SPECIAL ARTICLE

Infection by Influenza Virus in Childhood: A Call for Broader Influenza Vaccination

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Introduction

Influenza, described by Hippocrates in 400 BC, is a transmissible, highly contagious, rapidly propagating acute disease that causes serious problems in a population. Influenza can be sporadic, epidemic, or pandemic and all age groups are affected. Forty percent of preschoolers and 30% of school children may become infected during epidemics.[1] These children act as vectors for the disease in their homes and in the rest of the community because, while adults clear a small number of viruses for only a few days, children shed large quantities for 2 weeks,[2] creating an epidemic wave that precedes the peak incidence of the infection in the entire population.[3,4]

Until now vaccination has been for all individuals over 6 months of age with chronic diseases that render them susceptible to complications or for individuals who could transmit the virus to high-risk patients.[5-7] The vaccination calendar proposed in 2003 in the United States of America by the Committee on Infectious Diseases of the American Academy of Pediatrics also considered the possibility of regularly vaccinating all healthy children between 6 and 23 months old.[8]

With this recommendation in mind and given that such an immunization policy is not contemplated for Spain,[9] we considered it opportune to analyze the impact of influenza on the child population—where the disease is commonly perceived as innocuous—and to emphasize the role that children play in transmission. We also reviewed the efficacy of measures to prevent influenza and the types of vaccines in use, and focused on the advisability or not of broadening vaccination recommendations for the child population in Spain.

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Characteristics of the Influenza Virus

The influenza virus is different from other respiratory viruses in the following ways:

– Influenza virus is the only respiratory virus capable of causing recurrent annual epidemics that affect millions of people and generate high health care and social costs. This virus has caused pandemics that have decimated entire populations—as happened in the one occurring in 1918-1919, one of the most deadly pandemics in history. Other pandemics occurred in 1957, 1968, and 1977.

– Influenza virus is the one that most commonly leads to severe bacterial pneumonia—primarily pneumonococcus—perhaps because it decreases pulmonary clearance of *Streptococcus pneumoniae*,[10] thus increasing the bacteria load and the inflammatory response after the organism has been exposed.

– The epidemic process of influenza virus is unique in that some strains (influenza A virus) use a reservoir—host animals—where the pathogens interchange serovars and regularly shift their antigenic surface. These shifts explain not only the severity and spread of some epidemics—since most of the population do not have antibodies for the new strain[11]—but also the difficulty in eradicating the infection since the most common reservoir of all the known substrains of influenza A is water birds, which easily jump the host species barriers.[12]

Annual epidemics come from 1 or 2 predominant strains. At present, besides the influenza B virus, substrains H1N1 and H3N2 of the A virus are in circulation. Any of these strains is capable of becoming predominant at any time or place, in any country, on any continent—thus hampering attempts to predict the serotype and severity of influenza for each season.[12]

Clinical Expression of Influenza Among Children

Although in most cases influenza causes the usual symptoms of acute respiratory tract infection, clinical manifestations can vary widely. Pneumonia and otitis

media are common complications in the youngest children, owing to the loss of ciliary function and epithelial desquamation—both caused by the influenza virus. These changes facilitate the attachment of bacteria to respiratory cells and the subsequent penetration of the bacteria through the damaged epithelium or, in the case of the middle ear, through the eustachian tubes as a consequence of obstructed drainage.[13]

Pneumonia in such instances may be a primarily viral process. However the most common cause of pneumonia is superimposed bacterial infection facilitated by epithelial lesions. Such cases are severe and mortality is high.[14,15]

Acute otitis media may occur in as many as 25% of influenza cases among children[16] and the virus is a relatively common cause of ear infection. In a study of 456 children between the ages of 2 months and 7 years affected with acute otitis media, 186 cases were viral. Influenza A virus was found in 42% of these viral cases and respiratory syncytial virus (RSV) was detected in 74%.[17] These findings—together with other previous reports that vaccination decreases the incidence of middle ear infections in infants and children[18-20]—have led some authors to conclude that the availability of effective vaccines against the most common respiratory viruses would substantially reduce the incidence of acute otitis media.[21]

Other common manifestations of influenza are symptoms of bronchial hyperactivity, which can occur after or during the infection—in both healthy and asthmatic children. Several noteworthy studies deal with this phenomenon. For 2 seasons (November-December, 1993; March-April, 1995), Eriksson et al[22] studied 292 children hospitalized with influenza A infection. The authors evaluated the incidence of post-infection wheezing during the year following the children's hospitalization. They observed that as many as 60% presented at least 2 episodes of bronchial obstruction, 15% of which required hospitalization. In turn, Neuzil et al[23] evaluated consumption of antibiotics, visits to the pediatrician, and rates of hospitalization owing to cardiopulmonary problems among asthmatic children during all the influenza epidemics occurring over 19 consecutive years (1974-1993). To pinpoint the true role of the influenza virus, they compared these data with those collected during the off periods of each season, during which time RVS infections are common. They found that, regardless of age, asthmatic children required more pediatrician visits and more courses of antibiotics. Children younger than 3 years old also required more hospitalizations—3% of total annual hospitalizations—owing to influenza associated cardiopulmonary disease. These authors estimated that from 9 to 19 visits and from 13 to 15 antibiotic prescriptions for every 100 asthmatic children were due to influenza, which is potentially preventible by vaccination. Finally, Kramarz et al[24] studied recurrences in asthmatic children from 1 to 6 years of age, during 3 influenza seasons (1993-1994, 1994-1995, and 1995-1996) during the 2 weeks before and after receiving influenza vaccination. They found a preventive effect of vaccination that ranged from 59% to 78% and a decrease in recurrences from 22% to 41%.

Among the youngest children influenza infection can be especially severe, manifesting with septic shock, which on occasions is associated with croup or pneumonia. Dagan and Hall[25] and Kao et al[26] underscore the frequency of these manifestations among infants. During 2 epidemics of influenza A, Dagan and Hall diagnosed 12 infants younger than 3 months of age with clinical signs of sepsis due to influenza infection. Kao et al studied 37 infants younger than 1 year of age suspected of sepsis or meningitis. Influenza A virus was detected in all pharyngeal samples obtained from these patients.

Reye' s syndrome, among the possible complications of influenza infection, is a severe disease most commonly linked to influenza B and usually associated with the use of aspirin and other salicylates. Other rare complications include Guillain-Barré syndrome, encephalopathy, myocarditis and/or pericarditis.[11,16] The association of encephalitis or encephalopathy with influenza infection can have devastating effects, as demonstrated in a multicenter study carried out in 94 pediatric hospitals on the island of Hokkaido, Japan. During 5 successive epidemic seasons (1994-1999), 64 such cases were detected—47 of which were in children younger than 4 years old. Of the 64 children, 28 (43.8%) died and 13 (20.3%) presented neurological sequelae. These findings led the authors to propose vaccinating children at a younger age than was common practice in order to prevent the devastating consequences of influenza.[27]

The Impact of Influenza on Children

The beneficial effect of viral vaccination on children is difficult to calculate. Mortality data traditionally used to estimate the effect of vaccination on adults are insensitive indicators in children.[28] Among children, the contribution of other viruses, such as RSV, to the morbidity of certain respiratory diseases is much greater.[29] Nevertheless, the data obtained for population studies during influenza epidemics have shown, for the pediatric age group, a greater than expected increase not only for number of hospitalizations due to acute respiratory disease[30] but also for visits to primary health care physicians.[31] Moreover, the conviction exists among pediatricians that the younger the child, the greater the risk of suffering a severe case of influenza, and that infants, although healthy, suffer a higher number of infectious and noninfectious complications compared to older children and young adults.[32,33]

Recent studies have confirmed these convictions. For example, Neuzil et al,[34] in a study in healthy children that complemented their study in asthmatics evaluated the effect of influenza in terms of the same parameters. They found that during influenza epidemics a noticeable increase occurs in all parameters regardless of age but that the increase is especially significant in

children younger than 1 year old, who show an increase in rate of hospitalizations similar to that of high-risk adults, for whom vaccinations are recommended. These authors concluded that, if only individual morbility is taken into account, the impact of influenza on children may be underestimated and that influenza immunization should be considered for the youngest children.

These same authors also analyzed what happens among high-risk children—those under treatment for asthma or other chronic diseases, such as pulmonary bronchodysplasia, cystic fibrosis, immunodeficiencies, cardiopathology, cancer, diabetes, etc.[23] They found that in all such cases, independent of age, the number of hospitalizations was greater than expected but that in cases of children younger than 1 year old the rate of hospitalization was more than 2 to 4 times that of healthy children of the same age—comparable with the rate for high-risk adults. They noted an increase in outpatient visits (from 10% to 20%) during the influenza season and an increase in courses of antibiotics (between 6% and 14%). In other words, visits increased from 7 to 12 and courses of antibiotics increased from 5 to 7 among 100 low-risk children in the same population. They agree with other authors that influenza viral infection is more severe, although not more common, among children with underlying diseases and that the vaccination should be encouraged for all at-risk children.[35]

Izurieta et al,[36] in turn, evaluated whether the youngest children, although healthy, are more likely to be hospitalized with influenza virus infection and to suffer complications. They carried out a 5-year study to analyze the role of influenza virus on RSV, which poses a serious threat for this age group. The study was limited to periods during which the circulation of influenza virus predominated over RSV. They selected all influenza periods of 2 weeks or more, provided no less than 5% of the total number of seasonal isolations of influenza virus and no more than 5% of the positive tests for RSV were detected. Using this method they saw that children younger than 2 years of age with influenza infection require up to 12 times more hospitalizations than children of 5 to 17 years of age with no risk factors (231 versus 19/100 000 person-months), approximating the rates for older children with chronic diseases or a high-risk medical history (386/100 000 and 216/100 000 person-months, respectively). They concluded that regular vaccination against influenza virus for children younger than 2 years of age should be considered.

In a similar study Sugaya et al[37] evaluated the impact of the 1997-1998 influenza epidemic on the number of hospitalizations. They showed that 26.3% of all hospitalizations of patients younger than 15 years of age were due to infection by influenza A virus (H3N2) and that in 7 successive winters from 1991 to 1998, 14% of all admissions were associated with this infection—75% involving previously healthy children with a mean age of 4.4 years.

From another perspective Glezen et al[16] evaluated the risk of contracting influenza infection during the first year of life. On a weekly basis they monitored 209 healthy children during the first 12 months of life and observed that 1 in 3 contracted influenza infection, that only 26 of the 69 infections occurred prior to the sixth month, and that the most severe infections occurred during the last half of the first year. In view of these findings they recommended that active vaccination be initiated at 6 months of age combined with immunization of pregnant women.

The Implications of Vaccinating Children

In 1970 in Tecumseh, Michigan, in the United States of America, vaccination of school children was shown to protect both the children of that city and the adults.[38] Later, other studies showed that vaccination reduced not only the incidence of influenza infection but also the mortality and the number of hospitalizations. Despite this evidence, most programs in developed countries target the elderly. In Japan between 1962 and 1987, however, most of the school-age population received mandatory vaccinations. In 1987 vaccination became voluntary, and in 1994 vaccination was suspended owing to doubts regarding its effectiveness.[39,40] Since 1994 vaccination rates have fallen to very low levels in Japan. The overall results of this experience were recently evaluated by Reichert et al.[39] They analyzed monthly pneumonia- and influenza-related mortality rates from 1949 to 1998 by comparing results obtained in Japan and in the United States—based on the census of vaccinations in both countries. They found a positive effect of influenza vaccination in Japan (not apparent, however, in the United States) that was reflected in a decrease in mortality (3 to 4 times lower in Japan than in the United States) for the duration of the immunization campaign. The vaccination of Japanese children prevented between 37 000 and 49 000 deaths per year—almost 1 death for every 420 children vaccinated. Based on these findings these authors concluded that vaccination of school children provides protection and significantly reduces mortality among older people. As a result they urged reconsideration of the recommended use of vaccination, whether discontinued or held pending, both for children and for adults.

According to the findings reviewed here, once the benefits, risks, economic consequences, and logistics have been taken into account, we support the recent recommendations of the Centers for Disease Control and Prevention of the United States of America and propose that immunization of all children at risk over 6 months old should be considered and, whenever possible, vaccination should be extended to all children between the ages of 6 and 23 months.[5]

Types of Vaccines

At present most vaccines are prepared from inactivated viruses grown in albumin. These viruses may come from whole viruses (whole virions), viral

fragments, or surface antigens (subunits). Whole virions are not indicated for children since virions entail greater risk of postvaccination febrile reaction.[41]

The continuous antigenic drifting and shifting of the virus calls for annual vaccination. Each year the World Health Organization holds 2 meetings at which influenza experts decide on the strains that should be included in the latest vaccine. The meeting for Northern Hemisphere recommendations comes in February (in preparation for the campaign from October 2002 to April 2003 for example) and the September meeting is for the Southern Hemisphere (for the campaign from May to October 2003). The vaccine used in the most recent campaign, 2003-2004, for the Northern Hemisphere was composed of 2 influenza A viruses and 1 influenza B virus: A/New Caledonia/20/99 (H1N1)-like strain; A/Moscow/10/99 (H3N2)-like strain similar to A/Panama/2007/99 (H3N2); and B/Hong Kong/330/2001-like strain.

Dosage

Dosage and protocols for influenza vaccination vary according to the age of the child. Those younger than 35 months old should receive 0.25 mL, while those older than 3 years should receive 0.51 mL. Children younger than 8 years old who are to be vaccinated for the first time ever should receive 2 doses separated by an interval of 4 weeks.[42,43] Each dose should contain at least 15 µg of hemagglutinin for each of the strains in the vaccination. For young children the recommended location for vaccine administration is the anterolateral thigh.

Types of Vaccine to Use

Inactivated influenza vaccines are immunogenic and their safety has been tested for all age groups. The most common adverse effect is the appearance of erythema at the vaccination site during the first 2 days following the procedure and—more rarely—fever, asthenia, and mild muscular pain.[44,45]

Given the positive effects of influenza vaccination on the child population,[19,34] vaccination use and efficacy could be enhanced by using vaccinations that duplicate the patient's own infection and by looking for a way of administering injections that would avoid the unpleasantness of this annual experience. An alternative might be found by using attenuated vaccines, which induce a cellular and humoral type response in the upper and lower respiratory tract. Such a vaccine has infecting power and is thus highly immunogenic without producing the disease.[46] Nevertheless, the attenuated vaccine has been tentatively claimed by some to unleash epidemics.[47]

Development of the first attenuated vaccines began in 1960. Alexandrova et al[48] cultivated a strain that grew at 25ºC, a growing temperature that differed from that of wild-type viruses (38ºC to 39ºC). This cold-adapted strain was tested on young adults and children from 1 to 6 years of age by administering 2 intranasal doses. Later Rudenko et al[49,50] improved the vaccination strain by developing bi- and trivalent vaccines that yielded high response rates. Maasab[51] achieved attenuation of the influenza virus and later he and his team of researchers obtained good results with attenuated cold-adapted vaccines.[52]

At present the most commonly administered vaccine is a trivalent one with 2 influenza A virus subtypes and 1 influenza B virus. The efficacy of this vaccine is amply demonstrated[53] and it even increases with a second dose.[34,54] The Food and Drug Administration of the United States of America approved use of the trivalent vaccine in June 2003 but only for populations from 5 to 49 years of age.[55] Such a vaccine might seem ideal for the child population because it is easy to administer intranasally; it produces immunoglobulin (Ig) A, IgG, and IgM antibodies in nasal secretions of vaccinated children[56]; and it maintains its phenotype such that it is unable to be transmitted to immunocompromised persons in contact with vaccinated individuals.[43] However, a recent meta-analysis on the comparative efficacy of inactivated and live vaccines in children and adults showed no benefits from use of the latter.[47]

Before ending we wish to underscore that, if a public health problem of the magnitude of influenza is to be tackled, the efficacy and effectiveness of vaccination campaigns should be improved by including the healthy child population, since this group comprises the main transmitters of the disease.

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