vaccinated, with mortality in hospitals that did not offer vaccine, in which only 5% were vaccinated. They demonstrated an almost 40% reduction in all-cause mortality among the patients cared for by the HCPs in the hospitals with higher levels of healthcare worker influenza vaccination.¹¹ In addition to the patient safety imperative, vaccination of healthy adults also decreases work absenteeism and use of healthcare resources, particularly when the vaccine and circulating viruses are well-matched.^{5,12-17}

To assess the effect of influenza on acute care hospitals, the CDC conducted a Web-based survey of hospital epidemiologists in 221 institutions from all regions in the United States from

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December 2003 to February 2004. In this survey, 35% of hospitals reported staffing shortages during the peak of influenza season. Stated quite simply, influenza vaccination of HCPs saves money for employees and employers, prevents workplace disruption, and represents an important ethical and moral duty for those who choose to work in the healthcare field.

WHAT INFLUENZA VACCINES ARE AVAILABLE, AND WHICH ONES CAN BE GIVEN TO HEALTHCARE PROVIDERS?

Both live-attenuated seasonal influenza vaccine (LAIV) and trivalent inactivated influenza vaccine (TIV) contain three strains of influenza viruses that are antigenically equivalent to the annually recommended strains: one influenza A (H3N2) virus, one influenza A (H1N1) virus, and one influenza B virus. Each year, one or more virus strains in the vaccine is changed on the basis of global surveillance for influenza viruses and the emergence and spread of new strains. Therefore, each year, influenza vaccines are reformulated based on the strains predicted to circulate in the Northern hemisphere. Annual, seasonal vaccination is administered to provide optimal protection against strains that are predicted to circulate in the coming months, not because of rapid decline in vaccine-associated protective immunity.

Both LAIV and TIV are widely available in the United States. Although both types of vaccines have been shown to be effective, the vaccines differ in several respects. LAIV contains live, attenuated viruses that have the potential to cause mild signs or symptoms such as runny nose, nasal congestion, or sore throat. TIV contains inactivated viruses, and because it is injected, complaints such as swelling, redness, or discomfort are common. LAIV is administered intranasally by spray, whereas TIV is

administered intramuscularly by injection. LAIV is licensed for use among nonpregnant patients 2 to 49 years; safety has not been established in those with underlying medical conditions who confer a higher risk of influenza complications. TIV is licensed for use among patients older than 6 months, including those who are healthy and those with chronic medical conditions.



Both LAIV and TIV are widely available in the United States.

The efficacy of TIV in working adults is well established. Although a detailed discussion of influenza vaccine efficacy and effectiveness is beyond the scope of this review and appears elsewhere in this issue, a recent comparison study between LAIV and TIV in adults in preventing laboratory-documented influenza showed similar rates of protection.^{18,19} Either LAIV or TIV can be administered to most healthy, nonpregnant HCPs younger than 50 years. For HCPs who are 50 years and older, pregnant, have underlying chronic medical conditions, or who work directly with a severely immunocompromised population, such as patients undergoing hematopoietic stem cell transplantation, TIV should be used. LAIV is an attractive option for individuals who are particularly anxious about injections.

WHEN THE INFLUENZA VACCINE IS ACCEPTED, WHY DO HEALTHCARE PROVIDERS DECIDE TO RECEIVE IT?

To gain insight and understanding on why our influenza immunization rates among HCPs remain low, it is important to ascertain reasons why many decide to receive vaccine. Although more than 75% of physicians, nurses, and medical students who are immunized state that they do so because they do not want to get influenza, only 60% of technicians and health aides reason that they get vaccinated to prevent personal illness.²⁰ Ongoing efforts to educate HCPs on the patient safety imperative of receiving influenza vaccine have surely shown results because 78% of physicians state that they get immunized because they understand that they could transmit influenza to their patients. Efforts must continue, however, as fewer than two-thirds of nurses, medical students, technicians, aides, and administrative workers admitted to getting immunized to protect their patients. Convenient, free access is another primary reason that many HCPs accept influenza immunization.²⁰

WHEN PROVIDERS "OPT OUT" OF RECEIVING THE VACCINE, WHY HAVE THEY CHOSEN TO DO SO?

The primary barriers to widespread, seasonal, annual influenza vaccine for all HCPs include misconceptions about influenza illness and its risks, the role of HCPs in its transmission to patients, and the importance and true risks of vaccination. Although local reactions, such as injection site pain, redness, or swelling, are common (15% to 20% of immunized individuals), the majority of these reactions are self-limiting and mild. Fever and malaise are not common side effects of influenza vaccine, and influenza illness does not occur as a vaccine consequence. Because of the nature and timing of seasonal influenza vaccine programs, the development of respiratory viral infections (during "cold and flu season")

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is expected to coincide with having received the influenza vaccine. When this occurs, the immunized individual might be left with the notion that the vaccine caused the illness, when in fact the respiratory tract infection would have occurred whether they were immunized or not. Although this explanation seems logical and intuitive to physicians, many non-physician HCPs continue to assert that the flu shot gave them the “flu.”

Severe adverse reactions to influenza immunization are very uncommon. For example, anaphylactic allergic reactions, known to occur with any vaccine, are rare, with an estimated rate of less than one per million vaccinees. More than 3 decades ago, we learned that approximately one excess case of Guillain-Barré syndrome occurred per 100,000 vaccinated with the 1976 “swine influenza” vaccine. Ongoing vaccine safety surveillance indicates that, if this very rare association between Guillain-Barré syndrome and influenza immunization exists, it occurs in fewer than one case per million immunized.

Among the HCPs that reject or refuse influenza vaccine, nearly one in four do so because they “never get the flu.” Many who opt out say they decline vaccine because of vaccine shortage. Still others have concerns about vaccine side effects — a reason voiced more commonly by nurses, technicians, and aides (35%) than by physicians (17%). One-third of unimmunized medical students said it was “too inconvenient” to get vaccinated. Eighteen percent of physicians said they simply “forgot.”²³ Additional reasons for declining vaccination include medical contraindications (such as egg allergy), insufficient time, or needle avoidance.

Given the known reasons that HCPs accept or reject annual influenza vaccine, it is intuitive that education efforts need to be sustained. Physicians, our colleagues, coworkers, students, and families need to understand that

influenza vaccines are highly effective and protect our patients. The true adverse effects known to occur after influenza vaccine should be acknowledged and the usual misconceptions explained. In our practice settings, hospital and office alike, influenza illness is common. Transmission to our susceptible patients and coworkers can largely be prevented through routine annual immunization and close attention to infection control practices and hygiene.

WHAT ARE THE INFLUENZA VACCINE COVERAGE RATES IN HEALTHCARE PROVIDERS?

One of the CDC Healthy People 2010 objectives is to achieve HCP influenza vaccination coverage levels of 60%.²¹ We clearly have much work to realize this goal. In 2007, 45% of U.S. HCPs were immunized against influenza, but a comprehensive literature review of 32 studies performed to assess influenza vaccination coverage in HCPs between 1985 and 2002 in North America and Europe showed rates between 2% and 82%. This e-publication by the U.S. Health and Human Services indicates that high rates of coverage are, indeed, feasible. Identifying the specific reasons why some areas were highly successful, and other were not, has proven more difficult. Experts agree that education remains the most important aspect of any influenza vaccination campaign, but the data indicate that the strongest motivation to receive vaccine was to protect oneself. It is important to recognize that a popular secondary reason for HCPs to get immunized was a motivation to protect their patients.

HOW DO WE IMPROVE OUR IMMUNIZATION COVERAGE RATES IN HEALTHCARE PROVIDERS?

National HCP influenza vaccine coverage rates are still less than 50%

despite substantial efforts at improvement for more than 2 decades. It has become clear that single-action interventions have minimal effectiveness in achieving desired results.^{2,22} The most highly successful HCP vaccination programs are multifaceted and combine one or more of the following strategies, most often with an emphasis on education.

Education

Ongoing initiatives to educate HCPs regarding the safety and efficacy of influenza vaccine, and to clarify the common misconceptions about influenza vaccine and influenza illness, improve immunization rates. Structured in-service education or conferences are also helpful.^{23,24}

Role Models

Immunization of senior medical staff and/or opinion leaders is associated with higher vaccination acceptance among staff members.²⁵⁻²⁸

Improved Access to Vaccine

Influenza vaccine should be free and offered at convenient times during the regular work day.²⁹ Making vaccine readily accessible at common areas such as hospital wards or outpatient clinics, during/after conferences, or through use of a mobile cart vaccine delivery team has been demonstrated to improve vaccination coverage rates.³⁰⁻³³

Measurement and Feedback

HCP influenza vaccination coverage should be regularly measured and reported back to the entire team. Reasons for vaccine declination need to be assessed. Educational initiatives should address any common “themes” that recur.

LEGISLATION AND REGULATION

Should influenza vaccination of HCPs be mandated? Legislative and regulatory efforts have affected hepati-

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tis B vaccination rates favorably among HCPs.^{34,35} Fifteen states have enacted regulations regarding influenza vaccination of staff in long-term care facilities, six states require that the facilities offer influenza vaccine to all of their employees, and four states require that HCP either receive influenza vaccine or indicate a religious, medical, or philosophical reason for not being vaccinated.³⁶ Legislation directed toward hospitals is less inclusive³⁷ but is expected to result in incremental increases in coverage rates. Given the long history and extensive efforts of implementing influenza vaccination programs for HCPs, immunization rates higher than 50% might be expected. It has been argued that without directives issued in the form of Public Health Laws, we will continue to struggle to achieve higher immunization rates.²

Support from professional groups for routine annual seasonal influenza vaccine for all HCPs has also grown in the last several years. In 2007, the Infectious Disease Society of America (IDSA) recommended that the United States adopt a policy to include mandatory annual vaccine for HCP. Later that year, the American College of Physicians (ACP) recommended vaccine for every HCP with direct patient care. At the same time, the Joint Commission, which offers accreditation of healthcare organizations, set a new standard that influenza immunization be offered to all staff and licensed independent practitioners. As such, HCP vaccination rates in hospital employees becomes a quality control measure.

CONCLUSION

Influenza is a serious infection. Nosocomial transmission of seasonal influenza from HCPs to patients is largely preventable through strict adherence to current influenza immunization recommendations. Voluntary programs have not succeeded in at-

taining acceptable immunization rates despite clear guidance from the CDC and support from professional organizations. Legislation with more rigorous mandates may be the only way to achieve improvements in the current vaccination coverage rates.

With the emergence of influenza A (H1N1), we were presented with a new challenge. Current seasonal influenza vaccination does not provide protection against this novel virus. Though a vaccine against this strain has been developed, issues have emerged regarding its availability, safety, and implementation. Current efforts are focused on immunizing all HCPs with the seasonal trivalent influenza vaccine and the monovalent 2009 H1N1 vaccine, with hopes of achieving high coverage rates for both.

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Influenza-Associated Hospitalizations in the United States

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NATIONAL ESTIMATES OF influenza-associated mortality have been important for understanding the epidemiology of influenza over time and for resource planning for influenza epidemics and future influenza pandemics.¹⁻⁴ However, mortality incompletely reflects the severity of influenza infections because many severe illnesses do not result in death. In addition, influenza types and subtypes have differential effects on morbidity and mortality. For example, during some seasons, influenza A(H1N1) and B viruses are associated with substantial numbers of hospitalizations and outpatient visits but small increases in mortality.⁵⁻⁷ Furthermore, influenza-associated hospitalizations contribute an important proportion of the total health burden and economic costs of influenza epidemics and pandemics.^{2,8-10}

Previous studies have estimated numbers and rates of influenza-associated hospitalizations by age group, risk status, influenza type and subtype, and vaccine status.¹¹⁻²⁰ However, only 2 studies, both using National Hospital Discharge Survey (NHDS) data, have provided national estimates of influenza-associated hospitalizations in the United States.^{11,13} Barker¹¹ estimated influenza-associated hospitalizations from 1970

Context Respiratory viral infections are responsible for a large number of hospitalizations in the United States each year.

Objective To estimate annual influenza-associated hospitalizations in the United States by hospital discharge category, discharge type, and age group.

Design, Setting, and Participants National Hospital Discharge Survey (NHDS) data and World Health Organization Collaborating Laboratories influenza surveillance data were used to estimate annual average numbers of hospitalizations associated with the circulation of influenza viruses from the 1979-1980 through the 2000-2001 seasons in the United States using age-specific Poisson regression models.

Main Outcome Measures We estimated influenza-associated hospitalizations for primary and any listed pneumonia and influenza and respiratory and circulatory hospitalizations.

Results Annual averages of 94 735 (range, 18 908-193 561) primary and 133 900 (range, 30 757-271 529) any listed pneumonia and influenza hospitalizations were associated with influenza virus infections. Annual averages of 226 054 (range, 54 523-430 960) primary and 294 128 (range, 86 494-544 909) any listed respiratory and circulatory hospitalizations were associated with influenza virus infections. Persons 85 years or older had the highest rates of influenza-associated primary respiratory and circulatory hospitalizations (1194.9 per 100 000 persons). Children younger than 5 years (107.9 primary respiratory and circulatory hospitalizations per 100 000 persons) had rates similar to persons aged 50 through 64 years. Estimated rates of influenza-associated hospitalizations were highest during seasons in which A(H3N2) viruses predominated, followed by B and A(H1N1) seasons. After adjusting for the length of each influenza season, influenza-associated primary pneumonia and influenza hospitalizations increased over time among the elderly. There were no significant increases in influenza-associated primary respiratory and circulatory hospitalizations after adjusting for the length of the influenza season.

Conclusions Significant numbers of influenza-associated hospitalizations in the United States occur among the elderly, and the numbers of these hospitalizations have increased substantially over the last 2 decades due in part to the aging of the population. Children younger than 5 years had rates of influenza-associated hospitalizations similar to those among individuals aged 50 through 64 years. These findings highlight the need for improved influenza prevention efforts for both young and older US residents.

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through 1978 in 3 age groups using 3 mutually exclusive hospital outcomes: all-cause pneumonia and influenza, respiratory disease excluding all-cause pneumonia and influenza, and acute car-

diac failure. The assessment of influenza-associated hospitalizations was limited to seasons in which influenza A(H3N2) viruses predominated and the assessment used winter seasons in which in-

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fluenza A(H1N1) and B viruses predominated as the baseline period from which to estimate A(H3N2) excess hospitalizations. In the second study, Simonsen and colleagues¹³ estimated annual numbers of influenza-associated hospitalizations by virus type and subtype from the 1969-1970 through 1994-1995 seasons for primary pneumonia and influenza hospitalizations for 2 age groups (<64 years and ≥65 years). In most seasons, November hospitalizations were used as the baseline for estimating influenza-associated hospitalizations. In 6 seasons when the influenza circulation began late, a December baseline was used to estimate such hospitalizations.

We estimated annual numbers of influenza-associated hospitalizations from the 1979-1980 through the 2000-2001 respiratory seasons, a 22-year period for which national influenza laboratory surveillance data were available. We modified Poisson regression methods previously used to estimate influenza-associated mortality in the United States²¹ to estimate numbers and rates of influenza-associated hospitalizations.

METHODS

Definition of Respiratory Season

Influenza viruses typically circulate during winter months and across calendar years. Therefore, we defined July 1 through June 30 of the following year as a respiratory season so that an entire influenza season was studied.

National Viral Surveillance Data

In the United States, laboratory-based surveillance for influenza viruses is conducted from October through mid May (calendar week 40 through week 20). For the influenza virus surveillance periods from the 1979-1980 through 2000-2001 seasons, we obtained numbers of respiratory specimens that tested positive for influenza. Specimens are reported weekly by 50 to 75 US-based World Health Organization (WHO) collaborating virology laboratories to the Centers for Disease Control and Prevention. The laboratories provide numbers of total respiratory specimens tested for

influenza and positive influenza tests by virus type and subtype.²² The monthly percentages of specimens that tested positive for influenza viruses were used in estimating the effect of influenza circulation on monthly hospitalizations in the United States. For summary purposes, we defined a predominant influenza virus type or subtype for each season based on whether the influenza type or subtype constituted more than 20% of the total influenza specimens that had tested positive in a given season.

NHDS Hospital Discharge Diagnoses

Hospital discharge diagnosis records were obtained from the NHDS²³⁻²⁸ for the 1979-1980 through 2000-2001 seasons. National Hospital Discharge Survey hospital discharge data are collected and reported by month for approximately 270 000 inpatient records sampled from approximately 500 hospitals. These records represent approximately 1% of all inpatient hospitalizations in the United States.^{29,30} The sampling design assigns a discharge weight to each hospital record. The discharge weight is the number of hospitalizations that the hospital record represents, and use of these weights permits calculations of nationally representative numbers of hospitalizations. We summed the corresponding discharge weights by month to obtain nationally representative numbers of hospitalizations.

*International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes*³¹ were used to categorize hospitalizations. Monthly hospitalizations were summarized by both first-listed and any-listed ICD-9-CM discharge codes. We considered the first-listed discharge code as the primary discharge diagnosis. We examined 2 diagnostic categories: pneumonia and influenza hospitalizations (ICD-9-CM codes 480-487) and respiratory and circulatory hospitalizations (ICD-9-CM codes 390-519). Thus, pneumonia and influenza hospitalizations were a subset of respiratory and circulatory hospitalizations.

Statistical Analyses

We modified methods developed for estimating US influenza-associated mortality²¹ to estimate influenza-associated hospitalizations with NHDS data. One advantage of this method is that it permitted the effect of influenza circulation to vary by month, and therefore hospitalization estimates could also fluctuate with influenza activity. Poisson regression models were fit to 8 age groups: younger than 5 years, 5 through 49 years, 50 through 64 years, 65 through 69 years, 70 through 74 years, 75 through 79 years, 80 through 84 years, and 85 years or older. Influenza virus circulation terms representing the percentages of specimens testing positive for influenza A(H1N1), A(H3N2), and B viruses during each month in the study period were included in all models.

The age-specific Poisson regression models we used can be written as

$$Y = \alpha \exp(\beta_0 + \beta_1[t] + \beta_2[t^2] + \beta_3[t^3] + \beta_4[\sin(2t\pi/12)] + \beta_5[\cos(2t\pi/12)] + \beta_6[A(H1N1)] + \beta_7[A(H3N2)] + \beta_8[B])$$

where Y represents the number of hospitalizations during a particular month for a specific age group. The term α was the population offset. The term t was the number of months in a time series from July 1979 through June 2001. We estimated the following β coefficients: β_0 was the intercept, β_1 accounted for the linear time trend in months, β_2 and β_3 accounted for nonlinear time trends, β_4 and β_5 accounted for seasonal changes in hospitalizations, and β_6 through β_8 were coefficients associated with the percentages of specimens testing positive for specific influenza viruses in a given month. Estimates of monthly US age-specific populations were used to account for changes in population trends over time and were obtained from the Census Bureau.³² Attempts to include a term for respiratory syncytial virus in these models were unsuccessful because of the high correlation between the cosine term and the respiratory syncytial virus term ($r=0.90$) when the data were modeled on a monthly rather than on a weekly

basis as was done in our recent mortality analyses.²¹ All analyses were performed using SAS statistical software version 8.2 (PROC GENMOD, SAS Institute Inc, Cary, NC). Because NHDS data sets are deidentified public-use data sets, their use does not require formal institutional review board approval.

We determined the number of weeks during each respiratory season for which at least 10% of specimens tested positive for influenza. We used these numbers in analyses to control for the length of the influenza season when examining trends in influenza hospitalization rates.

RESULTS

Annual Influenza Laboratory Surveillance

For the 1979-1980 through 2000-2001 seasons, an annual average of 30936 specimens (range, 14804-53427) were tested for influenza. During months in which specimens were tested for influenza, an average of 13.3% of specimens tested positive for influenza. Influenza

A(H1N1), A(H3N2), and B viruses were detected in 2.1%, 7.9%, and 3.3% of the total specimens tested, respectively. During the 22 respiratory seasons included in this study, A(H1N1), A(H3N2), and B viruses predominated in 7, 15, and 11 respiratory seasons, respectively. There were 11 seasons in which more than 1 virus type or subtype predominated. The average number of months in which at least 10% of specimens tested positive for influenza during each respiratory season was 2.8 months (range, 0-4 months).

Annual Trends in Primary Hospital Discharge Diagnoses

During the study period, there were annual averages of 1 097 564 primary and 1 681 449 any listed pneumonia and influenza hospitalizations (TABLE 1). There were annual averages of 8 843 498 primary and 14 722 488 any listed respiratory and circulatory hospitalizations. Primary pneumonia and influenza hospitalizations represented 12.4% of the primary respiratory and circulatory hospitalizations. The total numbers of pri-

mary pneumonia and influenza hospitalizations increased in a linear fashion from the 1979-1980 through the 2000-2001 respiratory seasons (FIGURE). The total numbers of primary respiratory and circulatory hospitalizations decreased from the 1982-1983 through 1990-1991 respiratory seasons but increased from the 1991-1992 through 1999-2000 respiratory seasons.

Annual Estimates of Influenza-Associated Hospitalizations

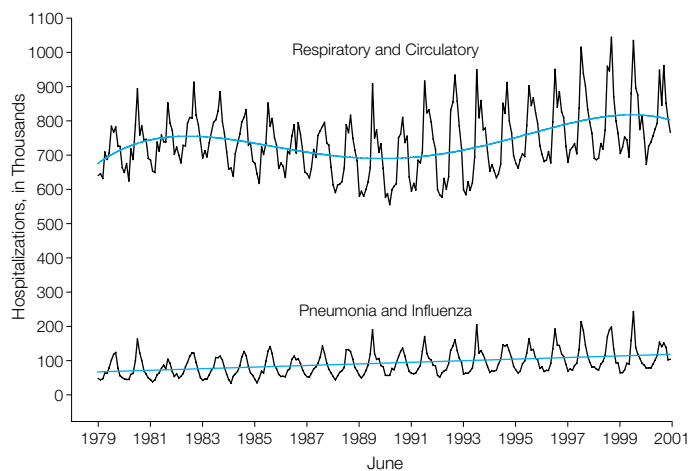
We estimated annual averages of 94 735 (range, 18908-193 561) primary and 133 900 (range, 30 757-271 529) any listed pneumonia and influenza hospitalizations were associated with influenza viruses in the United States during the 1979-1980 through 2000-2001 respiratory seasons (TABLE 2). These influenza-associated hospitalization estimates represented 8.6% of all primary and 8.0% of any listed pneumonia and influenza hospitalizations. Similarly, we estimated annual averages of 226 054

Table 1. Annual Numbers of Hospitalizations*

Season	Predominant Type or Subtype	Pneumonia and Influenza		Respiratory and Circulatory	
		Primary	Any Listed	Primary	Any Listed
1979-1980	B	865 831	1 287 370	8 439 463	12 481 589
1980-1981	A(H3N2) and A(H1N1)	919 527	1 397 719	8 731 481	13 016 836
1981-1982	B and A(H1N1)	798 497	1 244 653	8 764 245	13 274 939
1982-1983	A(H3N2)	969 494	1 461 657	9 200 449	14 011 837
1983-1984	A(H1N1) and B	911 404	1 441 032	9 159 882	14 293 230
1984-1985	A(H3N2)	897 709	1 410 075	8 719 647	13 775 287
1985-1986	B and A(H3N2)	965 195	1 512 549	8 656 732	13 615 762
1986-1987	A(H1N1)	949 472	1 469 651	8 531 884	13 552 625
1987-1988	A(H3N2)	1 015 771	1 538 481	8 558 141	13 811 340
1988-1989	B and A(H1N1)	1 007 311	1 535 909	8 205 538	13 529 005
1989-1990	A(H3N2)	1 121 925	1 665 437	8 143 846	13 490 326
1990-1991	B	1 052 748	1 593 078	7 966 791	13 377 130
1991-1992	A(H3N2)	1 140 515	1 720 867	8 682 815	14 675 059
1992-1993	B and A(H3N2)	1 164 851	1 752 072	8 581 400	14 755 415
1993-1994	A(H3N2)	1 203 076	1 801 235	8 567 533	14 904 193
1994-1995	A(H3N2) and B	1 218 022	1 835 374	8 752 360	15 139 232
1995-1996	A(H1N1) and A(H3N2)	1 222 394	1 888 145	9 140 502	16 062 778
1996-1997	A(H3N2) and B	1 313 052	2 014 834	9 263 679	16 214 492
1997-1998	A(H3N2)	1 358 560	2 104 097	9 613 565	17 125 197
1998-1999	A(H3N2) and B	1 402 983	2 127 729	9 648 804	17 306 149
1999-2000	A(H3N2)	1 323 393	2 088 237	9 618 752	17 451 112
2000-2001	A(H1N1) and B	1 324 683	2 101 675	9 609 444	18 031 197
Mean (SD)		1 097 564 (180 045)	1 681 449 (280 113)	8 843 498 (496 483)	14 722 488 (1 616 326)

*Estimates are based on weighted monthly data.

Figure. Monthly Numbers of Hospitalizations by Primary Discharge Type From the 1979-1980 Through 2000-2001 Respiratory Seasons



The curve plotting the respiratory and circulation data is a fourth-order polynomial curve, and the pneumonia and influenza curve represents a straight linear regression line.

(range, 54 523-430 960) primary and 294 128 (range, 86 494-544 909) any listed respiratory and circulatory hospitalizations were associated with influenza viruses. For the respiratory and circulatory hospitalizations, these estimates represented 2.6% of all primary and 2.0% of any listed hospitalizations during the study period.

When we examined the year-to-year variability in influenza-associated hospitalizations, we noted a substantial increase in hospitalizations during the 1996-1997 through 1999-2000 influenza seasons, a period when A(H3N2) viruses predominated. Influenza-associated hospitalizations in the 2000-2001 season were the lowest since the 1995-1996 influenza season, and this corresponded with circulation of A(H1N1) viruses.

A summary of the numbers and rates of influenza-associated hospitalizations by discharge diagnosis and age group are presented in TABLE 3. Among children younger than 5 years, we estimated annual averages of 3454 (18.5 hospitalizations per 100 000 person-years) primary and 4916 (26.3 hospitalizations per 100 000 person-years) any listed pneumonia and influenza hospitalizations. For the same age

group, we estimated 20031 (107.9 hospitalizations per 100 000 person-years) primary and 21 156 (113.9 hospitalizations per 100 000 person-years) any listed respiratory and circulatory hospitalizations. Persons aged 5 through 49 years had the lowest rates of influenza-associated hospitalizations. Influenza-associated hospitalization rates increased dramatically with age. For example, among persons aged 85 years and older, we estimated annual averages of 21 788 (628.6 hospitalizations per 100 000 person-years) primary and 26 988 (777.3 hospitalizations per 100 000 person-years) any listed pneumonia and influenza hospitalizations. In this age group, we estimated annual averages of 40 813 (1194.9 hospitalizations per 100 000 person-years) primary and 57 350 (1669.2 hospitalizations per 100 000 person-years) any listed respiratory and circulatory influenza-associated hospitalizations.

Influenza-Associated Hospitalizations by Predominant Influenza Type and Subtype

In seasons during which A(H1N1) viruses predominated, 22.6 primary pneumonia and influenza and 55.9 pri-

mary respiratory and circulatory hospitalizations per 100 000 person-years were associated with influenza virus circulation. For B viruses, we estimated 37.7 and 81.4 influenza-associated hospitalizations per 100 000 person-years for primary pneumonia and influenza and primary respiratory and circulatory hospitalizations, respectively. A(H3N2) viruses were associated with the highest annual rates of influenza-associated hospitalizations. During seasons in which A(H3N2) viruses predominated, there were 43.5 primary pneumonia and influenza and 99.0 primary respiratory and circulatory hospitalizations per 100 000 person-years associated with influenza viruses.

Age-Specific Trends in Influenza-Associated Hospitalization Rates

Influenza-associated hospitalization rates increased annually during the study period among persons aged 50 through 64 years, 65 through 69 years, 70 through 74 years, 75 through 79 years, 80 through 84 years, and 85 years and older ($P < .01$ for each trend). After controlling for the length of the influenza season, a significant increase in the rates over time was still found among persons aged 65 through 69 years, 70 through 74 years, 75 through 79 years, 80 through 84 years, and 85 years and older ($P < .05$ for each trend).

Significant increases in influenza-associated hospitalization rates for respiratory and circulatory hospitalizations were found among persons younger than 5 years and those aged 65 through 69 years, 70 through 74 years, 75 through 79 years, 80 through 84 years, and 85 years and older ($P < .05$ for each trend). However, after controlling for the length of the influenza season, there were no significant increases in trends over time.

Length of Hospital Stay by Age Group and Diagnosis

Length of hospital stay varied by diagnosis and age group (TABLE 4). The median length of stay for primary pneumonia and influenza hospitalizations

increased with age. The median length of stay was 3 days for those younger than 5 years; 4 days for those aged 5 through 49 years; 6 days for those aged 50 through 64, 65 through 69, and 70 through 74 years; and 7 days for those aged 75 through 79, 80 through 84, and 85 years and older. The median length of stay for primary respiratory and circulatory hospitalizations was 3 days for those younger than 5 years and those aged 5 through 49 years; 4 days for

Table 2. Annual Numbers and Rates of Influenza-Associated Hospitalizations*

Season	Predominant Type or Subtype	Pneumonia and Influenza Hospitalizations				Respiratory and Circulatory Hospitalizations			
		Primary		Any Listed		Primary		Any Listed	
		No. of Cases	Rate†	No of Cases	Rate†	No. of Cases	Rate†	No. of Cases	Rate†
1979-1980	B	44 871	19.7	61 237	26.9	120 929	53.2	151 544	66.7
1980-1981	A(H3N2) and A(H1N1)	44 488	19.4	67 710	29.5	167 812	73.1	189 048	82.4
1981-1982	B and A(H1N1)	21 806	9.4	30 983	13.4	61 211	26.4	86 494	37.3
1982-1983	A(H3N2)	62 577	26.8	93 660	40.0	213 256	91.2	245 524	105.0
1983-1984	A(H1N1) and B	55 941	23.7	81 225	34.4	148 277	62.8	226 551	96.0
1984-1985	A(H3N2)	96 941	40.7	143 532	60.2	303 390	127.3	333 024	139.8
1985-1986	B and A(H3N2)	71 141	29.6	98 431	40.9	169 359	70.4	212 129	88.2
1986-1987	A(H1N1)	18 908	7.8	30 757	12.7	54 523	22.5	121 678	50.1
1987-1988	A(H3N2)	61 510	25.1	89 242	36.4	172 151	70.3	207 454	84.7
1988-1989	B and A(H1N1)	81 471	32.9	114 112	46.1	175 998	71.2	273 273	110.5
1989-1990	A(H3N2)	90 396	36.2	130 204	52.1	241 456	96.7	278 118	111.4
1990-1991	B	78 075	31.0	104 821	41.6	157 911	62.6	221 412	87.8
1991-1992	A(H3N2)	104 245	41.0	149 944	58.9	263 614	103.6	326 331	128.2
1992-1993	B and A(H3N2)	110 926	43.2	149 157	58.0	226 541	88.1	304 898	118.6
1993-1994	A(H3N2)	114 049	43.9	160 482	61.8	271 655	104.6	322 736	124.3
1994-1995	A(H3N2) and B	101 480	38.7	140 105	53.4	226 657	86.4	288 417	109.9
1995-1996	A(H1N1) and A(H3N2)	87 497	33.0	124 205	46.9	196 502	74.1	296 312	111.8
1996-1997	A(H3N2) and B	180 214	67.3	248 557	92.8	382 969	142.9	490 246	182.9
1997-1998	A(H3N2)	193 561	71.4	271 529	100.2	430 960	159.1	530 225	195.7
1998-1999	A(H3N2) and B	190 331	69.5	263 270	96.1	390 446	142.5	503 894	183.9
1999-2000	A(H3N2)	184 098	66.4	265 300	95.7	426 662	153.9	544 909	196.6
2000-2001	A(H1N1) and B	89 636	32.0	127 328	45.4	170 899	60.9	316 588	112.9
Mean (SD)		94 735 (51 549)	36.8 (18.2)	133 900 (71 496)	52.0 (25.2)	226 054 (106 463)	88.4 (37.9)	294 128 (126 583)	114.8 (43.6)

*Estimates are based on weighted monthly data.
†Rate per 100 000 person-years.

Table 3. Age-Specific Annual Average Numbers and Rates of Influenza-Associated Hospitalizations*

Variable	Age Groups, y								Total
	<5	5-49	50-64	65-69	70-74	75-79	80-84	≥85	
Pneumonia and influenza hospitalizations									
Primary									
Number	3454	11 431	13 476	6871	10 609	14 226	12 879	21 788	94 735
Rate†	18.5	6.8	37.9	71.1	127.8	219.5	302.2	628.6	36.8
Any listed									
Number	4916	19 442	18 917	10 283	17 209	20 185	15 959	26 988	133 900
Rate†	26.3	11.5	53.3	106.4	207.4	312.2	376.2	777.3	52.0
Respiratory and circulatory hospitalizations									
Primary									
Number	20 031	34 867	29 447	18 301	26 501	27 516	28 578	40 813	226 054
Rate†	107.9	20.8	83.8	189.7	321.2	431.1	686.1	1194.9	88.4
Any listed									
Number	21 156	47 745	39 198	22 168	40 552	31 319	34 640	57 350	294 128
Rate†	113.9	28.3	111.3	229.7	491.9	489.4	829.1	1669.2	114.8

*Estimates are based on weighted monthly data.
†Rate is per 100 000 person-years.

those aged 50 through 64 years; 5 days for those aged 65 through 69, 70 through 74, and 75 through 79 years; 6 days for those aged 80 through 84 years and those 85 years and older.

COMMENT

We used monthly influenza surveillance data and nationally representative hospital discharge data to estimate influenza-associated hospitalizations in the United States by discharge category, discharge type, and age group. We found that the numbers and rates of influenza-associated hospitalizations generally increased during the study period.

Our results are consistent with our recent mortality analyses, which found substantial increases in influenza-associated mortality among persons 65 years and older during the 1990s.²¹ We postulate that these increases in influenza-associated hospitalizations and deaths were due to several factors, including the aging of the population, the predominance of A(H3N2) viruses in many recent seasons, and the general trend for influenza viruses to circulate or to be detected for longer periods in respiratory seasons during the 1990s.

Using the nationally representative estimates of influenza-associated hospitalizations from this study and of deaths from our mortality study,²¹ we can estimate relative risks (RRs) describing the risk of an influenza-associated hospitalization compared with the risk of an in-

fluenza-associated death. For example, among children younger than 5 years, the RR for an influenza-associated hospitalization relative to death is 270; while among persons aged 50 through 64 years, the RR is 11. Young children are at much greater risk for an influenza-associated hospitalization compared with an influenza-associated death; this difference greatly diminishes with increasing age. These results will be useful for national cost-effectiveness and policy analyses which assess the pros and cons of alternative vaccination strategies to reduce the morbidity and mortality from influenza, including vaccinating all children or universal immunization.

An important implication of our results is that the use of primary pneumonia and influenza discharges to estimate influenza-associated hospitalizations does not fully capture the total effect of influenza virus activity on morbidity in the United States. Our estimates of any listed respiratory and circulatory hospitalizations were about 3 times as high as our estimates of primary pneumonia and influenza hospitalizations. Other studies also suggest that influenza virus activity is associated with an increase in hospitalizations for a broad range of cardiopulmonary diagnoses, and not just primary pneumonia and influenza discharges.^{11,19}

Generally, our estimated annual numbers and rates of influenza-associated hospitalizations are similar to previous national estimates made using NHDS

data. Barker¹¹ estimated 370 influenza-associated pneumonia and influenza hospitalizations per 100 000 persons who were at least 65 years during 5 A(H3N2) seasons in the 1970s while we estimated 281 any listed pneumonia and influenza hospitalizations per 100 000 persons during the 1979-1980 through 2000-2001 respiratory seasons for this age group. Barker's estimate for the sum of influenza-associated hospitalizations for respiratory disease and acute cardiac failure was an annual average of 419 hospitalizations per 100 000 persons who were at least 65 years. We estimated 581 any listed respiratory and circulatory hospitalizations per 100 000 annually, which was slightly higher but would be expected given the continued aging of this age group.

In the other study that used NHDS data, Simonsen and colleagues¹³ estimated 49 influenza-associated primary pneumonia and influenza hospitalizations per 100 000 persons for all ages, while we estimated 37 hospitalizations per 100 000 person-years for the same outcome. Comparing the results from these 2 studies during overlapping seasons (1979-1980 through 1994-1995), the annual estimates of influenza-associated pneumonia and influenza hospitalizations were highly correlated ($r=0.73, P<.01$). Across the entire study period, Simonsen and colleagues¹³ estimated higher rates of primary pneumonia and influenza hospitalizations among persons younger than

Table 4. Descriptive Statistics for Length of Stay

No. of Days	Age Groups, y							
	<5	5-49	50-64	65-69	70-74	75-79	80-84	≥85
Pneumonia and influenza hospitalizations								
Primary								
Median	3	4	6	6	6	7	7	7
Average	4.3	5.8	7.5	8.0	8.4	8.7	9.0	8.9
Any listed								
Median	3	5	7	7	7	7	8	7
Average	4.9	7.5	10.0	10.5	10.6	10.8	10.6	10.0
Respiratory and circulatory hospitalizations								
Primary								
Median	3	3	4	5	5	5	6	6
Average	3.7	4.8	6.6	7.4	7.7	7.8	8.0	8.1
Any listed								
Median	3	3	5	5	6	6	6	6
Average	4.5	5.8	7.1	7.8	8.1	8.3	8.5	8.6

65 years relative to our study (33 vs 13 hospitalizations per 100 000 persons, respectively). Conversely, we estimated higher rates of primary pneumonia and influenza hospitalizations among persons who were aged at least 65 years (174 vs 205 per 100 000 persons, respectively). The difference in rates among those younger than 65 years in the study by Simonsen et al most likely reflect the increased influenza morbidity found among younger individuals during the 1968-1969 pandemic period.

The results of this study are also consistent with several studies of influenza-associated hospitalizations restricted to young children. These studies found high rates of hospitalizations among both high-risk and healthy young children.^{16,33-35} Although none of these previous studies were nationally representative, the estimated rates are in general quite similar. For example, for all children younger than 5 years, Mullooly and Barker¹² estimated 1.2 hospitalizations per 1000 person-years, Neuzil and colleagues¹⁶ estimated 2.6 hospitalizations per 1000 person-years among healthy children, and Izurieta and colleagues³⁵ estimated 0.9 hospitalizations per 1000 person-years among healthy children. In our study, we estimated an annual average of 1.1 hospitalizations per 1000 person-years among all children younger than 5 years, which also compares favorably with a recent study that found a laboratory-confirmed influenza hospitalization rate of 0.6 per 1000 among children younger than 5 years during a single mild influenza season.³⁶

This study has several limitations. Because NHDS data do not include previous health information, it was not possible to determine which individuals were at risk for influenza complications due to underlying conditions (eg, asthma, heart disease, etc) or to control for changes in the prevalence of these conditions over time. Nor was it possible to identify individuals who had received influenza vaccine prior to the respiratory season in which the individual was hospitalized in order to assess

vaccine effectiveness. Although our influenza mortality estimates were made using similar methods and weekly death data, in this study we were limited to making hospitalization estimates using monthly hospital discharge data. Use of weekly hospitalization and influenza circulation information would have permitted fluctuations in both data sources to be more closely associated and would have provided more precise estimates of influenza-associated hospitalizations. We were also not able to control for the circulation of respiratory syncytial virus, which is known to circulate at similar times as influenza viruses and is often associated with significant morbidity and mortality. Finally, we were unable to stratify data further for children younger than 5 years due to the few numbers of hospitalizations that occurred for children aged 2 to 4 years. Despite these limitations, our use of NHDS data provided nationally representative annual estimates of influenza-associated hospitalizations that can be compared over 2 decades. Smaller data sources often used to assess influenza vaccine effectiveness cannot offer these advantages.

Currently, we estimate that more than 200 000 respiratory and circulatory hospitalizations are associated with influenza each year in the United States, substantially more than estimates of pneumonia and influenza hospitalizations.¹³ As noted in our report describing influenza-associated mortality, the aging of the US population is an important contributor to the increasing numbers of influenza-associated hospitalizations and deaths.²¹ For example, between 1976 and 2001 the number of US citizens aged 85 and older had more than doubled.^{32,37} Based on US census estimates, the numbers of very elderly people in the United States will continue to increase and thus we expect that the numbers of influenza-associated hospitalizations and deaths will likely increase over time. Additional efforts are needed to ensure that current recommendations for influenza vaccination for all high-risk individuals, household contacts of high-risk individuals, health-

care workers, and young children are fully implemented. Recent observational studies have suggested that influenza vaccination may reduce respiratory and circulatory hospitalizations substantially, particularly among the elderly.^{19,38-39} Efforts to vaccinate older Americans and their contacts annually must continue to be a priority for immunization programs. Consideration should also be given to other influenza prevention methods for older Americans given the potential for decreased immune responsiveness to vaccines in the very elderly.^{40,41}

After the elderly, the second highest rates of influenza-associated hospitalizations are found in young children. This point was highlighted during the 2003-2004 A(H3N2)-influenza season, which may have been particularly severe among children. Through July 2004, data on 152 deaths among children with laboratory-confirmed influenza virus infection during the last influenza season has been collected nationally.⁴² The Council of State and Territorial Epidemiologists voted in June 2004 to add deaths of children with evidence of influenza virus infection to its list of nationally reportable conditions. Clearly, new measures to prevent influenza-associated morbidity and mortality among young children are needed.

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Study concept and design: Thompson, Shay, Weintraub, Cox, Fukuda.

Acquisition of data: Weintraub, Brammer, Cox.

Analysis and interpretation of data: Thompson, Shay, Weintraub, Brammer, Bridges, Cox, Fukuda.

Drafting of the manuscript: Thompson, Shay.

Critical revision of the manuscript for important intellectual content: Thompson, Shay, Weintraub, Brammer, Bridges, Cox, Fukuda.

Statistical analysis: Thompson, Weintraub, Brammer.

Administrative, technical, or material support: Thompson, Weintraub, Bridges.

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