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Asthma, influenza, and vaccination

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Exacerbations of asthma in children are usually triggered by virus infections. Many different respiratory viruses are associated with these exacerbations, but influenza viruses are frequently associated with those requiring hospitalization and are the only ones for which specific treatment and prophylaxis are available. Current studies have shown that influenza vaccines are safe for patients with asthma. The efficacy of inactivated influenza vaccines in preventing exacerbations of asthma has been questioned. The live attenuated influenza vaccine has been licensed recently in the United States, and studies have shown it to be safe and protective. A direct comparison of the inactivated and live attenuated influenza vaccines in children with asthma demonstrated superior protection by the latter. Live attenuated influenza vaccine, given by nasal spray, is better accepted by children for annual vaccination and is easier to administer. Universal vaccination of all children in school-based clinics will facilitate control of epidemic influenza and provide an infrastructure for control of future influenza pandemics. (*J Allergy Clin Immunol* 111:1000-1005, 2003.)

Key words: *Asthma in children, influenza-triggered asthma exacerbations, influenza vaccines, inactivated and live attenuated, safety and efficacy of influenza vaccines in children with asthma*

Asthma is the most common chronic condition of children and young adults.¹ In the last 2 decades, the prevalence of asthma has doubled to include almost 9% of the pediatric age group. Asthma exacerbations account for a large proportion of healthcare encounters for children and about one third of school absences. The stated risk factors for increased asthma prevalence and mortality in the

Abbreviations used

CAIV-T: Cold-adapted influenza vaccine, trivalent

LAIV: Live attenuated influenza vaccine

United States are urbanization and poverty (lack of access to health care). Studies of defined populations in Houston show hospitalization rates for uninsured populations that are almost 10 times higher than for covered groups.² That children in low-income families with high infection rates from all causes also have the highest morbidity as a result of asthma is counter to the hygiene hypothesis, which proposes that early childhood infections modify the immune response and reduce the tendency to produce IgE antibodies to environmental antigens. Even in the Tucson longitudinal study, the children with severe acute lower respiratory illnesses in infancy were most likely to have persistent asthma at 6 years of age with abnormal pulmonary function.³

Exacerbations of asthma in children are likely to be triggered by a respiratory virus infection.⁴ Many different viruses are associated with these episodes, particularly respiratory syncytial virus, influenza viruses, parainfluenza viruses, and rhinoviruses. In studies of children and young adults admitted to the hospital with acute respiratory conditions—usually exacerbations of asthma—respiratory syncytial virus was most frequently associated with hospitalizations of children <5 years of age.^{2,5} Influenza and rhinovirus infections frequently accompanied those involving school-age children and young adults. Parainfluenza virus infections were common in all age groups.

The mechanisms of the interaction between atopy and virus infections are obscure.^{6,7} Volunteer studies suggest that atopic individuals infected with a rhinovirus followed by exposure to an allergen like ragweed will experience an augmentation of the inflammatory response in the airways. The data suggest a synergistic effect of exposures in that sequence, providing a hypothesis that the virus infection exposes the host to a more prolonged and augmented late-phase eosinophil response when exposed to an allergen.

Whatever the mechanism, the evidence of the importance of virus infection of the respiratory tract as a trigger

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for asthma attacks has been enhanced by more sensitive tests for detecting the virus infections, such as the use of the PCR.⁷ The new methods have allowed detection of virus infections from a high proportion of children with asthma exacerbations. Increased recognition of rhinovirus infections has contributed most, but identification of the human metapneumovirus, a paramyxovirus most closely related to human parainfluenza viruses, has also added to the array of virus infections related to wheezing illness in children.⁸⁻¹¹ The problem with detection of the rhinoviruses only by PCR is that the viruses cannot be antigenically typed or characterized for other properties that might lead to treatment or prophylaxis. Of the virus infections associated with asthma, only influenza virus infections can be treated or prevented. For this reason, this article focuses on the problems and opportunities for treatment and prevention of influenza virus infections in persons with asthma.

INFLUENZA

Influenza is an acute respiratory tract infection caused by influenza virus, an orthomyxovirus.¹² Influenza viruses are negative-sense, single-stranded RNA viruses with 3 major types—A, B, and C—and multiple subtypes of influenza A. Influenza C virus causes mainly upper respiratory tract illness, usually without complications. It will not be considered further. Influenza A and B viruses possess 2 surface antigens: hemagglutinin and neuraminidase. To initiate infection, the hemagglutinin attaches to respiratory epithelial cells and facilitates the transfer of viral RNA into the cell. The neuraminidase promotes release of new virus from the cell after replication. These surface antigens not only are important for pathogenesis of infection but also generate the protective immune response and are essential components of vaccines. Another important property of influenza viruses is the presence of a segmented genome. Eight segments are present that determine 10 different proteins. This property allows ready reassortment of viruses in the laboratory and is useful in the production of vaccines. To produce the seed virus for inactivated influenza vaccine production, the target wild virus is reassorted with an egg-adapted virus that grows to high titer in embryonated eggs. The live attenuated virus vaccine is produced by reassorting the parent attenuated virus with the wild strain to produce a 6:2 reassortant: a virus with 6 gene segments of the attenuated parent and the 2 gene segments for the hemagglutinin and neuraminidase of the target wild strain.

Influenza B is a uniquely human pathogen; however, influenza A is primarily an avian virus. Sixteen different subtypes of influenza A are found in birds—primarily migrating aquatic birds—throughout the world. The avian viruses usually produce almost inapparent infections in wild ducks and geese; however, when introduced into domestic fowl—chickens and turkeys—virulent mutations may occur that result in fatal disseminated infections.^{13,14} The original fowl plague virus, influenza

A(H7N7), was isolated in 1912, even before human influenza viruses had been identified.

PANDEMIC INFLUENZA

Currently, a virulent strain of avian influenza A(H5N1) is producing epizootics in domestic fowl, particularly in southeast Asia, eastern Europe, and Africa.¹³ On notable occasions, virulent avian A(H5N1) strains have been transmitted from sick chickens to humans who were in close contact; devastating illnesses have resulted in some of the human contacts with >50% mortality. Thus far, clusters of human infections have been largely limited to families, suggesting a genetic predisposition to infection with the avian virus; facile human-to-human spread has not occurred. The danger is that the avian virus will acquire the ability to spread readily in the community and ignite a pandemic. How this might occur is illustrated by description of the viruses that caused the 3 pandemics of the 20th century (Table I). The most frightening scenario is provided by the examination of nucleic acid fragments of the virus that caused the Great Pandemic of 1918; current analysis suggests that the 1918 virus was an avian virus that mutated to allow ready human-to-human transmission.¹⁵ This example justifies urgent consideration and preparation for the next pandemic, although some comfort can be taken by the fact that this has not occurred despite several years of intense epizootics caused by the H5N1 virus. The other two 20th century pandemics resulted from reassortment in nature of an avian virus with a prevalent human virus. Reassortment of influenza viruses is facilitated by the fact that they have a segmented genome as described. The reassortment event requires that the 2 viruses coinfect a single cell. Pigs have been suggested as the likely mixing vessel for this reassortment because the porcine respiratory epithelium includes receptors for both avian and human influenza viruses. The pandemic virus of 1957, influenza A(H2N2), had 3 avian gene segments matched with 5 from the contemporary human virus; the 1968 pandemic virus, A(H3N2), had 2 avian gene segments matched with 6 human gene segments. The 1968 pandemic was relatively mild compared with the earlier ones. This may have been because the 1968 virus retained the neuraminidase surface antigen, N2, from the contemporary circulating human virus. To reduce the likelihood of mutation of an avian virus, as occurred in 1918, it is necessary to control the avian epizootics. This has been accomplished in several countries, but much more needs to be done. To reduce the likelihood of emergence of a reassortant virus, as occurred in 1957 and 1968, the probability of coinfection of an avian with a human virus should be minimized both by controlling avian outbreaks and by reducing spread of human viruses by vaccination and use of antivirals, particularly for persons who have regular contact with poultry. The most productive way to prepare for the next pandemic is to demonstrate control of interpanemic influenza.

TABLE I. Origin of 20th century pandemic strains*

Gene segment	Year		
	1968	1957	1918
PB1	Avian	Avian	Avian
PB2	Human	Human	Avian
PA	Human	Human	Avian
HA	Avian	Avian	Avian
NA	Human	Avian	Avian
NP	Human	Human	Avian
M	Human	Human	Avian
NS	Human	Human	Avian

*The 1968 and 1957 viruses were reassortants of human and avian strains. The 1918 virus was an avian strain that mutated to allow human-to-human transmission.

INTERPANDEMIC (SEASONAL) INFLUENZA

An epidemic caused by influenza A or B or both occurs each winter. Although the severity of epidemics may vary, children will have high attack rates every year. An alarming trend for a worsening effect of influenza epidemics has been recognized in recent years.¹⁶ Most of the serious morbidity and mortality have been associated with outbreaks of influenza A(H3N2). Almost 80% of the deaths attributed to influenza for the period from 1990 to 1999 were caused by the H3N2 subtype. The hemagglutinin of influenza A(H3N2) has demonstrated frequent point mutations (so-called *antigenic drift*). These mutations often occur in the antibody combining sites adjacent to the receptor binding site of the hemagglutinin. As few as 9 amino acid replacements in these critical locations will prevent attachment of antibodies directed to the previous variant.¹⁷ Emergence of new variants requires that the vaccine formula be updated to the new strain. Since H3N2 viruses emerged to cause the 1968 pandemic, a total of 20 significant variants have been detected, and these variants have caused at least 25 severe epidemics (Table II). The crude death rate for 3 consecutive H3N2 epidemics, 1996 to 1999, was twice as high as that for the 1968 pandemic. Only part of this increase in mortality can be attributed to aging of the population. Rates of hospitalizations attributable to influenza have increased steadily in all age groups from age 50 years up since 1979 (Fig 1).¹⁸ The rates continued to increase despite an increase in vaccine coverage for the vulnerable elderly population from 32% in 1989 to 67% in 1997. By the year 2025, the US population will approach 350 million, and the number of persons ≥ 65 years of age will double.¹⁹ This means that the number of excess deaths and hospitalizations caused by influenza will also double if greater efforts are not made to control influenza. These facts establish the need to consider better control methods for persons who have asthma. Persons with asthma—particularly in low-income populations—have high hospitalization rates for asthma. Children with asthma make up a high proportion of the pediatric population and therefore also contribute to the spread of influenza in the community.

TABLE II. Antigenic variants of influenza A (H3N2), 1968 to 2006

Year	Variant
1968-72	A/Hong Kong/68
1972-73	A/England/72
1974-75	A/Port Chalmers/73
1975-76	A/Victoria/75
1977-78	A/Texas/77
1980-83	A/Bangkok/79
1984-85	A/Philippines/73
1985-86	A/Stockholm/85
1987-88	A/Sichuan/87
1989-90	A/Shanghai/87
1991-92	A/Beijing/89
1993-94	A/Beijing/92
1994-95	A/Shangdong/93
1995-96	A/Johannesburg/94
1996-97	A/Wuhan/95
1997-00	A/Sydney/97
2001-02	A/Panama/99
2003-04	A/Fujian/02
2004-05	A/California/04
2005-06	A/Wisconsin/05

INFLUENZA BURDEN IN ASTHMA

In a study of a defined population representative of those living in the Houston area, influenza virus infection was most frequently associated with hospitalization for acute respiratory conditions including asthma and chronic obstructive pulmonary disease over a 4-year period from 1990 to 1995.² The rates for hospitalization of persons from low-income populations (uninsured) were almost 10 times higher than those in the middle-income group (Fig 2).² Most of the hospitalized persons <35 years of age had a diagnosis of asthma. Overall, about 15% had proven influenza infections, including 21% of school-age children (Fig 3). A 20-year study in low-income children in Tennessee found rates of influenza-attributable hospitalizations of children with high-risk conditions (mostly asthma) that were 2 to 4 times higher than the rates for healthy children.²⁰ The annual rates for the high-risk children were 19, 8, and 2 per 1000 for age groups <1, 1 to 3, and 3 to 15 years, respectively. These rates are substantial, but despite recognition of the burden of disease, the uptake of influenza vaccine has been poor for children with asthma, usually <10%.

INFLUENZA VACCINATIONS

Part of the reluctance of the medical community to endorse influenza immunization of children with asthma has been a concern that the vaccine might increase airway resistance and exacerbate disease. This concern has been put to rest by the large study in the Vaccine Safety Datalink sponsored by the Centers for Disease Control and Prevention.²¹ Through 3 influenza seasons, the rates of

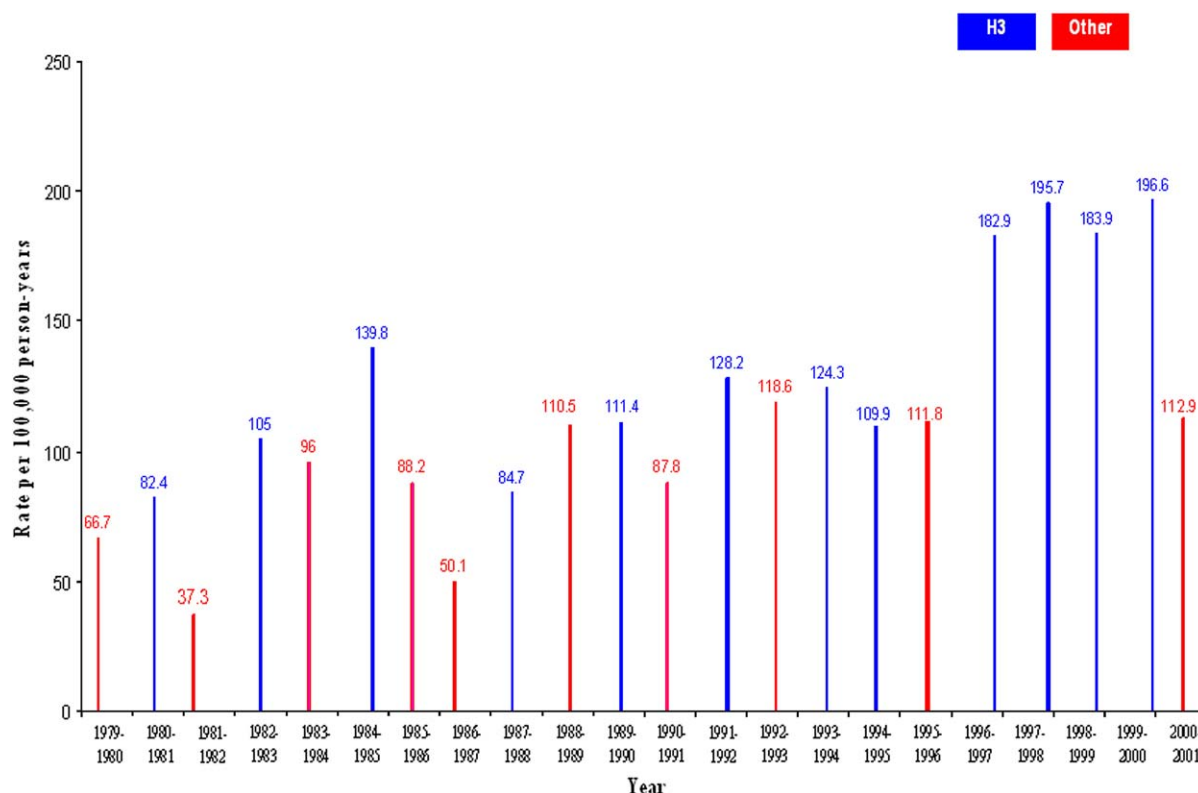


FIG 1. Annual rates of influenza-attributable hospitalizations in the United States, 1979-2001. Solid blue bars indicate years that influenza A(H3N2) viruses were predominant. Adapted with permission from Thompson WW, Shay DK, Weintraub E, Brammer L, Bridges CB, et al. Influenza-associated hospitalizations in the United States. *JAMA* 2004;292:1333-40.¹⁸ Copyright © 2004, American Medical Association. All rights reserved.

asthma exacerbations during the first 14 days after administration of the inactivated vaccine were calculated and were found consistently to be below the expected rates. This study should allay concerns about use of the inactivated vaccine.

Another concern has been whether the immune response to influenza vaccine in children receiving corticosteroids would be diminished. Short-term steroid treatment was found not to affect the antibody response to influenza vaccine.²² A larger study examined the immune response in subjects age 3 to 64 years who were receiving no or low-dose inhaled corticosteroids compared with those receiving medium-dose or high-dose inhaled corticosteroids or oral corticosteroids.²³ The antibody responses to the influenza A antigens were comparable for all groups. High-dose inhaled corticosteroids appeared to reduce the response to influenza B antigens, but this needs further study.

The third concern has to be the efficacy of inactivated influenza vaccine for the prevention of asthma exacerbations caused by influenza virus infection. In a large uncontrolled study from the Centers for Disease Control and Prevention, it was concluded that influenza vaccination protected against exacerbations after controlling for severity of the underlying disease.²⁴ The conclusion was reached after adjusting for biases between vaccinated and unvaccinated groups. Children who received vaccine

were found to have higher rates of medical encounters and pharmacy dispensings off-season. It was assumed that children who received vaccine had more severe asthma. When the results were controlled for this higher baseline morbidity, the results favored vaccination with reductions ranging from 22% to 45%. Earlier uncontrolled observations from Japan found protection against laboratory-confirmed influenza in children with asthma for the 1992 to 1993 epidemic.²⁵ Children ≥ 7 years of age had significant protection against both influenza A(H3N2) and B infections, but children < 7 years of age were not protected against influenza B infections.

Other studies have failed to show evidence of protection. A retrospective study in Rochester, NY, matched 400 children with asthma 1 to 19 years of age who received influenza vaccine for the 1996 to 1997 season with 400 who did not.²⁶ They found that the vaccinated children had a significantly higher risk for clinic and emergency department visits than did unvaccinated children. No mention was made of the timing of vaccine administration in relation to the influenza epidemic. Two studies from The Netherlands have failed to show benefit of influenza vaccine. The first was a case-control study performed in adults age 18 to 64 years with asthma or chronic obstructive pulmonary disease.²⁷ Rates of vaccination were compared for cases with exacerbations and 4 to 6 age-matched controls. No benefit of vaccination was discerned by this method for

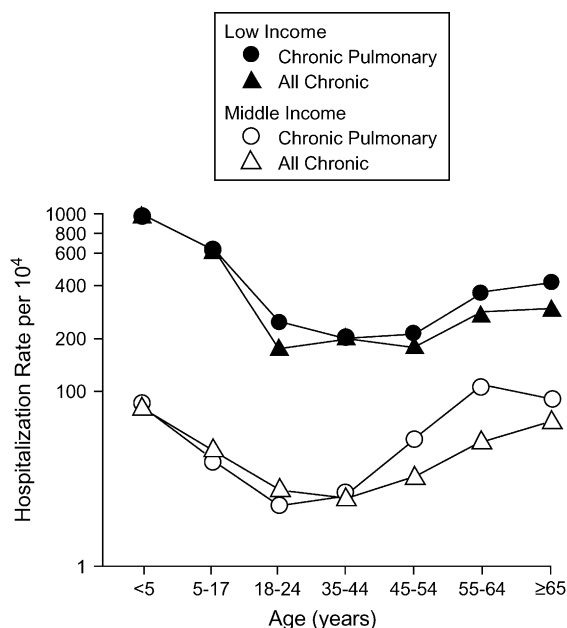


FIG 2. Hospitalization rates by age group for acute respiratory conditions experienced by middle-income and low-income patients with chronic underlying conditions and for subsets with chronic pulmonary disease. Reprinted with permission from Glezen WP, Greenberg SB, Atmar RL, Piedra PA, Couch RB. Impact of respiratory virus infections on persons with chronic underlying conditions. *JAMA* 2000;283:499-505.² Copyright © 2000, American Medical Association. All rights reserved.

2 consecutive seasons, 1998 to 2000. The second study was a randomized, double-blind, placebo-controlled trial of inactivated influenza vaccine in children with asthma age 6 to 18 years during 2 winter seasons, 1999 to 2001.²⁸ The children were cultured for respiratory virus infections at the time of exacerbation of asthma. Three hundred forty-nine children received placebo and 347 the vaccine. Of 47 culture-positive influenza-associated exacerbations, 24 occurred in the vaccine group and only 18 in the placebo group. Although the exacerbations lasted 3.1 days shorter in the vaccine group, the difference was not significant; the authors found that vaccination provided no benefit in prevention of influenza-associated asthma exacerbations in frequency, severity, or duration. They concluded that further studies would be needed to justify routine influenza vaccination of children with asthma. Their conclusion, however, should be modified to specify routine influenza vaccination with inactivated influenza vaccine.

LIVE ATTENUATED INFLUENZA VACCINE IN CHILDREN WITH ASTHMA

The live attenuated influenza vaccine (LAIV) has been licensed in the United States for healthy children age 5 years and older.²⁹ Children with high-risk conditions, such as asthma, are recommended to receive the inactivated vaccine. A new formulation of this vaccine, the

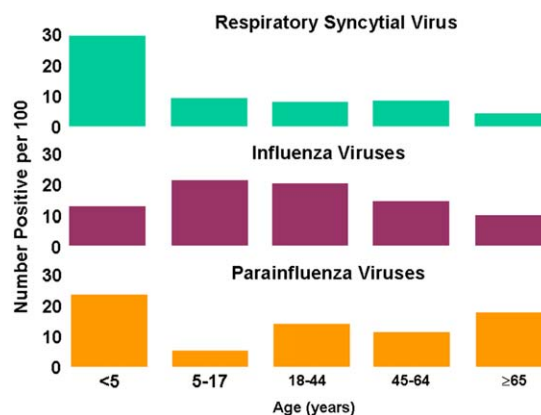


FIG 3. Proportions of patients with chronic underlying conditions hospitalized for acute respiratory conditions who had infections with respiratory syncytial, influenza, or parainfluenza viruses by age in Houston, Tex, 1991 to 1995. Reprinted with permission from Glezen WP, Greenberg SB, Atmar RL, Piedra PA, Couch RB. Impact of respiratory virus infections on persons with chronic underlying conditions. *JAMA* 2000;283:499-505.² Copyright © 2000, American Medical Association. All rights reserved.

cold-adapted influenza vaccine, trivalent (CAIV-T), is stable at refrigerator temperature and has been compared directly with inactivated influenza vaccine in children with asthma.³⁰ This trial was performed in more than 2000 children with asthma age 6 to 17 years from Europe and Israel. The outcome measure was a culture-confirmed influenza illness. The incidence of culture-confirmed influenza was 4.1% in children who received CAIV-T by nasal spray compared with 6.2% in children who received inactivated vaccine shots. The relative efficacy of CAIV-T was 34.7% with the 95% CI at 3.9% to 56.0%. Protection was demonstrated against influenza B, the major epidemic virus, and influenza A(H1N1). No protection was evident against a relatively small number of infections with influenza A(H3N2); a new H3N2 variant, A/Fujian, antigenically different than the vaccine strain, was detected among those infected. CAIV-T was well tolerated by children with asthma. The incidence of asthma exacerbations was similar for the treatment groups in the first 42 days after vaccination. No significant differences were observed between the 2 groups in mean peak expiratory flow rates, asthma symptom scores, or nighttime awakening scores. The majority of subjects in both groups reported no asthma symptoms during screening and through 15 days postvaccination.

This study reported 2 important findings: (1) the LAIV was well tolerated by children with asthma, and (2) LAIV was more efficacious than the inactivated influenza vaccine. Both of these findings should be examined in the light of present knowledge. First is the question of the safety of LAIV. A large safety double-blind, placebo-controlled assessment performed in Northern California among children 1 to 17 years of age found an increased risk of asthma-coded encounters in children 18 to 35 months of age during the 42-day period after administration of LAIV.³¹ No clustering of these episodes occurred

TABLE III. Influenza antiviral medications for treatment and prophylaxis

Antiviral agent	Type of inhibition	Route of administration	Comments
Amantadine	M2 – A only	Oral	Not used 2005-06
Rimantadine	M2 – A only	Oral	Not used 2005-06
Oseltamivir	Neuraminidase	Oral	Both A and B
Zanamivir	Neuraminidase	Inhalation*	Both A and B

From Harper SA, Fukuda K, Uyeki TM, Cox NJ, Bridges CB. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2005;54:1-40.⁴²

*May be irritating to airways of persons with reactive airways disease; suggest close monitoring with short-acting bronchodilators available.

during the 6-week period after vaccination. Examination of the medical records of the coded encounters revealed that many were follow-up visits without wheezing illness. If the nonwheezing illness visits were excluded, no excess episodes of asthma occurred in the vaccinated group. Furthermore, if another code for wheezing and cough was included, no excess wheezing illness in vaccine recipients was detected. Finally, both younger and older vaccinated subjects had significantly fewer asthma codes than did the placebo recipients. It appears that the excess of asthma codes in the recipients 18 to 35 months old was spurious.

This conclusion is supported by observations over a 4-year period, 1997 to 2001, during a large field trial in Central Texas, where 18,780 doses of LAIV were administered to 11,096 children 18 months to 18 years of age, including 4529 doses given to children <5 years of age.³² Children with mild, intermittent asthma were not excluded from receiving LAIV in this trial. No increase in wheezing illness or any medically attended acute respiratory illness was seen 0 to 14 days after vaccination with LAIV. During 1 year only, an excess of wheezing illness occurred among children <5 years of age during the period 15 to 42 days after vaccination; the biologic plausibility of this association more than 2 weeks after the limited infection caused by the LAIV is nebulous. The association may be the result of failure to adjust for multiple (190) comparisons.

No evidence of wheezing illness was discerned among participants in the pivotal efficacy trial in children <5 years of age, and no increased morbidity was associated with as many as 4 sequential annual vaccinations with LAIV.³³ A small controlled trial in children and adolescents with moderate to severe asthma, controlled, found no change in the percent predicted FEV₁.³⁴ Two LAIV recipients had mild asthma exacerbations within 28 days after vaccination that required increased bronchodilator or oral steroid usage but did not require emergency department visits or hospitalizations. In summary, LAIV is safe for administration to children with stable asthma.

Early studies with bivalent influenza A live attenuated vaccine suggested that LAIV would be superior to inactivated influenza vaccine in children.^{35,36} In a direct 3-arm comparison including placebo, the LAIV was found to give better protection against a new variant of influenza A(H1N1) that was not included in the vaccine. LAIV also was protective into the second season, whereas inactivated vaccine had no residual protection. The observations of heterovariant protection and persistence of protection to

the second season were confirmed by observations in the Central Texas Field trial.^{37,38} Children who had received only a single dose of the previous influenza A(H1N1) variant were significantly protected during the influenza A(H1N1) epidemic of 2000 to 2001. The relevance of this observation is heightened by the fact that influenza A(H1N1) had not circulated for 5 years before the 2000 to 2001 epidemic, ruling out interim boosting of immunity by natural infection.

Several large trials have now confirmed the superiority of LAIV to inactivated vaccine for children. More than 2000 infants and toddlers 6 to 71 months of age were enrolled in a direct comparison between 2 doses of LAIV or inactivated influenza vaccine in Europe and Israel.³⁹ Only 2.3% of the LAIV recipients had culture-positive illnesses, compared with 4.8% of the recipients of inactivated influenza vaccine, giving a relative efficacy of 52.7% for the LAIV. No statistically significant differences were observed between the 2 vaccines for wheezing illnesses within 10 or 42 days after either the first or second dose. In a large multinational study reported by Belshe⁴⁰ at the 2006 Pediatric Academic Societies meeting, 7836 children between 6 and 59 months of age were enrolled in a direct comparison between LAIV and inactivated influenza vaccines. The incidence of culture-positive influenza illness was 55% lower in the LAIV recipients than in recipients of inactivated vaccine. A slight excess of wheezing illness occurred in toddlers 6 to 18 months of age who received LAIV (3.2% compared with 2.0%) during the period from 0 to 42 days after the first dose only. Most of these wheezing illnesses occurred more than 10 days after vaccination, and the children were not tested for other respiratory viruses that may have produced an intercurrent illness. In conclusion, LAIV appears to have superior efficacy and is safe for children at least ≥18 months of age. LAIV has the potential to provide better protection for children with asthma. The new safety data should be considered by the US Food and Drug Administration for extension of the indications for LAIV to include children with asthma <5 years of age, with the lower age limit to be determined.

INFLUENZA PANDEMIC PREPAREDNESS

Universal influenza vaccination for all children is now under consideration. The current recommendations include all children 6 to 59 months of age, older children

with high-risk conditions, and the household contacts of all children <5 years of age and all high-risk patients. When these groups are combined, a sizable proportion of all children is recommended for annual vaccination, but the coverage is poor for high-risk patients and household contacts; probably less than 15% receive vaccine each year. A recommendation for universal vaccination of all school children and children in day care would increase coverage considerably. The live attenuated influenza vaccine administered by nasal spray is the logical instrument to effect such a program.²⁹ LAIV is easy to administer and readily accepted by children for annual vaccination. The refrigerator-stable product should be licensed in the United States soon. This will simplify storage of the vaccine. Although the cost of LAIV is about double that of trivalent inactivated influenza vaccine, the efficacy of LAIV is usually superior to that of inactivated vaccine. This is especially true when a new influenza variant appears after the vaccine formula is set, as has happened in each of the last 3 years, 2003 to 2006. The cost for low-income and uninsured children recommended to receive influenza vaccine is covered by the Vaccines for Children Program. Universal vaccination of children would not only prevent serious morbidity, reduce school absenteeism, and antibiotic use in children, but also reduce spread of influenza in the community and reduce the exposure of vulnerable high-risk patients, as was demonstrated in the Japanese School Program of influenza immunization.⁴¹ Because children with asthma make up 5% to 10% of the total population, it is important that they participate fully in the influenza immunization program. School-based clinics could facilitate the rapid deployment of influenza vaccine to all segments of the population. If this infrastructure can be established now, it will be invaluable for controlling the next pandemic.

ANTIVIRAL TREATMENT AND PROPHYLAXIS

School-based clinics could be important for implementation of other control measures such as the judicious use of antiviral drugs effective against influenza.⁴² Surveillance that includes rapid detection of influenza infection should be established for the community, and information about influenza prevalence should be rapidly disseminated to all clinicians. This would allow antiviral drug therapy to be initiated early in the course of illness, at least within the first 48 hours. Early treatment of influenza illness would not only reduce the likelihood of complications for the treated patients but also reduce the spread of the virus to immediate contacts. Because school children are the first in the community to be infected, it is logical to coordinate antiviral control programs with school-based clinics. This then becomes the first line of defense for the pandemic virus that will probably arrive before vaccine is available.

Antiviral treatment should also be used for breakthrough infections in children with asthma, whether vaccinated or not. Use of oseltamivir in children with

asthma has produced improvement in pulmonary function.⁴³ In a double-blind, placebo-controlled trial in influenza-infected children with asthma, the improvement in FEV₁ was significant for those treated compared with those who received placebo. Treated patients also experienced fewer asthma exacerbations until day 7 after onset. Oseltamivir was safe and well tolerated by children with asthma. This is an example of what may be accomplished by early recognition and treatment of influenza infections in children. Other available antivirals are listed in Table III.⁴² The prevalent epidemic virus for the 2005 to 2006 influenza season was resistant to the M2 inhibitors amantadine and rimantadine; use of these drugs was not recommended for the season. On the other hand, many of the recent isolates of the avian A(H5N1) have been sensitive to M2 inhibitors, broadening the possibilities for treatment and prophylaxis if this virus should acquire the ability to spread readily in human populations. It will be important to monitor the bulletins from the Centers for Disease Control and Prevention concerning the effectiveness of the battery of influenza antiviral drugs against the currently circulating influenza viruses. Antiviral therapy and prophylaxis can be an important part of the armamentarium to control influenza, both pandemic and inter-pandemic.

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