Effectiveness of trivalent inactivated influenza vaccine in influenza-related hospitalization in children: A case-control study

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ABSTRACT

Influenza is known to be associated with asthma exacerbation but the effectiveness of the trivalent inactivated flu vaccine (TIV) in children, especially children with asthma, in preventing hospitalization is unknown. We assessed the effectiveness of the TIV in all children and especially children with asthma to prevent hospitalization with influenza. We conducted a nested case control study of all pediatric subjects (6 months to 18 years old) who were evaluated at the Mayo Clinic, Rochester, MN, who had laboratory-confirmed influenza during each flu season from 1999 to 2006 to evaluate the efficacy of TIV in preventing hospitalization. A case-control analysis was performed with the cases and the controls being the subjects who did and did not required hospitalization with the influenza illness, respectively. There were 261 subjects with laboratory-confirmed influenza from 1996 to 2006. There was an overall trend toward higher rates of hospitalization in subjects who got the TIV when compared with the ones who did not get the TIV (odds ratio [OR], 3.67; CI, 1.6, 8.4). Using the Cochran-Mantel-Haenszel test for asthma status stratification, there was a significant association between hospitalization in asthmatic subjects and TIV ($p = 0.001$). TIV did not provide any protection against hospitalization in pediatric subjects, especially children with asthma. On the contrary, we found a threefold increased risk of hospitalization in subjects who did get the TIV vaccine. This may be a reflection not only of vaccine effectiveness but also the population of children who are more likely to get the vaccine.

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Immunization is the major public health measure for the prevention of influenza virus infection.[1] Influenza causes more illness each year than any other vaccine-preventable illness.[2]

For the 2007 influenza season, the Advisory Committee on Immunization Practices (ACIP) reemphasized the importance of administering 2 doses of vaccine to all children aged 6 months to 8 years if they had not been vaccinated previously against influenza.[3,4] ACIP also recommended that children aged 6 months to 8 years who had received only 1 dose in their 1st year of vaccination receive 2 doses the following year.[3] The efficacy (prevention of illness among vaccinated persons in controlled trials) and effectiveness (prevention of illness in vaccinated populations) of influenza vaccines depend primarily on the age and immunocompetence of the vaccine recipient, the degree of similarity between the viruses in the vaccine and those in circulation, and the outcome being measured.[3]

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Few studies have been published on the effectiveness of the influenza vaccine among children over multiple influenza seasons.[5] One or more mismatches between the vaccine strain and the circulating strain may contribute to lower vaccine effectiveness in a particular influenza season. Conversely, antigenic similarity between vaccine strain and circulating strain is likely to increase vaccine effectiveness.

Many studies in children <2 years of age have shown suboptimal protection with a single dose in naïve children. We conducted a nested case-control study to evaluate the effectiveness of the trivalent inactivated influenza vaccine (TIV) against medically attended, laboratory-confirmed cases of influenza needing hospitalization in Olmsted County residents who sought care at the Mayo Clinic and associated hospitals between 6 months and 18 years of age over eight influenza seasons.

MATERIALS AND METHODS

Study Population

Children between 6 months and 18 years of age at the start (November 1st) of the influenza seasons (1999–2000 to 2006–2007) were included in the study. The influenza season was defined from November 1 to April 30 for the respective season for all of the seasons in the study period. Only Olmsted County residents

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were included in the study to ensure accurate ascertainment of immunization history. We obtained the unique patient identifier numbers of all influenza-positive polymerase chain reaction (PCR) and viral culture results from the Mayo Microbiology Laboratory for all eight influenza seasons. Real-time PCR/RNA probe hybridization was ordered more often than viral culture because it has proven to be highly sensitive (similar to viral culture) and has a rapid turnaround.[6] Only one laboratory (Mayo Microbiology Laboratory) performed the laboratory tests. The criteria for obtaining respiratory tract specimen for influenza PCR were based on the clinician's suspicion for influenza and were individualized. All of the patients had medically attended influenza illness who may/may not have been hospitalized. This study was approved by the Institutional Review Board and Ethics Committee. Clinical charts were reviewed only for those patients who had provided research authorization.

Case Definition

Cases needed to meet all of the following inclusion criteria:

1. Aged 6 months to 18 years at the start of each of the respective influenza seasons.
2. Laboratory-confirmed influenza virus infection.
3. Resident of Olmsted County.
4. Availability of immunization information.
5. Inpatient hospitalization for influenza.

Control Subjects

A control was selected randomly from among the Olmsted County residents who had been tested for influenza and did have a medically attended influenza (positive result for influenza) but did not need inpatient hospitalization. The controls were Olmsted County residents but not randomly selected from the population. Additional inclusion criteria were as follows:

1. Medically attended, laboratory-confirmed influenza that could be an outpatient/urgent care or emergency room visit.
2. Availability of immunization information.
3. No hospitalization for influenza-related illness.

The diagnosis of asthma was physician based as recorded in the medical charts.

Vaccination Status

Vaccination status was ascertained per immunization records. Electronic medical records were reviewed for immunization history and documentation of influenza vaccination. Vaccination status was ascertained for up to 2 weeks before the episode of medically attended, laboratory-confirmed influenza for the cases. In other words, the subjects were not considered vaccinated until 2 weeks after the shot. Each case had a unique control in each flu season. The case and controls were coded as completely, partial, or unvaccinated following the algorithm shown in Fig. 1 (adapted from ACIP recommendation[3]).

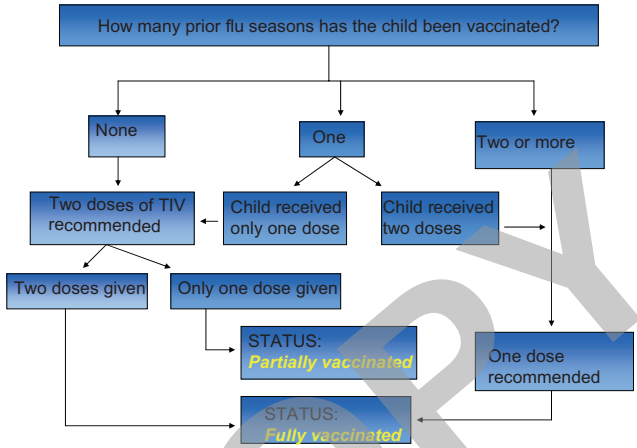

Figure 1. Recommended doses of trivalent inactivated influenza vaccine (TIV) in each influenza season for children 6–59 months of age. (Adapted from 2007 Recommendations of the Advisory Committee on Immunization Practices [ACIP]).

Antigenic Characterization of Vaccine and Viral Isolates

Table 1 shows the antigenic characteristics of the vaccine strain and the circulating strain across the study period. A subtype of influenza was defined as being mismatched if ≥50% of the circulating strains of that subtype (as reported to Center for Disease Control and Prevention) were different and showed poor cross-reactivity to the antigen contained in that year's vaccine.[7]

Statistical Analysis

Our hypothesis for the study was that the TIV vaccination was associated with lower rates of medically attended, laboratory-confirmed influenza-related hospitalization (Table 2).

A contingency table was used to assess the association between TIV and medically attended, laboratory-confirmed influenza-related hospitalization. Vaccination status was used as a categorical exposure.

Statistical analysis was performed using a conditional logistic regression model (JMP software, Version 7.0.1; JMP, Cary, NC) and all reported p values were two sided with a type 1 error rate of 0.05.

Reliability Estimates

The primary abstractor (A.J.) was unaware of the case or the control status of the subject while reviewing their immunization record.

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Table 1 **Distribution of vaccine strain and circulating strain for influenza (1999–2006 flu seasons)**

Years	Influenza A/H3N2			Influenza A/H1N1			Influenza B		
	Vaccine Strain	Circulating Strain	Mismatch Yes/No	Vaccine Strain	Circulating Strain	Mismatch Yes/No	Vaccine Strain	Circulating Strain	Mismatch Yes/No
1999–2000	A/Sydney/05/97	A/Sydney/05/97 (97%)	No	A/Beijing/262/95	A/Bayern/07/95 (32%)* A/New Caledonia/20/99 (67%)	Yes	B/Yamanashi/166/98	B/Beijing/184/93	No
2000–2001	A/Panama/2007/99	A/Panama/2007/99 (100%)	No	A/New Caledonia/20/99	A/New Caledonia/20/99 (95%) A/Bayern/07/95 (5%)*	No	B/Beijing/184/93	B/Beijing/184/93 (11%) B/Sichuan/379/99 (89%)*	No
2001–2002	A/Panama/2007/99	A/Panama/2007/99 (100%) (Neuraminidinase) H1N2	Yes	A/New Caledonia/20/99	H1N2	Yes	B/Sichuan/379/99	B/Sichuan/379/99 (23%) B/Victoria lineage virus (77%)	Yes
2002–2003	A/Panama/2007/99	A/Panama/2007/99 (85%)	Yes	A/New Caledonia/20/99	H1N2	Yes	B/Hong Kong/330/01	B/Hong Kong/330/01 (99%)	No
2003–2004	A/Panama/2007/99	A/Panama/2007/99 (11%) A/Fujian/411/2002 (89%)	Yes	A/New Caledonia/20/99	H1N2 H1N7	Yes	B/Hong Kong/330/2001	B/Sichuan/379/99 (95%) B/Hong Kong/330/2001 (5%)	Yes
2004–2005	A/Fujian/411/2002	A/Wyoming/3/2003 (22%) A/California/7/2004 (78%)	Yes	A/New Caledonia/20/99	A/New Caledonia/20/99	No	B/Shanghai/361/2002	B/Shanghai/361/2002 (68%) B/Shanghai/361/2002 (6%)# B/Victoria/2/87 lineage (26%)	Yes
2005–2006	A/California/07/2004	A/California/07/2004 (73%) A/Wisconsin/67/2005 (27%)#	No	A/New Caledonia/20/99	A/New Caledonia/20/99 (97%) A/New Caledonia/20/99-like (3%)#	No	B/Shanghai/361/2002	B/Shanghai/361/2002 (3%) B/Florida/07/2004-like (15%)* B/Ohio/1/2005 (82%)	Yes
2006–2007	A/Wisconsin/67/2005	A/Wisconsin/67/2005 (24%) A/Wisconsin/67/2005-like (76%)#	Yes	A/New Caledonia/20/99	A/New Caledonia/20/99 (90%) A/Solomon Islands/3/2006(9%)#	No	B/Malaysia/2506/2004	B/Ohio/01/2005 (38%)* B/Ohio/01/2005-like (38%)# B/Yamagata lineage (24%)	Yes

**High titers of antibody to vaccine strain can cross-react with this circulating strain.*
#Reduced titers to ferret antisera produced against vaccine strain.
Source: www.cdc.gov/flu/weekly/fluactivity.htm.

Table 2 **Association of hospitalization and influenza vaccine**

Hospitalization	Yes	No	Total
TIV			
Yes	11	23	34
No	26	200	226

Odds' ratio of hospitalization in TIV recipients: 3.67 (95% CI, 1.6, 8.4).
p = 0.003.
TIV = trivalent inactivated influenza vaccine.

A reliability study was conducted in a smaller sample (25 subjects) of the study subjects by another physician (V.I.) for ascertainment of immunization status. There was complete agreement between the two researchers.

RESULTS

There were 261 subjects with medically attended, laboratory-confirmed influenza illness in the 8-year study period. Two hundred twenty-six (86.5%) subjects were unvaccinated and 35 (13.5%) subjects were vaccinated. Of these 35 vaccinated subjects, 34 subjects received TIV during the respective flu season, and 1 subject received the live attenuated influenza vaccine (LAIV) and was excluded from the analyses. Of the 261 subjects who had a medically attended, laboratory-confirmed influenza illness, there were 57 (21.8%) subjects with asthma, of which 19 (34%) had persistent asthma and 38 (66%) had mild intermittent asthma. In the asthma subset, 13 (23%) had received the TIV vaccine and 44 (77%) subjects were unvaccinated. None of the asthmatic subjects received the LAIV.

Vaccine Effectiveness Estimates

The median age of the cases was 12.2 years (interquartile range, 1.3, 14.4) and the controls were a little older with a median age of 13.9 years (interquartile range, 11.4, 16.0).

Among the 34 cases, 11 were vaccinated (32.4%), and 26 controls were vaccinated (11.5%).

The children vaccinated against influenza (both completely and partially vaccinated) according to the 2007 ACIP guidelines had a higher risk of laboratory-confirmed medically attended influenza-related hospitalization (odds ratio, 3.67; 95% CI, 1.6, 8.4; $p = 0.003$) than the unvaccinated children. There were 4 children who were partially vaccinated and the analyses was rerun considering them unvaccinated and the risk persisted (odds ratio, 2.79; 95% CI; 1.12, 6.92; $p = 0.03$). Using the Cochran-Mantel-Haenszel test for asthma status stratification, there was a significant association between hospitalization in asthmatic subjects and TIV ($p = 0.005$).

In addition, we did not find any association between the severity of asthma and the risk of hospitalization. We also adjusted for socioeconomic issues in an asthmatic subset and we did not find a correlation between access to medical care (using various health care plans as a surrogate) and the risk of hospitalization. There was also no association between length of hospital stay or emergency room visit and the receipt of TIV.

Antigenic Characterization of Vaccine and Viral Isolates

As shown in Table 1, during the 8 years of the study, influenza A/H1N1 circulated all 8 years; in 4 of those years the circulating strain was mismatched from the vaccine strain. In the same time period, influenza A/H3N2 circulated all 8 years; in 5 of those years, the circulating strain was a mismatch. There was an H1N2 circulating strain in 2001–2002, 2002–2003, and 2003–2004 seasons and the H1 component was a close match to the vaccine strain of H1N1. Influenza B circulated during all 8 years of our study; 4 of these years were mismatched with the vaccine strain.

DISCUSSION

This analysis shows that when given as recommended by the ACIP, TIV is not effective in preventing laboratory-confirmed influenza-related hospitalization in children.

There are a few studies comparing the immunogenicity of TIV against LAIV and LAIV has shown superior efficacy not only in children with asthma[8] but also in other children with recurrent respiratory tract infections.[9]

LAIV has shown overall to be more immunogenic in children[10–12] but there is reluctance on the part of the primary care physicians to administer the LAIV in asthmatic children with the perceived risk of transient wheezing, but multiple studies have disproved this risk in toddlers and older children[13–15] as well as in asthmatic patients.[13,16] We only had one subject who had received the LAIV who was excluded from the analyses.

Our study is strengthened by inclusion of only incident cases of influenza from a defined population over a defined time frame and the controls were derived from the same population over the same time frame, thus limiting incidence/prevalence bias.[17]

We tried to limit referral bias[17] by limiting our study only to Olmsted county residents. Our data collection and analysis was designed to reduce exposure suspicion bias.

Our study has several limitations. The inherent limitation of the study is its retrospective nature. We sam-

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pled based on laboratory-confirmed influenza (dependent variable) and evaluated the influenza vaccine status for that influenza season (independent variable). Because this was an observational study, vaccination status could not be randomized. Our controls were drawn from the same cohort. This group was more similar to the case group in terms of healthcare seeking behavior. Our sample size was essentially fixed because it was driven by the incident cases of influenza.

Another concern is about the extrapolation of these study results; Olmsted county is a fairly homogeneous population with >85% population being white, which can affect the generalizability of these results. However, studies of various chronic diseases in Olmsted County with other communities in the United States indicate that data from this population can be extrapolated to a large part of the population of the country.[18]

In addition, most of our cases (70%) came from just two influenza seasons, 2003–2004 and 2004–2005, which may affect the generalizability of our study results.

In conclusion, TIV did not provide any protection against laboratory-confirmed influenza-related hospitalization in children. On the contrary, there was a threefold increased risk of hospitalization in the vaccinated subjects. This may be a reflection not only of the vaccine effectiveness but also the population of children who are more likely to get the vaccine because high-risk subjects are more likely to be vaccinated. We need more studies to assess not only the immunogenicity but also efficacy of different influenza vaccines in asthmatic subjects and possibly consider LAIV in light of its superior immunogenicity and increased efficacy over TIV in children.

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