AMERICAN ACADEMY OF PEDIATRICS

TECHNICAL REPORT
Reduction of the Influenza Burden in Children

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ABSTRACT. Epidemiologic studies have shown that children of all ages with certain chronic conditions, such as asthma, and otherwise healthy children younger than 24 months (6 through 23 months) are hospitalized for influenza and its complications at high rates similar to those experienced by the elderly. Annual influenza immunization is already recommended for all children 6 months and older with high-risk conditions. By contrast, influenza immunization has not been recommended for healthy young children. To protect children against the complications of influenza, increased efforts are needed to identify and recall high-risk children. In addition, immunization of children between 6 through 23 months of age and their close contacts is now encouraged to the extent feasible. Children younger than 6 months may be protected by immunization of their household contacts and out-of-home caregivers. The ultimate goal is universal immunization of children 6 to 24 months of age. Issues that need to be addressed before institution of routine immunization of healthy young children include education of physicians and parents about the morbidity caused by influenza, adequate vaccine supply, and appropriate reimbursement of practitioners for influenza immunization. This report contains a summary of the influenza virus, protective immunity, disease burden in children, diagnosis, vaccines, and antiviral agents. *Pediatrics* **2002;110(6). URL: http://www.pediatrics.org/cgi/content/full/110/6/e80;** ***influenza, vaccine, treatment, diagnosis, antiviral.***

ABBREVIATIONS. HA, hemagglutinin; NA, neuraminidase; IgA, immunoglobulin A; HAI, hemagglutinin-inhibiting; AOM, acute otitis media; CDC, Centers for Disease Control and Prevention; PCR, polymerase chain reaction; TIV, trivalent inactivated influenza vaccine; T-CAIV, trivalent live-attenuated, cold-adapted influenza vaccine; FDA, Food and Drug Administration; GBS, Guillain-Barré syndrome; CI, confidence interval; HIV, human immunodeficiency virus; MMR, measles-mumps-rubella; NIH, National Institutes of Health; TCID, tissue culture infectivity dose.

THE VIRUS

Influenza viruses are classified as orthomyxoviruses and are negative-sense (complementary to mRNA) RNA viruses that contain 8 separate gene segments of RNA. The segmented nature of the genome is important, because it facilitates genetic reassortment, a process by which different influenza viruses coinfecting the same host cell can exchange genes, resulting in progeny viruses containing genes from both parent viruses. Influenza viruses are classified as A, B, or C. Influenza A and B viruses are responsible for seasonal epidemics of influenza, and C viruses are thought to cause sporadic cases of mild cold-like illness. Influenza A viruses are further categorized into subtypes (H1N1 and H3N2) on the basis of the surface glycoproteins, hemagglutinin (HA) and neuraminidase (NA), but B strains are not subtyped. Influenza A viruses cause seasonal wintertime epidemics and, on occasion, global pandemics of disease. Influenza B viruses also can cause seasonal epidemics but are not thought to initiate pandemics. In the current era, influenza A(H3N2) viruses generally have been associated with more severe epidemics than have influenza A(H1N1) or B viruses. At the level of individual patients, however, all strains of influenza A and B can cause clinically indistinguishable disease.

Influenza viruses usually infect and replicate within ciliated respiratory epithelial cells. The HA glycoprotein enables the virus to attach to the cell receptors and fuse with the cell membrane. The NA glycoprotein is less abundant on the viral surface, and its function is less well understood. However, it possesses an enzymatic activity that is essential for efficient release of progeny virions from an infected cell.

ANTIGENIC CHANGE

Antigenic change is one of the hallmarks of influenza viruses and occurs through 1 of 2 distinct mechanisms. Antigenic drift refers to a process by which point mutations in the RNA genome of influenza A or B viruses result in antigenic variants that become predominant. As an increasing number of individuals in the community develop antibody against the circulating strain, selective pressure favors the emergence of one of the variant strains, which becomes the new predominating strain. An antigenic strain typically predominates for a few years and then is displaced by the next emerging strain. Influenza viruses circulate among a diverse range of host species, including birds, horses, swine, and humans. To date, all known 15 subtypes of HA and 9 distinct subtypes of NA have been described among wild bird populations, which are thought to be the ultimate reservoirs for influenza viruses. Antigenic shift refers to the emergence among humans of influenza viruses bearing a new HA or HA/NA combination. Shift

Recommendations in this report do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

occurs through 1 of 2 mechanisms. Genetic reassortment between animal and human influenza viruses can occur if a suitable host, such as a pig, is coinfected by human influenza viruses and nonhuman animal influenza viruses. In this situation, progeny viruses can result that bear a novel HA or HA/NA combination. A second mechanism is when animal influenza viruses directly "jump the species barrier" to infect humans. Although animal influenza viruses are not thought to infect humans commonly, an outbreak occurred in Hong Kong in 1997 when avian influenza A(H5N1) viruses circulating among poultry began infecting humans. Antigenic shift occurs less frequently than antigenic drift. Antigenic shift of influenza B viruses has not been described.

PANDEMIC INFLUENZA

Pandemic influenza refers to a global epidemic of influenza that occurs when an influenza A virus bearing a novel HA or HA/NA combination emerges and spreads. Three influenza pandemics occurred during the 20th century. In 1918–1919, the emergence and spread of influenza A(H1N1), or "Spanish flu," resulted in more than 20 million deaths worldwide, including more than 500 000 deaths in the United States. In 1957–1958, the emergence of influenza A(H2N2) led to a pandemic of "Asian flu." There were approximately 70 000 deaths in the United States in 1968–1969 in association with the emergence of influenza A(H3N2), or "Hong Kong flu." Currently, there is considerable anticipation regarding the emergence of the next pandemic strain.

In 1997, 18 persons were hospitalized and 6 persons died in Hong Kong from complications of influenza A(H5N1) infections, which formerly had been found only in birds. Lack of efficient transmission of this virus among humans and the slaughter of all chickens in Hong Kong are thought to be reasons why this virus did not cause widespread disease.

IMMUNITY

Serum antibody, secretory immunoglobulin A (IgA), and cell-mediated immunity are important in limiting influenza virus infection and promoting recovery.[1,2] Studies also suggest a role for neutrophils in the control of influenza virus infection,[3] and there is strong evidence that influenza virus-induced neutrophil dysfunction is important in the pathogenesis of secondary bacterial infections.[4]

Studies have demonstrated that the concentration of circulating hemagglutinin-inhibiting (HAI), virus-neutralizing antibodies is a good predictor of an individual's relative resistance to natural infection. HAI antibodies are functional in that they block attachment of the viral HA to sialic acid-containing receptors present on the cell surface. An HAI titer $\geq$1:32 against the circulating strain correlates with protection. A strong correlation also exists between concentrations of secretory IgA in the respiratory tract and protection against influenza virus infection.[1,2,5,6] Antibodies to NA limit spread from cell to cell and severity of influenza infection. Natural infection induces immunity to the infecting strain that is long lasting. However, in natural and vaccine-induced immunity, the protective efficacy of antibodies is dependent on how closely the current circulating virus HA and NA proteins match those of the virus strain to which the antibodies were formed.

INFLUENZA IN CHILDREN

Young children have the least immunologic experience with influenza virus infection. In community studies, school-aged children have had the highest rates of infection and disease. Prospective surveillance studies of influenza illness in preschool- and school-aged children demonstrate that annually, between 15% and 42% of children are infected.[7,8] It is estimated that influenza causes an average of 13.8 to 16 million respiratory illnesses yearly among individuals younger than 20 years.[9] When children are infected, they shed infectious virus for longer periods and at higher titers than adults do, which may explain in part why children in child care and school play a central role in the spread of virus in a community. Studies in Texas have documented that during the early stages of epidemics, there is a predominance of cases among school-aged children and that school absenteeism precedes work absenteeism in a community.[7] During influenza outbreaks, hundreds of thousands of children are brought to local emergency departments, clinics, and physicians' offices because of symptoms and complications of influenza infection. Depending on the influenza season, rates of annual outpatient visits attributable to influenza vary from 6 to 29 per 100 children.[8,10]

There is evidence that influenza may be an important factor in the pathogenesis of acute otitis media (AOM) during influenza seasons.[11] It is estimated that 3% to 5% of children experience influenza-associated AOM annually.[8,12] Interestingly, 1 study showed that in 8 children with influenza detected in middle ear fluid, pneumococcus was also isolated in all.[11] The mechanisms by which the influenza virus is thought to contribute to the development of AOM include alteration of eustachian tube function, direct invasion of the middle ear epithelium, alteration of leukocyte function, enhancement of adherence of bacteria to respiratory tract epithelial cells, and decreased mucociliary clearance.[13–18] There is evidence that concurrent viral and bacterial middle ear infection significantly worsens the course of AOM.[19]

Influenza and its complications lead to a 10% to 30% increase in the number of antimicrobial courses prescribed to children during influenza season.[20] It now also has been shown that an antecedent influenza infection is associated with development of severe pneumococcal pneumonia in children.[21]

Only recently has it become fully appreciated that the risk of influenza-associated hospitalization for healthy young children is similar to that for previously recognized high-risk groups. They also appear to be at higher risk of hospitalization from influenza than are healthy 50- to 64-year-olds, for whom routine immunization has been recommended since 2000 (Table 1).[8,20,22–25] Bronchiolitis and severe laryngotracheobronchitis[26] are well-recognized complications of influenza. One study in Japan demonstrated

TABLE 1. Estimated Influenza-Associated Hospitalization Rates (per 100 000 Persons) From Selected Studies

Study Years	Population	Age Group	Persons in Previously Recognized High-Risk Group	Persons Not in Previously Recognized High-Risk Group
1973–1993[20,22]	Tennessee Medicaid	0–11 mo	1900	496 (0–5 mo)–1038 (6–11 mo)
		1–2 y	800	186
		3–4 y	320	86
		5–14 y	92	41
1974–1999[8]	Vaccine clinic	<2 y	—	300–400
1992–1997[23]	Health maintenance organizations	0–23 mo	—	144–187
		2–4 y		0–25
		5–17 y		8–12
1968–1973[24]	Health maintenance organization	15–44 y	56–110	23–25
		45–64 y	392–635	13–23
		≥65 y	399–518	—
1969–1995[25]	National hospital discharge data	<65 y		20–42
		≥65 y		125–228

Adapted from Centers for Disease Control and Prevention. Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep.* 2001;50(RR04):1–46.

among hospitalized children that influenza A was associated with a higher incidence of febrile seizures and of repeated seizures in the same febrile illness than were adenovirus or parainfluenza infections.[27]

Deaths attributable to influenza are far less common in children than they are in the elderly. The fatality rate in children has been estimated to be 3.8 per 100 000.[28] High rates of hospitalization of the young during influenza seasons have been appreciated for decades,[10,29,30] but it has been difficult to determine the percentage of "influenza season" hospitalizations that were attributable to respiratory syncytial virus.[8,20,23] The recently published studies have made reasonable attempts to separate the relative contributions of the 2 viruses.

Estimates of rates of hospitalizations associated with influenza by age group are shown in Table 1. Rates vary greatly among studies because of differences in methodology and severity of influenza seasons. However, it is observed consistently that young children are at substantially higher risk of hospitalization than are older children and that the risk of hospitalization attributable to influenza infection increases in younger children. The percentage of excess hospitalization in young children attributable to influenza in winter months is approximately 20%.[20]

Although serious morbidity and mortality can occur in any person, the risk of complications is increased among pregnant women,[31] those with underlying chronic cardiopulmonary diseases,[22,32] and those with immunocompromising diseases.[33,34] Persons with renal, metabolic, and hematologic diseases are presumed to be at higher risk of severe influenza and its complications.

CLINICAL DIAGNOSIS OF INFLUENZA

Differentiation of sporadic illness attributable to influenza from that attributable to other respiratory viruses is difficult on the basis of clinical signs alone. In contrast, during periods of the year when influenza viruses are circulating in the community, the clinical diagnosis of influenza may have an accuracy of 85%. A timely diagnosis of influenza is important for initiation of antiviral therapy within 48 hours and for consideration of prophylactic measures for the child's family members to decrease intrafamilial spread.

Influenza has an incubation period of approximately 1 to 4 days, depending on the size of viral inoculum. In older children and adults, uncomplicated influenza commonly begins with sudden onset of fever, myalgia, malaise, headache, nonproductive cough, rhinitis, and sore throat. Chills and sweats often accompany fever. Myalgia often correlates with the height of the fever. In children, but less commonly in adults, constitutional symptoms may include vomiting and diarrhea. In children younger than 5 years, the most common findings are fever, cough, and rhinitis. In infants, rhinitis may be the only respiratory manifestation of disease. Host factors, such as young or old age, diminished immune status, or presence of chronic medical conditions like congenital heart disease or chronic lung disease (including asthma), increase the likelihood of developing complications after influenza infection.

Current knowledge about the circulation of influenza in the local community is important in making an accurate diagnosis of influenza during the respiratory virus season. State and local health departments participating in the Centers for Disease Control and Prevention (CDC)'s national surveillance for influenza commonly have information about local influenza activity. Each week from October through mid-May, the CDC posts weekly influenza surveillance reports and other information about influenza on the Internet at http://www.cdc.gov/ncidod/diseases/flu/fluvirus.htm. The weekly surveillance reports include: 1) data (reported by laboratories collaborating with the World Health Organization and the National Respiratory and Enteric Virus Surveillance System) on the total national number of respiratory specimens tested each week for influenza and the number of positive tests by type and subtype; 2) weekly levels of pneumonia and influenza-related mortality (as reported by vital registrar's offices of 122 cities in the United States); 3) state and territorial

levels of influenza activity (as reported by state and territorial epidemiologists); and 4) the weekly percentage of patient visits for influenza-like illness in the offices of more than 600 sentinel physicians.

COMPLICATIONS OF INFLUENZA

Influenza infection can lead to viral pneumonia and to secondary bacterial pneumonia. Typically, the course of influenza pneumonia progresses over a few days with continued fever and new onset of dyspnea and cyanosis. Viral pneumonia is associated with a high mortality rate. In contrast, secondary bacterial pneumonia, usually attributable to *Streptococcus pneumoniae* and occasionally caused by group A β-hemolytic streptococcus or *Staphylococcus aureus*, generally develops after a period of improvement of the primary illness with recrudescence of fever associated with symptoms of pneumonia. Children with a history of stable asthma may experience an acute exacerbation with progression to status asthmaticus. Nonpulmonary complications include myositis with myoglobinuria rarely progressing to renal failure. The development of tenderness in the gastrocnemius or soleus muscles in association with an elevated creatine phosphokinase concentration suggests the possibility of influenza. This is more common after influenza B than after influenza A infection. Myocarditis and pericarditis also have been described. Central nervous system complications include Guillain-Barré syndrome (GBS), transverse myelitis, postinfectious encephalitis, and encephalopathy. Reye syndrome has become increasingly rare after varicella or influenza infection with recent decreases in aspirin use.

Sporadic cases of encephalitis or encephalopathy have been reported from several countries. Since 1994, more than 200 cases of severe, acute necrotizing encephalopathy associated with influenza infection in young children have been reported in Japan.[35–37] It typically manifests as sudden onset of high fever, severe convulsions, and rapid progression to coma. Radiographic imaging has revealed bilateral thalamic necrosis and brainstem involvement in some cases. In most of the reported cases, influenza infection has not been detected directly in cerebrospinal fluid or the brain. However, influenza virus occasionally has been documented in the cerebrospinal fluid by culture or polymerase chain reaction (PCR) assay.[38,39] The pathogenesis of the disorder remains uncertain, and it is possible that the disease process is not a direct result of influenza infection but the result of another factor, such as a medication, associated with influenza. There is a high case fatality rate, and survivors are often severely neurologically damaged.

LABORATORY DIAGNOSIS

A diagnosis of influenza can be confirmed by 1 of 4 approaches: virus isolation, detection of viral proteins, detection of viral RNA, or serologic diagnosis. In children and adults, influenza virus can be isolated most often from respiratory secretions that are obtained by nasal swab, throat swab, or nasal aspirate within the first few days of illness. In young children, viral titers are higher, and viral shedding may continue for several more days than in adults. Viral culture is considered the "gold standard," because it has high specificity and high sensitivity, but the sensitivity is lower than that with PCR assay. Specimens should be placed in transport media on wet ice and can be inoculated into eggs or tissue culture (including MDCK and primary RMK cells). Virus can be detected in cell culture from about two thirds of infected patients within 3 days and from almost all with positive specimens in fewer than 7 days. Viral culture remains important because characterization of viral isolates yields more genetic data than any other technique, and the information provided is critical for annually updating influenza vaccine information and for identifying potential pandemic viruses. However, the practicality of cell culture for making clinical decisions about management is limited because of time requirements, expense, and the need for special handling.

One of the important advances in influenza diagnosis is the introduction of rapid diagnostic assays.[40] The expression of viral antigens can be detected by immunofluorescence within 24 to 48 hours by centrifugation of respiratory secretion specimens directly onto a monolayer of cells in a shell vial.[41] Tests for influenza antigens on exfoliated nasopharyngeal cells using direct or indirect immunofluorescence have shown variable sensitivity (40%–100%) and specificity (86%–99%). Several rapid diagnostic kits that rely on immunoassay or detection of viral NA are commercially available. These so-called rapid antigen detection kits can be used for office-based testing to provide a result within 30 minutes. Currently, 5 such kits are available and 2 are waived under the Clinical Laboratory Improvement Amendments of 1988 (Public Law 100-578). One assay detects only influenza A, 1 assay detects influenza A or B and distinguishes between the 2, and the remaining 3 tests detect influenza A or B but do not distinguish between the 2. Using the appropriate respiratory secretion specimens, these assays may have a high degree of specificity for influenza virus (greater than 90%), although sensitivity in some assays and settings may be modest. PCR assay techniques recently have become available for rapid detection of influenza virus RNA in respiratory secretions, offering high sensitivity and specificity, although contamination of specimens is a concern.[42] The optimal use of rapid tests in the clinical setting remains uncertain because of their relatively low sensitivity and because testing of all patients with respiratory illness is impractical. Nonetheless, the rapid and accurate diagnosis of influenza has become more important with the availability of more influenza-specific antiviral agents, all of which must be started within the first 48 hours of illness to be optimally effective. The one situation in which rapid tests clearly are useful is in the diagnosis of outbreaks of respiratory disease. Rapid diagnosis also may decrease nosocomial transmission and unnecessary antimicrobial use.

Serologic diagnosis of influenza requires the demonstration of a fourfold or greater increase in antibody titer between paired acute and convalescent

serum samples obtained at least 2 weeks apart. Measurement of antibody titer in a single serum sample is of little or no value, with the exception of the unusual situation in which infection with a novel influenza virus is in question. Measurements of HAI antibodies are used most commonly, although complement-fixation testing is also used. Serologic diagnosis is used primarily in epidemiologic studies.

VACCINES

Currently, the only influenza vaccine licensed for use in children in the United States is the trivalent inactivated influenza vaccine (TIV), which has been used for decades. A biologic licensing application for a trivalent live-attenuated, cold-adapted influenza vaccine (T-CAIV) administered intranasally was submitted to the Food and Drug Administration (FDA) in October 2000 and is currently under review. T-CAIV and TIV for use in the United States are produced in embryonated hen eggs. Current formulations of these vaccines contain 3 virus strains: A(H1N1), A(H3N2), and B. The strains are updated annually to match the anticipated epidemic strain.

INACTIVATED INFLUENZA VACCINE

Manufacturing, Handling, and Administration

TIV virus is inactivated using formalin or β-propiolactone and then, in most instances, preserved with thimerosal (1:10 000). The removal of thimerosal from routine childhood vaccines has decreased the theoretical risk of adverse effects, if any, from the small amount of thimerosal in influenza vaccine. TIV contains 15 μg of each HA antigen in a total volume of 0.5 mL. The vaccine should be stored at 2° to 8°C and should not be frozen, because freezing would destroy its potency. Currently, the manufacturers distributing TIV in the United States are Aventis Pasteur, Swiftwater, Pennsylvania (Fluzone); Evans Vaccines, Liverpool, England (Fluvirin); and Wyeth-Lederle Vaccines, Philadelphia, Pennsylvania (FluShield). The amount of time that each of these vaccines can remain at room temperature varies and is included in the package inserts. TIV is given intramuscularly. Children younger than 9 years receiving TIV for the first time should be given 2 doses 1 month apart, with the second dose administered before December. Older children or individuals who received TIV in previous years need only 1 dose. Fluvirin, which can be obtained thimerosal-free, is not licensed for children younger than 4 years, because safety and efficacy have not been established in this age group. A limited number of doses of thimerosal-free Fluzone will be available for the 2002–2003 season.

Safety of TIV

The most common adverse effects associated with TIV are soreness at the injection site and fever. More subjective symptoms, such as nausea, lethargy, headache, muscle aches, and chills, are also reported. Fever is more common in children younger than 2 years (10%–35% of recipients), usually occurring 6 to 24 hours after immunization.[43] Local reactions occur in approximately 6% of young children given the split-virus vaccine and in 15% to 20% of older children and adolescents given whole-virus vaccine, which is no longer used.[44–46] Evaluation of immunization with TIV in children with asthma demonstrates no association with an increase in bronchial hyperactivity.[47,48]

An increase in the number of cases of GBS was reported after the "swine flu" vaccine program in 1976. Intensive surveillance for GBS cases demonstrated a relative risk of 6.2 in immunized versus nonimmunized adults during the 10 weeks after administration of vaccine. This translates into fewer than 10 cases per million immunized.[49–50] Additional investigation revealed that in 3 of 4 influenza seasons studied (between 1977 and 1981), the overall relative risk estimates for GBS after influenza immunization were slightly increased, but the difference was not significant.[51–53] The most recent study of GBS and influenza vaccine examined the 1992–1993 and 1993–1994 seasons and showed a relative risk of GBS of 1.7, which just met significance (95% confidence intervals [CI]: 1.0–2.8; $P = .04$). The number of cases was shown to peak 2 weeks after immunization.[54] Thus, it appears that there may be a slight increase in the risk of GBS (approximately 1 additional case of GBS per 1 million vaccine recipients) among adults after influenza immunization, at least in some years. Rare cases of GBS after TIV immunization in children have been reported. It is unknown whether influenza immunization of individuals with a history of GBS increases the recurrence rate.

Studies of the safety of TIV immunization of children and adults with human immunodeficiency virus (HIV) infection have yielded conflicting results. Some have demonstrated a transient (2- to 8-week) increase in HIV-1 replication and/or a decrease in $CD4^+$ T-lymphocyte cell counts,[55–58] but others have shown no significant effect.[59–63] Most experts believe that the benefits of immunization of children with HIV infection outweigh possible risks.

Allergic Reactions to TIV

Because influenza vaccine is grown in embryonated eggs, children demonstrating severe anaphylactic reaction to chicken or egg proteins rarely can experience a similar type of reaction to influenza vaccine and generally should not receive inactivated influenza vaccine. Inactivated influenza containing thimerosal should not be given to individuals with hypersensitivity to thimerosal. Urticarial reactions to TIV have been reported.

Immunogenicity of TIV

Immunologic priming in young children appears to be important for response to TIV. Children without preexisting serum HAI antibody to vaccine antigens have lower antibody response rates after immunization.[64] Immunogenicity is inconsistent and generally poor in infants younger than 6 months.[65,66] It has been shown repeatedly that seroresponse rates of antibody to HA increase with increasing age of the group immunized, ranging from 70% to 100% among adolescents.[44,46,67] Children younger than 9 years are less likely to have been primed by natural infection

and thus are recommended to receive 2 doses 4 weeks apart the first season they are immunized. In one study, after 2 doses of TIV, between 89% and 91% of 6- to 24-month-old children had an HAI titer of ≥1:40 and/or a fourfold increase in antibody to influenza A(H1N1), A(H3N2), and B.[68]

The ability of immunocompromised patients to respond to TIV immunization depends on the degree of immunosuppression. Most HIV-infected children and adults produce significant antibody increases after immunization with inactivated influenza A, but their absolute antibody concentrations are lower than those seen in age-matched individuals who are not immunized.[58,69–72] However, among patients who have advanced HIV disease and low $CD4^+$ T-lymphocyte cell counts, influenza vaccine might not induce protective antibody titers.[73] Children with cancer who were not receiving chemotherapy more frequently achieved HAI antibody concentrations of ≥1:32 in response to immunization, compared with children receiving chemotherapy.[74] In 1 small study of children with sickle cell disease, HAI response to TIV immunization was adequate.[75]

Efficacy of TIV

Efficacy estimates vary depending on the age group, season, degree of antigenic match between the circulating viruses and vaccine strains, and end points studied. Efficacy studies using laboratory confirmation for diagnosis have higher estimates of protection than do effectiveness studies using clinical illness as the end point, because clinical illness end points include disease caused by other agents. Protective efficacy against influenza illness confirmed by positive culture varies between approximately 60% and 95% when the vaccine strains match the predominant circulating strains.[44,46,64,68,76] Studies in the United States and Japan raise the possibility that immunization of schoolchildren results in diminished incidence of disease in all age groups, including the elderly.[77,78]

Studies on whether influenza immunization protects against AOM have produced conflicting results. The overall incidence of AOM in a group child care center was 36% lower among 187 TIV-immunized children than among the 187 nonimmunized children in other child care centers. In that evaluation, there was an 83% decrease in influenza-associated AOM. The numbers of children with documented influenza and AOM in this nonrandomized study were small.[76] In a second child care center study, 186 children 6 to 30 months of age were randomly assigned to receive TIV or no vaccine and then were followed biweekly by blinded observers. Receiving influenza vaccine was found to be protective against AOM during the influenza season (odds ratio: 0.69; 95% CI: 0.49–0.98).[79] However, a randomized, placebo-controlled study of TIV immunization in prevention of AOM among more than 750 children 6 to 24 months of age failed to show decreases in the incidence of AOM or in duration of middle ear effusion among vaccine recipients compared with placebo receipients.[68]

Vaccine Coverage

Despite recommendations to immunize all children with asthma, only approximately 10% to 31% of this population receive TIV each year.[80–82] In 4 health maintenance organizations studied, 40% of patients with asthma attending an allergy clinic were given influenza vaccine; however, only 1% of all children with asthma made a visit to an allergy clinic.[80] According to parents surveyed, the most important determinant of immunization was physician recommendation.[82]

CURRENT LOGISTIC CONSTRAINTS TO UNIVERSAL IMMUNIZATION OF HEALTHY CHILDREN

Limited Vaccine Quantity

In recent years, approximately 70 million to 90 million doses of TIV have been available annually, which generally meets national demands. However, the national distribution of vaccine has been delayed during the past 2 seasons. Currently, vaccine is recommended for more than 100 million persons traditionally considered to be at high risk of serious complications from influenza. Approximately half of all vaccine is used by persons not at high risk of complications. Vaccine demand among both groups has been increasing, and therefore, a larger, more dependable supply of vaccine is desirable before a universal recommendation for young children is implemented.

Seasonal Vaccine Availability

Global surveillance of circulating influenza strains permits recommendation during spring of the strains to be included in vaccine for the following fall. Once the strains are selected, they must be adapted for growth in embryonated hen eggs, after which large-scale production may begin. The size and number of lots of vaccine that can be grown at any one time in a production facility is limited, and the timing of vaccine lot release cannot be predicted accurately. The earliest that influenza vaccine becomes available generally is September, and immunization needs to begin before widespread influenza outbreaks occur, most of which are in January and February. Consequently, immunizations must be completed in a 3- to 5-month period. This challenge is made more difficult by the necessity to deliver 2 doses of vaccine to immunologically naive children.

Multiple Injections

At this point, the only licensed influenza vaccine is given by intramuscular injection. Until additional combination vaccines become available, US children receive up to 20 separate injections of vaccines during the first 2 years of life. The addition of 1 to 2 more injections may not be well accepted by practitioners, parents, or children. Availability of an intranasally administered vaccine would obviate this issue in some children. However, safety and efficacy data on T-CAIV are limited in children younger than 18 months, and thus, it may not be approved at least initially for use in young children.

Complicated Schedule

It generally is assumed that TIV can be given at the same visit with other childhood immunizations, although studies of this practice are lacking. The same may not be assumed with the live, attenuated T-CAIV. Safety and immunogenicity studies of concurrent immunization with measles-mumps-rubella (MMR) and varicella vaccines are underway.

Recall Systems

Currently, many practitioners lack the computerized tracking and recall systems necessary to efficiently and effectively identify children eligible for immunizations. More widespread availability and use of immunization registries will alleviate this problem.

Personnel Demands

Additional clerical, nursing, and physician time would be required during the fall months to provide influenza immunization to all 6- to 24-month-old children. Not all practices may have the flexibility and capacity to absorb this seasonal increased time demand. Investigators at the University of Rochester, in collaboration with the CDC, are conducting feasibility and implementation studies. Such evaluations need to be performed in multiple out-of-home care settings before it is assumed that universal immunization can be implemented without undue hardship for clinical practices, parents, and children. Cost-effectiveness studies have demonstrated that universal influenza immunization is more likely to be of cost benefit if immunization is performed in group settings that do not require that parents take time off from work. The feasibility of evening and weekend "immunization clinics" in practice settings needs to be evaluated.

Reimbursement Issues

An important determinant of feasibility is whether practitioners will be fairly compensated for the widespread administration of influenza vaccine to young children. Compensation should be determined before it can be assumed that the cost of the additional work and expense of influenza vaccine can be absorbed.

LIVE-ATTENUATED INFLUENZA VACCINE

Viral Strains and Manufacturing

CAIV master strains (influenza A and B) were developed by passaging the viruses at successively lower temperatures in tissue culture.[83] These CAIV strains grow at 25°C, and their replication is restricted at 38°C to 39°C. CAIV strains, similar to the high-growth influenza A strains contained in TIV, are produced through genetic reassortment. The CAIV strains contain 6 genes from the cold-adapted, attenuated-donor virus vaccine strain originally developed by Hunein Maassab, PhD, MPH, as well as 2 genes for the surface glycoproteins, HA and NA, from circulating viruses. Vaccines derived from the master strains developed by Massab and colleagues have been used in clinical trials since 1976. Studies were sponsored by the National Institutes of Health (NIH) from 1976 through 1990, by the NIH and Wyeth Ayerst Research from 1991 through 1993, and by the NIH and Aviron from 1995 to present. Initial NIH- and Wyeth Ayerst-sponsored studies were of monovalent and bivalent influenza preparations administered intranasally. T-CAIV–containing influenza A(H1N1), A(H3N2), and B strains administered intranasally have been evaluated in trials supported by Aviron in conjunction with the NIH. Cold-adapted intranasal vaccines have been used for many years in Russia. The master strains from which they are derived differ from the US vaccine strains and will not be reviewed in this report.

Storage, Administration, and Schedule

Current CAIV formulations used in trials in the United States must be stored frozen (−15°C or colder). The vaccine is thawed immediately before use or may be stored in a refrigerator for no more than 24 hours. Once it is at room temperature, the vaccine must be used within 30 minutes. Each 0.5-mL dose of vaccine contains approximately 10^7 tissue culture infectivity doses ($TCID_{50}$) of influenza A(H1N1), A(H3N2), and B. It is administered intranasally (0.25 mL in each nostril) using a Becton Dickinson (Franklin Lakes, NJ) AccuSpray device, which resembles a tuberculin syringe. This device produces large aerosol particles with an average diameter of 62 μm that deposit in the nose and nasopharynx. As with TIV, children younger than 9 years being immunized against influenza for the first time should receive 2 doses given 1 month apart before the influenza season begins.

Safety in Healthy Children

A total of 15 241 healthy children 12 months to 18 years of age have received T-CAIV in prelicensure trials at a dose of up to $10^{7.0}$ $TCID_{50}$ (manufacturer's data, on file). Second and third annual doses have been given to 2656 and 642 children, respectively. The safety profile did not change with repetitive dosing. In placebo-controlled trials, an increase of approximately 10% in the rate of rhinitis or nasal congestion and an increase of approximately 4% in the rate of low-grade fever (>100°F) have been seen in children given vaccine compared with those given placebo, which was allantoic fluid. The peak incidence of these reactogenicity events is on day 2 or 3 after immunization, and they typically last 1 to 2 days. The largest safety study, performed in northern California by Kaiser Permanente (Oakland, CA), compared medically attended events in vaccine and placebo recipients. In general, the incidence of reactions was higher after the first dose than after subsequent doses of vaccine (see Table 2).[8,84–86] Abdominal pain was reported significantly more often among vaccine recipients than among placebo recipients in the pediatric efficacy study of T-CAIV.[85] In the analysis of medical visits among participants in the Northern California Kaiser Vaccine Trial, abdominal pain was increased in 2 analyses and decreased in 2 others. The overall incidence of abdominal pain was less than 1% in both treatment groups. The

TABLE 2. Reactogenicity Rates in Studies of T-CAIV (10^7 $TCID_{50}$) in Healthy Children 1 to 8 Years of Age

Events*	After Dose 1		After Dose 2	
	T-CAIV (%)	Placebo (%)	T-CAIV (%)	Placebo (%)
Cough	26.9	28.7	27.4	29.0
Runny nose/nasal discharge	57.6	48.0	42.9	42.2
Congestion	10.0	8.6	6.6	7.4
Sore throat	9.5	7.1	6.1	6.4
Headache	4.2	4.1	3.6	2.3
Chills	6.8	4.4	6.0	4.4
Vomiting	16.1	13.1	12.5	11.8
Decreased activity				
Fever				
Grade 1†	16.4	12.3	11.3	10.1
Grade 2‡	2.9	3.5	2.3	3.5
Grade 3§	0.0	0.1	0.3	0.5

* Days 0 to 10 after immunization.
† Oral temperature >100°F, rectal or aural temperature >100.6°F, or axillary temperature >99.6°F.
‡ Oral temperature >102°F, rectal or aural temperature >102.6°F, or axillary temperature >101.6°F.
§ Oral temperature >104°F, rectal or aural temperature >104.6°F, or axillary temperature >103.6°F.

pathogenesis and clinical significance of this observation is unknown, because the cases did not temporally cluster after immunization, and there was not a consistent clinical presentation (S. Black, oral presentation at the Vaccine and Related Biologics Products Advisory Committee, FDA, Bethesda, MD, July 26, 2001). No cases of intussusception have been reported. In the pediatric efficacy study, pneumonia was observed after the first dose in the first year of the study in 7 of 1070 (0.65%) vaccine recipients and in 1 of 532 (0.18%) placebo recipients (relative risk: 3.48; 90% CI: 0.69–39.25). Pneumonia rates in the Northern California Kaiser Vaccine Trial among all vaccine recipients after all doses were 2.21 per 1000 person months versus 2.86 per 1000 person months in placebo recipients (relative risk: 0.77; 90% CI: 0.47–1.28). The pneumonia rates for both studies were not significantly different between the vaccine and placebo groups (manufacturer's data, on file).

Safety in High-Risk Children and Adolescents

More than 1000 children with a history of wheezing illness or mild intermittent asthma have received T-CAIV in the first 2 years of a community protection study in Texas. No clustering of medical care for acute respiratory illness, including wheezing, was observed during the 14 days after immunization. Children were excluded from the Texas study if they were on daily or every-other-day asthma medication, had experienced wheezing in the 2 weeks before enrollment, or had visited an emergency department or had been hospitalized for asthma in the year preceding the study.[87] Data are limited on the safety of T-CAIV in children with moderate to severe asthma. Forty-eight children and adolescents 9 to 17 years of age with moderate to severe asthma, as defined by the National Heart, Lung, and Blood Institute expert panel report, were randomly assigned to receive T-CAIV or allantoic fluid as placebo. There was no significant difference between T-CAIV and placebo recipients in percent change in forced expiratory volume in 1 second from baseline to postimmunization or in any other measures of asthma stability. Two vaccine recipients experienced asthma exacerbation on day 2 and 3 after immunization.[88]

In a study of 41 individuals with cystic fibrosis randomly assigned to receive CAIV or TIV, respiratory and systemic symptoms were infrequent and did not differ significantly between vaccine groups.[89] An immunization crossover trial with T-CAIV enrolled 24 mildly symptomatic HIV-infected children and 25 healthy children. No significant differences were found in rates of reactogenicity events after administration of placebo or the first dose of CAIV within the HIV status groups or between groups. In addition, neither HIV viral load nor CD4 counts or percentages were affected by T-CAIV.[90] Although pregnancy has been a contraindication for participation in CAIV trials, 9 participants were pregnant at the time of immunization (7 T-CAIV recipients and 2 placebo recipients). One woman given T-CAIV had an elective abortion, and the other 6 delivered healthy infants (manufacturer's data, on file).

Transmissibility

Studies of transmission of CAIV strains to nonimmunized contacts have included nasal secretion cultures and serologic evaluation. Several studies have failed to document transmission.[91] However, in 1 child care trial in which 80% of 98 vaccine recipients shed vaccine virus, 1 of 99 placebo recipients shed type B vaccine virus on a single day.[92] The proposed explanation for uncommon occurrence of transmission is that the vaccine virus is shed for a shorter duration and in a much smaller quantity than are wild-type strains. In seronegative children, virus shedding usually occurs from day 2 to day 9 after immunization, and the average peak virus titers approach 10^3 plaque-forming units/mL. The maximal virus shedding observed has been 10^4 to 10^5 plaque-forming units/mL, which is 10- to 100-fold less than that typically seen with natural infection.[93]

Coadministration of CAIV With Other Vaccines

In one small study, 35 children received monovalent influenza A(H1N1) vaccine or placebo with routine childhood vaccines at 2 and 4 months or 4 and 6 months of age, and no significant effect on the immunogenicity of the childhood vaccines was seen.[94] Although no data about concurrent administration of T-CAIV and routine childhood vaccines are currently available, a study is underway of coadministration of T-CAIV with MMR and varicella vaccines.

Genetic Stability

In multiple studies conducted over 20 years, no reversion of the CAIV strains to a virulent phenotype in vaccine recipients has been detected. The stability of CAIV is attributed to the fact that the donor strains contain attenuating mutations in at least 3 genes and that the overall replication of the vaccine virus in the human mucosa is low. Consequently, the probability of generating mutants that have lost the attenuated phenotype is small.[95–100]

Reassortment

If an individual infected with CAIV strains is coinfected with wild-type influenza, mixing of viral genes could take place, resulting in production of reassortant viruses. It is likely that such reassortant strains would be attenuated compared with the wild strains, and the worst outcome would be that the reassortant strain was as virulent as the wild strain. However, there are clearly epidemiologic situations in which use of a CAIV would be unwise. It could be problematic if a CAIV strain bearing novel HA or NA surface proteins were introduced in anticipation of a pandemic that did not take place, such as the outbreak of an influenza A(H5N1) virus in Hong Kong that did not spread as widely as anticipated. Premature introduction of CAIV strains with novel surface proteins should be avoided, because reassortment between, for example, an H5 CAIV strain and wild-type human influenza could result in a transmissible strain containing H5, to which the population is not immune.

Immunogenicity in Healthy Children

Because CAIV is a live vaccine administered intranasally, the resulting immune response is likely to mimic the multicomponent immunity induced by infection with wild-type influenza viruses. Studies have demonstrated that immunization with CAIV stimulates HAI antibodies in serum, IgA in nasal secretions, T-cell responses, and interferon production.[101] Nasal IgA antibodies and serum HAI antibody have been correlated with protection from influenza infection.[86,102,103] No precise immunologic correlates of protection by CAIV have been determined, however. Dose escalation studies indicate that the proportion of children who develop an immune response to CAIV increases with increasing dosages of CAIV up to 10^7 $TCID_{50}$.[84,104] Also, in young seronegative children, a 2-dose regimen of trivalent CAIV administered at a 1- to 2-month interval stimulates a serum antibody response in a higher proportion of children than does a single-dose regimen.[85] The immune response varies by vaccine strain[85,105] and by the individual's previous immune status. CAIV stimulates serum antibody responses more readily in recipients who lack previous immunity to the strains in the vaccine.[67,85,103,105,106] This may be the result of more extensive replication of the vaccine virus in the absence of previous immunity[103] or it may be because preexisting antibody titers mask new immune responses.[67,105,106] Apparent viral interference of influenza A(H3N2) replication on the immunogenicity of the A(H1N1) component in trivalent[107] and bivalent[95] vaccines has been demonstrated in 2 studies in young children. Another study demonstrated that a lower percentage of children shed B vaccine virus after immunization with a low-dose (10^4 $TCID_{50}$) trivalent vaccine, compared with the monovalent B vaccine at the same dose. This was overcome by increasing the dose of influenza B virus in the trivalent vaccine to 10^6 $TCID_{50}$.[108]

The proportion of all children who received 2 doses of T-CAIV at 10^7 $TCID_{50}$ demonstrating a fourfold increase in HAI antibody and the proportion who achieved an HAI titer ≥1:32 are shown in Table 3 (manufacturer's data, on file). As anticipated, children who were seronegative at the time of first immunization showed higher rates of fourfold increases but lower or similar rates of achieving a postimmunization HAI titer of ≥1:32. The proportion with a fourfold increase in HAI titer varied from 43% to 99%, and between 22% and 94% of children had an ultimate titer ≥1:32, depending on the vaccine strain and preimmunization serostatus.

Efficacy of CAIV Against Influenza in Healthy Children

A summary of all published field studies of CAIV in healthy children is presented in Table 4.[46,67,85,86,96,106,109,110] Vaccine efficacy conferred by CAIV has varied from 34% to 100%. As with TIV, those studies in which efficacy was relatively low tended to occur during a season when the vaccine and wild-type virus strains were not well matched. The 2 largest of these studies were a trial conducted in Tennessee and a multicenter US study. In the Tennessee study, 791 children younger than 16 years were randomly assigned to receive TIV or inactivated influenza B vaccine with bivalent (H1N1, H3N2) CAIV at varying doses over a 5-year period. Efficacy of the vaccine varied by strain and year of study. Vaccine efficacy against influenza illness confirmed by positive culture was higher during influenza A(H1N1) outbreak years (95.5%; 95% CI: 66.7–99.4) than it was during A(H3N2) outbreak years (67.7%; 95% CI: 1.1–89.5).[46] Vaccine efficacy against

TABLE 3. Immunogenicity of 2 Doses of T-CAIV (10^7 $TCID_{50}$)

Vaccine Strain	Prevaccine* Serostatus	Fourfold HAI Increase n/N (%)	HAI Titer ≥1:32 n/N (%)
A/Shenzhen/95(H1N1)†	Seronegative	389/476 (82)	231/476 (49)
	All children	389/500 (78)	256/501 (51)
A/Texas/91(H1N1)†	Seronegative	78/153 (51)	34/153 (22)
	All children	90/209 (43)	8/209 (41)
A/Wuhan/95(H3N2)	Seronegative	388/391 (99)	361/391 (92)
	All children	438/709 (62)	668/710 (94)
B/Harbin/94	Seronegative	464/469 (99)	349/469 (74)
	All children	520/709 (73)	555/710 (78)

Data integrated for serum HAI responses in 3 studies.
* Seronegative indicates ≤1:4 HAI titer.
† The A/Texas/36/91(H1N1) strain was used in 2 studies and A/Shenzhen/227/95 was used in 2 studies.

TABLE 4. Published Efficacy Field Studies of CAIV in Healthy Children

Study	Vaccine Strain(s)	Number Immunized*	Number of CAIV Doses and (Titer Log_{10})	Study Season	Comparison Group (*n*)	Outbreak Strain	End Points	Efficacy† % (95% CI)
Monovalent Vaccine Studies								
Feldman et al[109]	A(H1N1)	28	1 (6.2)	1982–1983	A(H3N2) CAIV (16) A(H3N2) inactivated (12) Placebo (23)	A(H1N1)	ILI plus PC or SCR	34‡ (−75–76)
Belshe et al[110]	A(H3N2)	52	1 (6.5)	1982–1983	A(H1N1) CAIV (51)	A(H3N2)§ A(H1N1)	Febrile illness	62 (7–85)
Wright et al[96]	A(H3N2)	10	1 (6.4)	1980–1981	Age-matched (26)	A(H3N2)	Febrile illness	100 (−4–100)
Monovalent and Bivalent Vaccine Study								
Gruber et al[95]	A(H3N2) or A(H3N2) and A(H1N1)	93	1 (6.2)	1991–1992	A(H1N1) or placebo (88)	A(H3N2)	ILI plus PC	67 (18–85)
Bivalent Vaccine Studies								
Clover et al[67]	A(H1N1) and A(H3N2)	56	2 single annual doses (7.0)	1986–1987	TIV (54), placebo (82)	A(H1N1)	ILI plus PC	81‖ (1–97)
Piedra et al[106]	A(H1N1) and (H3N2)	61	1, 2, or 3 single annual doses (7.0)	1987–1988	TIV (62), placebo (69)	A(H3N2)	ILI plus PC	89 (35–98)
	NA	54	None given	1988–1989	TIV (55), placebo (60)	A(H1N1)		100 (18–100)
Neuzil et al[46]	A(H1N1) and A(H3N2)	250¶ 257¶	Annual (5.7–7.3)#	1986–1987 and 1988–1989 1987–1988 and 1989–1990	TIV (277) Inactivated B (259)	H1N1 A(H3N2)	ILI plus PC	96** (68–99) 68** (1–90)
Trivalent Studies								
Belshe et al[85,86]	A(H1N1), A(H3N2), and B	1070	2 dose year 1†† (6.7)	1996–1997	Placebo (532)	A(H3N2) B	ILI and PC	95 (88–97) 91 (79–96)
		917	1 dose year 2 (7.0)	1997–1998	Placebo (441)	A(H3N2) B		87 (78–93) 100 (79–100)

ILI indicates influenza-like illness; PC, positive culture for influenza; SCR, fourfold antibody increase; NA, not applicable.
* Recipients of CAIV vaccine matching the type or subtype of circulating influenza strains listed under outbreak.
† Estimated efficacy compared with placebo recipients.
‡ Compared with recipients of placebo.
§ Outbreak was predominantly influenza A(H3N2), but 21% of isolates were A(H1N1).
‖ In 3- to 9-year-old children, estimated efficacies were 81% after 2 annual doses and 46% after 1 annual dose.
¶ Person-years are shown.
# Children younger than 3 years received a 10-fold lower dose. Therefore, children younger than 3 years received doses of 4.7 to 6.3, and those 3 years and older received doses of 5.7 to 7.3.
** In recipients of annual doses.
†† 18% of children received only 1 dose year 1.

influenza A(H3N2) and B outbreaks was demonstrated in the US pediatric multicenter trail of T-CAIV.[85] In this trial, 1602 children between 15 and 71 months of age were randomly assigned to receive 1 dose (288 children) or 2 doses (1314 children) of T-CAIV at approximately 10^7 $TCID_{50}$ or placebo during the first year of the study. The wild-type strains that circulated the first season after immunization were influenza A(H3N2) and B. Efficacy of 2 doses of T-CAIV against influenza illness confirmed by positive culture was 96.0% (95% CI: 89.4–98.5) for influenza A(H3N2) and 90.5% (95% CI: 78.0–95.9) for influenza B. There were no differences noted in vaccine efficacy by age of the vaccine recipient. Protective efficacy in children who received only 1 dose of vaccine was also high; it was 86.9% (95% CI: 46.6–96.8) against influenza A(H3N2) and 91.3% (95% CI: 45.6–98.6) against influenza B. Illness was milder in the 14 vaccine recipients who developed influenza, compared with placebo recipients who did. Overall, there were 21% fewer febrile illnesses among the vaccine recipients ($P = .001$) as well as 29% fewer febrile illnesses treated with concomitant antimicrobials. Eighty-five percent of the children who participated in the US multicenter study returned for reimmunization before the next influenza season and received vaccine or placebo as they had previously. The influenza (A/Sydney/H3N2) that circulated in year 2 was a drifted strain that did not match the vaccine strain (A/Wuhan). Despite the strain differences, the T-CAIV was 85.9% (95% CI: 75.3–91.9) efficacious in preventing influenza illness confirmed by positive culture attributable to influenza A/Sydney, indicating good heterotypic protection against this strain.[86]

The efficacy of T-CAIV against influenza A(H1N1) infection could not be determined in the multicenter US trial, because A(H1N1) did not circulate during either season. Therefore, a challenge study was performed in 222 randomly chosen previous vaccine and placebo recipients. Six to 8 months after reimmunization in year 2 of the study, children were given the influenza A(H1N1) vaccine strain intranasally at a 10^7 $TCID_{50}$, and viral shedding was monitored. Previous immunization was 82.9% (95% CI: 60.2–92.7) efficacious in preventing shedding of influenza A(H1N1) vaccine strain virus after challenge. In addition, vaccine recipients who had positive cultures for influenza A(H1N1) terminated shedding significantly sooner than did previous placebo recipients.[111]

Efficacy of CAIV Against AOM

A study in which 183 children were randomly assigned to receive monovalent influenza A(H3N2), monovalent influenza A(H1N1), bivalent influenza A(H3N2/H1N1) vaccine, or placebo was followed by circulation of influenza A(H3N2) wild-type virus. Four percent of the 93 children who received an influenza A(H3N2)-containing vaccine were determined to have AOM associated with an influenza illness confirmed by positive culture, compared with 14% of the 88 children who received influenza A(H1N1) vaccine or placebo. The point estimate of vaccine efficacy against influenza A(H3N2)-associated otitis media was 67% in this study.[95] In the US multicenter T-CAIV efficacy study, the vaccine efficacy against otitis media associated with influenza illness confirmed by positive culture was 97.5% (85.5, 99.6). The overall decrease in all episodes of otitis media during the influenza season among vaccine recipients compared with placebo recipients was 8.7% (95% CI: −5.5–20.8), and the decrease in all episodes of febrile otitis media was 30.1% (95% CI: 11.3–45.0).[85,86]

Conclusion

T-CAIV appears to be safe and effective in healthy children and, if licensed, will afford an alternative route of immunization for eligible children. Recommendations for its use will be issued after the vaccine is licensed by the FDA.

COMPARISON OF IMMUNOGENICITY AND EFFICACY OF TIV AND CAIV IN CHILDREN

In comparison with TIV, the HAI seroresponse rates and enzyme-linked immunosorbent assay antibody concentrations induced by CAIV are lower. Because CAIV also provides protection by stimulation of local secretory IgA, serum antibody responses may underestimate the degree of protection afforded. The optimal comparison of TIV and CAIV are "head-to-head" comparative trials of protective efficacy. No such studies have been conducted in children using T-CAIV. There are, however, 2 studies in which children were randomly assigned to receive bivalent influenza A(H1N1/H3N2) CAIV at 10^7 $TCID_{50}$, TIV, or placebo. The results are summarized in Table 5. The Baylor Family Study[44,67,106] enrolled 578 children between 3 and 18 years of age. The enrollment was by family, and any family remaining in the study for more than 1 year received the same treatment each year. Children received bivalent CAIV during years 1, 2, and 3. Efficacy was determined only for the second (1986–1987), third, and fourth year of the study, because influenza A did not circulate during the first season. In the fourth year, no vaccine was given, but surveillance for influenza continued. The influenza A(H1N1) strains in the vaccine given during year 3 were well matched with the strain that circulated during year 4, and CAIV and TIV conferred protection that lasted through the fourth season. Point estimates of protective efficacy were higher with CAIV than with TIV, but there were no statistically significant differences between CAIV and TIV efficacy rates.

A study conducted at Vanderbilt University compared efficacy rates of TIV and bivalent CAIV at $10^{5.7}$ to $10^{7.3}$ $TCID_{50}$ in children and adults over a 5-year period.[97] The subset of 791 children younger than 16 years has been analyzed recently.[46] In this study, influenza A(H1N1) and A(H3N2) each circulated during 2 seasons. In both years, the wild-type influenza A(H3N2) was a drifted strain, and in another year, the circulating influenza A(H1N1) did not match the vaccine strain. There were no significant differences between the efficacies of the 2 vaccines for all years combined. Efficacy of TIV against influ-

TABLE 5. Comparative Efficacies* of TIV and Bivalent CAIV

Subtype	Year 2		Year 3		Year 4*	
	CAIV % (95% CI)	TIV % (95% CI)	CAIV % (95% CI)	TIV % (95% CI)	CAIV % (95% CI)	TIV % (95% CI)
Baylor Family Study (Clover,[67] Piedra[106])						
A(H1N1)	81 (1–97)	56 (−17–84)	—	—	100 (18–100)	78 (35–97)
A(H3N2)	—	—	89 (35–98)	67 (−6–90)	—	—

Strain	CAIV	TIV
Vanderbilt Study (Edwards,[105] Neuzil[46])		
A(H1N1)	96 (67–99)	91 (64–98)
A(H3N2)	68 (1–90)	77 (20–94)

* No immunization given in year 4.

enza A(H1N1) was 91.4% (95% CI: 63.8–98.0) versus 95.5% (66.7–99.4) for CAIV. Against influenza A(H3N2), TIV provided a protective efficacy of 77.3 (95% CI: 20.3–93.5) and CAIV was 67.7% (95% CI: 1.1–89.5) efficacious.

COSTS OF INFLUENZA IMMUNIZATION

Whether universal immunization of young children would result in a net cost or a net savings to society depends on several factors. The factors that have the biggest effect on the economics of routine immunization of children against influenza are the attack rate, the rates of health outcomes (ie, outpatient visits, hospitalizations, and deaths), and the costs of immunization. The attack rate and rates of health outcomes can vary considerably from year to year, and regional variation is possible for both of these factors within a given season. These variations make it impossible to generate a single, precise estimate of the cost-effectiveness or the cost-benefit of universal immunization of children.

The total cost of immunizing a single child consists of direct and indirect costs. The direct costs include supplies (eg, syringe, vaccine), personnel, and administrative expenses. Indirect costs can be a significant component of the total cost of immunization. One of the most important components of the indirect costs is the time lost by parents or caregivers from work when they take children to be immunized. Three studies have suggested that universal childhood immunization may save money if immunizations can be performed in a group-based setting, such as after-hours or weekend immunization clinics that do not require parents to miss work.[112–114] Another important unknown is the magnitude of decreased transmission that may occur from widespread immunization of children. A subcommittee of the Advisory Committee on Immunization Practices, after a review of the major economic studies of influenza immunization,[112–116] concluded that it is unlikely that universal pediatric influenza immunization will generate savings, from a societal perspective, unless the total costs of immunization are less than $20 to $25 per child immunized (M. Meltzer, oral presentation at the ACIP Influenza Workshop, Atlanta, GA, September 11, 2001).

ANTIVIRAL MEDICATION

Four influenza antiviral drugs are currently licensed in the United States: amantadine hydrochloride, rimantadine hydrochloride, zanamivir, and oseltamivir phosphate (Table 6).

M2 Inhibitors

Amantadine and rimantadine are tricyclic amines that inhibit the replication of influenza A virus at concentrations less than 1.0 μg/mL. In vitro, rimantadine is up to 10 times more active than amantadine. These antiviral agents inhibit the replication of influenza A by preventing hydrogen ion passage through a channel formed by the viral M2 protein.[117,118] This inhibits uncoating by preventing dissociation of the matrix proteins and the nucleoprotein complex within vacuoles of the infected cell and blocks viral replication. M2 inhibitors are licensed for chemoprophylaxis in children 1 year or older.[119]

Prophylaxis with either drug can prevent approximately 70% to 90% of influenza A illness, which is equivalent to protection from immunization.[120] The recommended dose for each drug for children younger than 10 years is 5 mg/kg of body weight per day in 1 or 2 doses, not to exceed 150 mg/day. For children 10 years and older, the dose is 100 mg twice a day.

Amantadine and rimantadine also are licensed for treatment of uncomplicated disease attributable to

TABLE 6. Antiviral Drugs for Influenza

	Amantadine	Rimantadine	Zanamivir	Oseltamivir
Virus	A	A	A and B	A and B
Administration	Oral	Oral	Inhalation	Oral
Treatment indications*	≥1 y of age	≥13 y of age	≥7 y of age	≥1 y of age
Prophylaxis indications*	≥1 y of age	≥1 y of age	Not approved	≥13 y of age
Adverse effects	Central nervous system, anxiety	Central nervous system, anxiety	Bronchospasm	Nausea, vomiting

* Approved ages.

influenza A.[119] Rimantadine has not been studied in young children and is not approved for treatment of disease in children younger than 13 years, although it is approved for prophylaxis and is sometimes used for treatment in this age group. Both drugs can decrease the severity and shorten the duration of influenza A illness in healthy subjects by approximately 1 day when therapy is started within 48 hours of onset of symptoms. In most studies, treatment decreased the amount of influenza virus shed in respiratory secretions, thereby decreasing infectivity. It is not known whether treatment with amantadine or rimantadine decreases the risk of serious complications in high-risk patients. Treatment does not appear to alter the overall immune response to infection, although it may decrease secretory antibody concentrations.[121]

Amantadine and rimantadine are excreted in the urine, and dosage adjustments are necessary for children with renal disease. Amantadine is excreted unmetabolized in the urine. Rimantadine undergoes metabolism in the liver before renal excretion, so adjustment of dosage is suggested for patients with severe liver disease. Disadvantages of amantadine and rimantadine include: 1) lack of activity against influenza B; 2) emergence of resistant viral isolates during treatment; and 3) occurrence of reversible adverse effects on the central nervous system, including nervousness, lightheadedness, difficulty with concentration, and rarely, tremors or seizures. It should be noted that these drugs are substantially less expensive than NA inhibitors, and they therefore have an important role, particularly in outbreak control.

NA Inhibitors

Zanamivir and oseltamivir are 2 members of a class of antiviral drugs called NA inhibitors that were first licensed by the FDA in 1999.[122] The NA inhibitors are analogs of sialic acid and were designed specifically to block the enzymatically active region of the NA glycoprotein molecule that resides on the surface of the influenza virion.[120] The NA active site is highly conserved among influenza A and B strains, including all known[9] influenza A NA subtypes, suggesting a possible role in control of the next influenza pandemic. NA activity cleaves the terminal sialic acid residue of the host cell receptor, enabling release of progeny viral particles from the surface of infected cells and destroying the receptor recognized by viral HA. NA activity also facilitates release of errant viral particles that attach to mucoproteins present in respiratory secretions, enhancing viral penetration through mucous secretions, preventing viral aggregate formation, and resulting in more efficient infection of respiratory columnar epithelial cells. Inhibition of NA activity decreases the risk of infection (prophylaxis) and shortens the duration of influenza illness (treatment). Concentrations more than 10^6-fold higher are necessary to inhibit NA activity from mammalian sources, indicating that the drugs are highly specific for the influenza NA.

Young children play an important role in the spread of influenza. Prevention of influenza among household contacts is important in minimizing community outbreaks. A recent study evaluated the efficacy of postexposure prophylaxis with oseltamivir among household contacts of a person infected with an index case of influenza.[126] Efficacy in prevention of clinical influenza among household contacts older than 11 years was 89%, compared with placebo recipients, when prophylaxis was initiated within 48 hours of exposure. This occurred even in the absence of treatment of the person with the index case of influenza. Oseltamivir is approved by the FDA for prophylaxis in individuals 13 years and older. A similar level of protection among persons 5 years and older using zanamivir has been demonstrated in a family study; however, this drug is not currently licensed for this indication.[127]

NA inhibitors are licensed by the FDA for treatment of uncomplicated disease caused by influenza A or B when symptoms have been present for fewer than 48 hours.[123] Zanamivir (Relenza [GlaxoSmith Kline, Research Triangle Park, NC]) is an inhaled topical powder that is licensed for treatment of influenza in children as young as 7 years. The drug is administered using a breath-activated inhalation device that delivers approximately 7% to 21% of the inhaled dose to the lungs. A dose of 10 mg is administered twice daily for 5 days. Patients should receive specific instructions on the use of the delivery system. Oseltamivir (Tamiflu [Roche Laboratories, Nutley, NJ]) is an oral formulation (tablet or suspension) that is cleaved by esterases in the gastrointestinal tract or blood, resulting in approximately 80% bioavailability. Oseltamivir has been licensed for treatment of children older than 1 year. For children, the dose is 2 mg/kg, administered twice daily (maximum adult dose is 75 mg twice a day) for 5 days. In clinical trials, viral shedding in nasal secretions was significantly decreased compared with placebo recipients, suggesting decreased risk of viral transmission in patients who receive treatment.

Zanamivir treatment was studied in a randomized, controlled trial in 346 children between 5 and 12 years of age who were infected with influenza A or B.[124] Treatment with zanamivir decreased symptoms by a median of 1.25 days compared with placebo, representing a 24% decrease in duration of symptoms and a 15% more rapid return to normal activity. No significant difference was found between zanamivir and placebo groups in terms of antimicrobial use (12% vs 15%). There was no difference in occurrence of adverse events between zanamivir recipients and placebo recipients.

Oseltamivir treatment of influenza has been evaluated in children between 1 and 12 years of age in a randomized, double-blind, placebo-controlled study.[125] Among 457 children with documented influenza infection who were treated within 48 hours of onset of symptoms, the median duration of illness was decreased by 36 hours in the oseltamivir group. Incidence of otitis media was decreased by 44% in oseltamivir recipients compared with the placebo group (12% vs 21%). There was a significant decrease in the number of antimicrobial prescriptions for chil-

dren receiving oseltamivir (31% vs 41%). Gastrointestinal disturbances occurred in 14.3% of oseltamivir recipients and 8.5% of placebo recipients, although fewer than 2% discontinued medication because of adverse effects.

Treatment with antiviral therapy should be considered for any high-risk child who develops influenza or for any other child with influenza in whom it may be useful to decrease the duration of symptoms.

The safety and efficacy of zanamivir in patients with chronic lung disease have not been established. Some patients with a history of asthma have experienced bronchospasm; therefore, zanamivir is generally not recommended for patients with underlying airway disease. Oseltamivir is associated with nausea and vomiting in approximately 10% of recipients. These adverse effects may be decreased if the drug is taken with food, which does not affect peak plasma concentration or bioavailability. Emergence of isolates that are resistant to NA inhibitors occurs; however, such mutants appear to be less infectious than wild-type isolates.

Conclusion

The availability of NA inhibitors will not alter guidelines for annual use of influenza vaccine, because immunization is the most efficient and cost-effective means of disease control. NA inhibitors have no activity against other respiratory viruses and should be used only for treatment of infections attributable to 1 of the influenza viruses. Treatment efficacy appears to be similar to that of amantadine and rimantadine. None of the antiviral agents are likely to be effective when symptoms have been present for more than 48 hours in an immunocompetent host, emphasizing the importance of rapid diagnosis. Studies of NA inhibitors to date provide only limited experience on effectiveness in high-risk children, and none of the 4 agents have been shown to prevent serious complications, such as bacterial or viral pneumonia. Most studies have evaluated efficacy in treatment of patients with uncomplicated influenza. Comparative studies between NA inhibitors and M2 inhibitors for treatment or prophylaxis are not available. Factors that will influence selection of one antiviral drug over another include cost, compliance, adverse effects, influenza strain, and route of administration.

CONCLUSIONS

Young children are hospitalized for influenza at rates similar to those experienced by the elderly. Among the young, hospitalization rates are inversely related to the age of the child, being highest in those younger than 6 months. However, no influenza vaccine is approved for infants younger than 6 months. Because they are at increased risk of cardiopulmonary complications from influenza infection, immunization is recommended for women who will be in their second or third trimester of pregnancy during influenza season. Studies are needed to determine if maternal immunization affords subsequent protection to the infant.

It appears that more widespread influenza immunization of young children and their close contacts is justified by the disease burden in this age group. The ultimate goal is to prevent disease in the young through immunization. An immediate recommendation for universal immunization appears to be premature, however, until logistic and economic issues have been further evaluated.

SUMMARY

1. Practitioners should increase their efforts through tracking and recall systems to ensure that children traditionally considered at high risk of severe disease and complications from influenza receive annual immunization. TIV is approved for children 6 months and older. Recommendations for appropriate use of the live-attenuated intranasal vaccine will be issued after it is licensed by the FDA. High-risk children and adolescents to receive priority for influenza immunization are those with the following (evidence grade II-3 [see Appendix A]):

   - Asthma or other chronic pulmonary diseases, such as cystic fibrosis
   - Hemodynamically significant cardiac disease
   - Immunosuppressive disorders or therapy
   - HIV infection
   - Sickle cell anemia and other hemoglobinopathies
   - Diseases requiring long-term aspirin therapy, such as rheumatoid arthritis or Kawasaki syndrome
   - Chronic renal dysfunction
   - Chronic metabolic disease, such as diabetes mellitus

   Other individuals who should receive priority for influenza immunization include:

   - Women who will be in their second or third trimester of pregnancy during the influenza season (evidence grade II-3)
   - Persons who are in close contact with high-risk children, including (evidence grade II-3):
     —All health care personnel in contact with pediatric patients in hospital and outpatient settings
     —Household contacts, including siblings and primary caregivers, of high-risk children
     —Children who are members of households with high-risk adults, including those with symptomatic HIV infection
     —Home caregivers for children and adolescents in high-risk groups

2. Young, healthy children also are at high risk of hospitalization for influenza infection; therefore, the American Academy of Pediatrics encourages influenza immunization of healthy children between 6 and 24 months of age to the extent logistically and economically feasible (evidence grade II-3). This applies to any child who will be 6 through 23 months of age anytime during influenza season, which extends from the beginning of October through March. Children should not be immunized before they reach 6 months of age.

Influenza immunization of household contacts and out-of-home caregivers of children younger than 24 months also is encouraged when feasible (evidence grade III). Immunization of close contacts of children younger than 6 months may be particularly important, because these infants will not be immunized.

3. Antiviral drugs are an adjunct to, not a substitute for, the prevention of influenza with immunization. Amantadine and rimantadine are licensed for chemoprophylaxis of influenza A in children 1 year or older. Oseltamivir may be used for prevention of influenza A and B in persons 13 years and older (evidence grade I). Chemoprophylaxis may be considered for the following situations (evidence grade III):

   - Protection of high-risk children during the 2 weeks after immunization while an immune response is developing or if the children are immunized after influenza circulation has been documented (chemoprophylaxis is not recommended if immunization occurs before influenza viruses have begun to circulate)
   - Protection of children at increased risk of severe infection or complications, such as high-risk children for whom the vaccine is contraindicated (ie, those with a history of anaphylactic reaction to eggs)
   - Protection of nonimmunized close contacts of high-risk children
   - Protection of immunocompromised children who may not respond to vaccine
   - Control of influenza outbreaks in a closed setting, such as an institution with high-risk children
   - Protection of immunized high-risk individuals if vaccine strain poorly matches circulating influenza strains

Appendix A. US Preventive Services Task Force Rating System of Quality of Scientific Evidence[128]

I: Evidence obtained from at least 1 properly designed randomized, controlled trial

II-1: Evidence obtained from well-designed controlled trials without randomization

II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferentially from more than 1 center or group

II-3: Evidence obtained from multiple time series with or without the intervention, or dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s)

III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

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