Published in final edited form as:

Pediatrics. 2008 November ; 122(5): 911–919. doi:10.1542/peds.2007-3304.

Vaccine Effectiveness Against Laboratory-Confirmed Influenza in Children 6 to 59 Months of Age During the 2003–2004 and 2004–2005 Influenza Seasons

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Abstract

Objectives—The goal was to estimate the effectiveness of influenza vaccination against laboratory-confirmed influenza during the 2003–2004 and 2004–2005 influenza seasons in children aged 6–59 months.

Methods—We conducted a case-control study in children with a medically attended acute respiratory infection who received care in the inpatient, emergency department or outpatient clinic setting during two consecutive influenza seasons. All children resided in Monroe County, NY, Davidson County, TN or Hamilton County, OH, were prospectively enrolled at the time of acute illness, and had nasal/throat swabs tested for influenza by culture and/or polymerase chain reaction. Children with laboratory-confirmed influenza were cases and children who tested negative for influenza were controls. Child vaccination records from the parent and from the

child's physician were used to determine and validate influenza vaccination status. Influenza vaccine effectiveness was calculated as $(1 - \text{adjusted odds ratio}) \times 100$.

Results—We enrolled 288 cases and 744 controls during the 2003–2004 season, and 197 cases and 1,305 controls during the 2004–2005 season. Six percent and 19% of all study children were fully vaccinated according to immunization guidelines in the respective seasons. Full vaccination was associated with significantly fewer influenza-related inpatient, emergency department, or outpatient clinic visits in 2004–2005 [vaccine effectiveness = 57% (95% CI: 28%–74%)], but not in 2003–2004 [vaccine effectiveness = 44% (95% CI: -42%–78%)]. Partial vaccination was not effective in either season.

Conclusions—Receipt of all recommended doses of influenza vaccine was associated with halving of laboratory-confirmed influenza-related medical visits among children aged 6–59 months in one of two study years, despite suboptimal matches between the vaccine and circulating influenza strains in both years.

Keywords

Children; Vaccine Effectiveness; Laboratory-confirmed; Influenza

Background

Influenza infections cause a substantial, often unrecognized, burden of disease in young children (1). This annual burden includes an estimated 0.7 to 0.9 hospitalizations, 50 to 95 outpatient visits, 6 to 27 emergency department (ED) visits, and 30 to 90 courses of antibiotics per 1000 children younger than five years of age (1–3). Rates of influenza-related hospitalizations, acute otitis media, and pneumonia are particularly high in children younger than two years of age (1, 3–6).

Recommendations for seasonal influenza vaccination by the Advisory Committee on Immunization Practices (ACIP) have recently expanded for young children. Vaccination of all 6 to 23 month-olds was *encouraged* for the 2002–2003 and 2003–2004 influenza seasons (7), and was *formally recommended* for this age group beginning with the 2004–2005 season. This influenza vaccine recommendation was expanded to include all children from 6 to 59 months beginning with the 2006–2007 season (8, 9). However, few studies have estimated vaccine effectiveness (VE) in young children (10–13). Since influenza vaccination rates may vary by age and by geographic location (14), and since vaccine match varies by season, it is important to assess influenza VE across settings and seasons.

Some previous studies are limited in that they used non-laboratory confirmed outcomes such as influenza-like illness or school attendance, which would result in a lower estimate of VE or have been conducted only during a single influenza season (10–12, 15). In this study, we report on VE over two influenza seasons among children 6 to 59 months using data from an ongoing population-based surveillance system, the New Vaccine Surveillance Network (NVSN), to identify laboratory-confirmed influenza cases from three different geographic regions (1). This geographic diversity allows for a more robust estimate of VE than would data from a single location. The primary objective of our study was to determine the effectiveness of trivalent inactivated influenza vaccine (no live, attenuated vaccine was used because of age) against laboratory-confirmed influenza disease in each of two consecutive influenza seasons.

Methods

Inpatient Population

A prospective, population-based study of hospitalizations attributable to laboratory-confirmed influenza was performed in counties that encompass Nashville, Rochester, and Cincinnati during the 2003-04 and 2004-05 influenza seasons. Each site conducted surveillance at sufficient hospitals to capture at least 95 percent of hospitalizations for acute respiratory illness (ARIs) or fever among children residing in each respective county. More detailed information on site selection, visit rates, and other characteristics of the NVSN have been previously described (1).

Study nurses enrolled children within 48 hours after admission to surveillance hospitals Sunday through Thursday in the 2003–2004 influenza season and seven days each week during the 2004–2005 season. Eligible children were county residents, younger than five years of age, with an admission diagnosis of ARI or fever. Study nurses pre-screened admitted children by presenting complaint. If ARI or fever was present, the child's medical record was reviewed to obtain age and county of residence. An attempt was made to enroll each child determined to be eligible. All eligible children were recruited prior to laboratory determination of their influenza status.

ARI was defined by a presenting complaint of cough, earache, fever (identified through medical documentation or parent report), nasal congestion/runny nose, shortness of breath/rapid or shallow breathing, sore throat, vomiting after cough, or wheezing. Excluded were children with fever and neutropenia associated with chemotherapy; children hospitalized in the prior 4 days or transferred from another surveillance hospital; newborns never discharged from the hospital; and children with symptom duration longer than 14 days (2003–2004 influenza season only). The symptom duration requirement was initially included because the likelihood of viral detection decreases with time (16). It was later removed because it had a minimal impact on enrollment.

Outpatient population

Prospective surveillance for laboratory-confirmed influenza among county residents younger than five years who presented to selected EDs and outpatient primary care practices with symptoms of ARI or fever was conducted during the 2003–2004 influenza season in Nashville, Tennessee (three primary care practices and one pediatric ED with 30% of county pediatric ED visits), Rochester, New York (four practices and one pediatric ED with 60% of visits), and Cincinnati, Ohio (one practice and the single pediatric ED with >95% of visits). During the 2004–2005 influenza season, ED surveillance was conducted in both pediatric EDs in Rochester (>95% of visits) and the pediatric ED in Cincinnati, and clinic surveillance was performed in Nashville (three practices) and Rochester (six practices). Children were enrolled one or two days per week in primary care practices and three or four days per week in EDs, with days and shifts rotated systematically (across all 7 days in EDs and 5-6 days in clinics) to obtain a representative sample. If multiple eligible children were available concurrently in an outpatient practice or ED, study nurses approached eligible children in the order in which they checked in.

In both influenza seasons, ED and outpatient surveillance began the first week after two positive tests for respiratory syncytial virus or influenza virus were identified in local clinical or research laboratories in two consecutive weeks. Surveillance ended after one or no positive tests were detected in these laboratories in two consecutive weeks. Study nurses systematically enrolled approximately six to eight children per setting per surveillance day at each study site in clinics and EDs using the same inclusion and exclusion criteria and enrollment procedure as used for inpatient surveillance.

The study was approved by the Institutional Review Boards at the three study sites, the participating surveillance hospitals and the Centers for Disease Control and Prevention (CDC).

Study Period

For this study, we defined each influenza season as the dates that surveillance started and ended. The dates and duration of each season varied according to site. The 2003–2004 influenza season started in November at all three geographic locations and lasted two months in Nashville, three months in Rochester, and five months in Cincinnati. In Nashville, the 2004–2005 influenza season started in November and lasted five months, while in Rochester and Cincinnati the 2004–2005 season started in December and lasted four months.

Demographic and Clinical Information

A standardized interview was administered to the parent or guardian to obtain demographic information and medical and social history. Demographic information included age, gender, and insurance type (private, public, or none). Underlying medical conditions for which influenza vaccination was routinely recommended during the two influenza seasons (7) were ascertained through parental report and through a chart review. These underlying medical conditions included asthma, cancer, diabetes, heart disease, immune deficiency, kidney disease, sickle cell disease, cystic fibrosis, and chronic lung disease. Neurologic conditions were not included in the list of conditions for which influenza vaccination is recommended until the 2005–2006 influenza season (17).

Virology

Nasal and throat swabs were obtained from each enrolled child and specimens were tested for influenza at each site's local research laboratory using viral culture and reverse transcription-PCR (RT-PCR) as described previously, with the exception that each site tested their subject samples locally under a common protocol, rather than batch-shipping samples to the CDC (18–20). Interlaboratory quality assurance testing was performed by annual analysis of prepared panels of serial dilutions of live influenza A and B viruses, as well as serial dilutions of prepared influenza A and B RNA extracts. The identity of all quality assurance panel specimens was masked, such that the analyses were performed blindly. All 3 sites accurately identified live influenza A and B viruses in culture and after RNA extraction by RT-PCR, and also similarly identified prepared viral RNA extracts [G. A. Weinberg et al., unpublished data]. The CDC served as an external validation source for influenza identification.

Case and Control Identification

Inpatient cases were defined by one positive viral culture or two positive RT-PCR assays and outpatient cases by two positive RT-PCR assays, as PCR was more sensitive than culture (19) and resources were limited for viral cultures of outpatient samples. Children whose specimens tested positive for influenza comprised the cases as of the date of their first symptoms, as determined by parent report. Children whose specimens tested negative for influenza viruses served as controls.

Influenza Vaccination Status

A child's influenza vaccination status at the time of the ARI visit was determined by an initial telephone call or fax to the child's primary care practice and subsequent extraction from the child's primary care medical record. Influenza vaccinations recorded on vaccination cards were also counted if provided by the parent or guardian at the time of the ARI visit. Children were defined as fully vaccinated if they were vaccinated according to the ACIP

guidelines for each season and received: 1) either two vaccine doses in the current influenza season that were administered at least 24 days apart with the second dose given at least 14 days before ARI onset, or 2) one or more vaccine doses in prior influenza season(s) and one dose in the current season administered at least 14 days before ARI onset. Children were defined as partially vaccinated if they received 1) only one of two recommended vaccine doses during the current season at least 14 days before ARI onset or 2) two vaccine doses during the current season, with the second dose within 14 days of ARI onset or less than 24 days after the first dose. The 24-day window was based on the recommended 4-week interval between the first and second influenza vaccine doses (21). Doses given five or more days earlier than 4 weeks apart are to be repeated, which gives an effective interval between doses of 24 days. Children were defined as unvaccinated for a given season if they were not vaccinated in the study season, or if they received the first dose of two recommended influenza vaccine doses within 14 days of ARI onset during the study season. Note that beginning in the 2007–2008 season, under ACIP guidelines children who received only one of two recommended vaccine doses during a prior season and one dose during the current season would not be considered fully vaccinated (22).

Statistical Analyses

All analyses were conducted separately for the two influenza seasons. Conditional logistic regression was used to model the association between influenza vaccination and laboratory-confirmed influenza-related medical visits after adjusting for possible confounders. Controls were matched to cases on geographic location (Nashville, Rochester, Cincinnati), visit setting (ED/Inpatient or Clinic), and two week period based on date of enrollment for controls and date of influenza symptom onset for cases. Enrolled children who had multiple visits captured by NVSN surveillance in a given season were included in the analysis on the visit that they received a laboratory-confirmed influenza diagnosis or on their last visit of the season if they were influenza negative at all visits. We assumed that enrolled children had not had a medical visit due to influenza prior to enrollment in a given season.

Vaccine effectiveness and 95% confidence intervals were estimated based on adjusted odds ratios (aORs) using the formula $\%VE = (1 - aOR) \times 100$. Fully-vaccinated children and partially-vaccinated children were compared to unvaccinated children. Vaccination status was included as complete, partial, or unvaccinated. Other covariates included in the models were age in months, insurance status (public/none versus private), and underlying medical condition (at least one versus none). The simple conditional logistic model had 80% power to detect a minimum VE for full vaccination (compared to no vaccination) of 45% in the first season and 35% in the second based on the number of cases and controls, the rate of full vaccination among controls, and the degree of concordance on vaccination status within matched groups (23).

Stratified VE estimates were calculated by age at visit (6 to 23 months, 24 to 59 months), high-risk status (presence of an underlying medical condition for which vaccination was recommended), and visit setting (inpatient/ED, outpatient). VE estimates were also calculated with the analysis limited to those who were unvaccinated and those who received two influenza doses in the current season with the appropriate intervals between doses and before ARI onset.

We compared non-enrolled eligible children to enrolled children on age (6 to 23 months, 24 to 59 months), gender, and ARI visit setting using Fisher's exact tests.

Analyses were performed using Intercooled Stata version 8.2 and SAS version 9.1.3 (24, 25).

Results

Study Population

2003–2004 Influenza Season—In the 2003–2004 influenza season, the NVSN enrolled 1,033 of 1,237 eligible children (83.5%) 6 to 59 months of age through hospital admissions, EDs, and outpatient clinics. Sixty-one children (6%, 5 cases and 56 controls) were excluded due to missing influenza vaccine status, leaving a study population of 972. Thirteen of the 972 children included in the analysis had multiple visits for a total of 986 captured visits.

Enrolled children did not differ from non-enrolled children by gender ($p = .163$) or age ($p = .644$), but a higher proportion of non-enrolled (52.5%) than enrolled (35.9%) children were screened during an outpatient visit ($p < .001$).

2004–2005 Influenza Season—In the 2004–2005 influenza season, 1,581 of 1,757 eligible children (90.0%) were enrolled in the NVSN from all three patient care settings. Seventy-nine children (5%, 7 cases and 72 controls) were excluded due to missing influenza vaccination status, leaving a study population of 1,502. Thirty-three children had multiple visits for a total of 1,535 captured visits.

Enrolled children did not differ from non-enrolled children by gender ($p = .523$), but they did by age and visit setting. Non-enrolled children were older (55.7% in the older age group) than enrolled children (42.4%; $p = .001$), and a higher proportion of non-enrolled (86.4%) than enrolled (48.5%) children were screened during an outpatient visit ($p < .001$).

Characteristics of Case and Control Patients

Table 1 describes the demographic characteristics and vaccination status for cases and controls in each season. In both age groups, the proportion of fully vaccinated children was higher in 2004–2005 than in 2003–2004 ($p < .001$). In the 2003–2004 season controls tended to be younger than cases, with 46.5% of cases in the 6 to 23 month age group compared with 58.1% of controls ($p = .002$). The median age for cases was 25 months and 21 months in the 2003–2004 and 2004–2005 seasons, respectively; whereas the median age for controls was 20 months in both seasons.

In the 2004–2005 season only, a higher proportion of cases than controls were male. The distribution of cases and controls across the three surveillance counties varied substantially, reflecting the geographic variability of influenza outbreaks. Children with influenza-associated illness accounted for a low of 8% (38/475) of all ARI visits during the 2004–2005 season in Cincinnati compared to a high of 45% (92/204) of all study participants during the 2003–2004 season in Nashville.

Children in both seasons were more likely than their counterparts to have been fully vaccinated if they were in the younger age group, had private insurance, or had an underlying medical condition. [**Table 2**]

Vaccine Effectiveness

2003–2004 Influenza Season—Among children ages 6 to 59 months, neither full nor partial vaccination was associated with a significant reduction in influenza-related visits compared to those who were unvaccinated at the time of the visit. [**Table 3**] One eligible control was not included in the regression models for lack of an appropriate matched case. VE estimates varied between age subgroups, but neither age group experienced a significant reduction in influenza visits as compared to unvaccinated children. When children missing vaccination information were included in the analysis as unvaccinated, the VE estimate for 6

to 59 month-olds went from 28% to 27% (95% CI: -82% to 71%). When the analysis was limited to children who received two doses in the current season compared to children who were unvaccinated, the VE estimate changed to 59% (95% CI: -165% to 90%) among 6 to 59 month-olds and 21% (95% CI: -225% to 81%) among 6 to 23 month-olds. There were not sufficient numbers of children 24 to 59 months old who were fully vaccinated by this definition to perform this analysis.

Figures 1 and 2 show VE estimates for fully vaccinated children compared to unvaccinated children, stratified by high risk status and visit setting (inpatient/ED or outpatient) respectively. Only the high risk stratum demonstrated a significant reduction in influenza-related medical visits compared to unvaccinated children for full vaccination (VE = 89%, 95% CI: 2%-99%). None of the strata had significant VE for partial vaccination (data not shown). Both figures also demonstrate the wide confidence intervals around the VE estimates.

2004–2005 Influenza Season—VE estimates for fully vaccinated compared to unvaccinated children aged 6 to 59 months and for each age subgroup were approximately 60%, with statistically significant results for both age groups and all ages combined. Partial vaccination was not associated with a significant reduction in influenza for all ages or for either age group. [Table 3] One eligible case and eight controls were not included in the regression models for lack of an appropriate matched group. When children with missing vaccination information were included in the analysis as unvaccinated, the VE estimate for 6 to 59 month-olds went from 57% to 53% (95% CI: 23% to 82%). When the analysis was limited to children who received two doses in the current season compared to children who were unvaccinated, the VE estimates were virtually unchanged for the 6 to 59 month and 6 to 23 month age groups (data not shown). There were not sufficient numbers of children 24 to 59 months old who were fully vaccinated by this definition to perform this analysis.

Among fully vaccinated children with and without underlying medical conditions, full immunization compared to no immunization was also associated with an approximately 65% reduction in influenza visits, and was statistically significant for children who were (VE = 67%, 95% CI: 13% to 88%) and were not high risk (VE = 65%, 95% CI: 16% to 76%). [Figure 1] VE estimates for fully vaccinated children stratified by visit setting were close to 60% (and statistically significant) for both inpatient/ED and outpatient settings. [Figure 2] Partial vaccination was not associated with a significant reduction in influenza-related inpatient/ED or outpatient visits (data not shown).

Discussion

We used prospective, laboratory-confirmed surveillance data from three geographically distinct, urban counties in the U.S. to estimate the effectiveness of the trivalent inactivated influenza vaccine in children during the 2003–2004 and 2004–2005 influenza seasons. We found that fully vaccinated children 6 to 59 months of age had 44% and 57% fewer influenza-related medical visits as compared to unvaccinated children in the respective seasons, although only the estimate from the 2004–2005 influenza season was statistically significant. During the 2004–2005 season, the VE for fully vaccinated children was 55% among 6 to 23 month-olds, the age group recommended for routine vaccination that season. Partially vaccinated children did not experience a decrease in influenza rate, compared to unvaccinated children. Our data provide further support for the current influenza vaccine recommendations for all children 6 to 59 months of age and underscore the importance of the two doses of influenza vaccine in the first year a young child is vaccinated.

There were too few fully vaccinated children in the 2003–2004 season (only 62 children) to draw conclusions about VE, but in the 2004–2005 season VE estimates for full vaccination were consistent across strata. This similarity in the VE estimates across strata is of note because of the implication that, in the 2004–2005 influenza season, full influenza vaccination appeared equally effective in preventing influenza morbidity across this age group, with a large range in terms of risk of severe influenza and of host vulnerability (1).

Our study contributes to the existing vaccine effectiveness literature by estimating VE across influenza seasons and patient care settings, using laboratory-confirmed influenza cases. An additional advantage of our study design is the ability to rapidly and efficiently determine VE using influenza-negative children as controls, identified during ongoing surveillance by the NVSN for influenza disease burden.

VE by Age Group

Although our VE estimates for the 2003–2004 influenza season appear to differ substantially by age, these results are not statistically significant and we cannot conclude that there is a true difference between age groups. The 44% VE estimate for children aged 6 to 59 months reflects a combination of the relatively high VE estimate (66%) for the older age group, and the lack of effectiveness in the younger group. Our VE estimates for the 2004–2005 influenza season do not suggest any difference in VE by age group.

Match Between Circulating and Vaccine Influenza Strains

The match between circulating influenza strains and strains included in the vaccine was considered suboptimal for both of these influenza seasons. In the 2003–2004 season, only 11% of influenza A virus specimens, which accounted for 99% of circulating strains, were similar to a strain included in the vaccine based on U.S. virologic surveillance, and the season began earlier and was associated with more pediatric deaths than usual (26). The 2004–2005 influenza season was less severe and the vaccine was a better match to circulating strains than in 2003–2004, but still only 36% of virus isolates were antigenically well-matched to vaccine strains (27). This difference in the match between circulating and vaccine strains between seasons may account for the higher VE estimates in 2004–2005, although differences in age distribution and proportion vaccinated may also have played a role. Characterization of a limited number of isolates from the three study counties agreed with the U.S. data. The seasonal and geographic variation in the proportion of children with influenza in our data reflects the variable nature of influenza epidemics. These variations demonstrate the importance of considering multiple sites and seasons in influenza VE analyses.

Other VE Estimates in Young Children

Our finding of no influenza VE in young children differs from three previous studies of TIV during the 2003–2004 influenza season, although all of these studies, including ours, found no VE for partially vaccinated children. For fully vaccinated children aged 6 to 23 months, Ritzwoller et al. (11) found 49% VE in preventing outpatient office and ED visits (92% of visits were office visits) for pneumonia and influenza, and Shuler et al. (10) found 52% VE in preventing office visits for laboratory-confirmed influenza. Allison et al. (12) found higher VE among fully vaccinated 6 to 21 month-olds: 69% in preventing influenza-like illness office visits and 87% for pneumonia/influenza office visits; these higher VE estimates may relate to the exclusion of children with chronic medical conditions. However, an additional study found VE for live attenuated vaccine, but not for TIV, among older children during the 2003–2004 season (28).

There are a number of possible explanations for the differences between the studies that found VE and our results, including power limitations, geography, the choice of comparison population, and the proportion of fully vaccinated children in the study population who received two vaccine doses in the current season. The small numbers of cases overall and low vaccination rates in the 2003–2004 season (prior to the recommendation for routine vaccination of 6 to 23 month-olds) limited our power to detect VE during that season. In particular, our study did not have sufficient power to estimate influenza VE among 6 to 23 month-old children with office visits, the group most comparable to the other study populations. However, despite limited power, when we restricted our analysis to children who received two vaccine doses in the current season and children who were unvaccinated, our VE estimates for children aged 6 to 59 months rose from 44% to 59%. This finding is consistent with data that suggest young children who receive one dose in the prior season and one in the current season may not be as well protected as those who receive two doses in the current season (29).

We studied different geographic regions than the other studies of young children, two of which were conducted in Colorado (11, 12) and one in Georgia (10), so influenza attack rates may have differed by location. If a higher proportion of cases in the regions we studied were caused by the influenza A drift variant, then we would expect to see lower VE than in the other studies.

Our comparison population, influenza-negative children with ARI, may also account for our finding of lack of VE, if there were differences in the likelihood of being included in NVSN surveillance activities by vaccination status. For example, it is possible that parents who know their children were vaccinated against influenza are less likely to seek care. On the other hand, it is even more likely that the propensity to seek vaccination is related to the propensity to seek medical care in general, and thus children who are vaccinated may be more likely to be seen in outpatient, ED or even inpatient settings due to unmeasured propensity to seek medical care. We were not able to assess factors that would make children more likely to be exposed to influenza virus, such as daycare attendance or number of siblings or family threshold to seek medical care. However, by using influenza-negative children who were receiving medical care and who were enrolled in the same study as a comparison group, we have controlled in large part for the propensity to seek care that can cause confounding in observational VE studies. All the studies that estimated VE in young children during the 2003–2004 influenza season accounted for the propensity to seek medical care to some degree, but including only children with ARI may be a more stringent control than those used in the other studies.

A disadvantage of using influenza-negative children with ARI as controls is that the comparison population can change from season to season depending upon the viruses that are co-circulating during the influenza season. However, we do not expect that fluctuations in the comparison population would compromise the accuracy of VE estimates calculated using influenza-negative children with ARI as a comparison, since influenza vaccine uptake should be similar in children with different types of non-influenza associated ARIs.

We found 55% VE among children aged 6 to 23 months, 63% VE among children 24 to 59 months, and 57% VE among children aged 6 to 59 months during the 2004–2005 influenza season. We know of no other published reports of VE in these age groups for the 2004–2005 season, but in healthy adults VE for TIV was estimated at 66%, despite the dissimilarity between circulating and vaccine influenza strains (30). Lewis and colleagues (31) conservatively estimated that if one half of U.S. children 6 to 59 months of age were fully vaccinated in a year with 50% VE, the direct benefit would be the prevention of

approximately 2,250 hospitalizations and 270,000 to 650,000 outpatient visits for influenza-attributable illnesses.

Limitations

Due to the relatively small number of cases in both seasons, we combined inpatient and ED visits to reflect more severe influenza disease; however, it is possible that VE differs for these settings, and larger studies with many more cases of influenza would be needed to evaluate this issue. Missing vaccination data were unlikely to have affected the results. The participation rate was lower for outpatients than inpatients in both years, but given the similarity of VE estimates across patient care settings, this disparity was unlikely to have affected our results. Similarly, although children in the older age group were less likely to be enrolled in the 2004–2005 season, VE estimates were similar across age groups that season.

Children were not selected at random to receive vaccination, so there are differences in the populations of children who did and did not get vaccinated. Most significantly, children with underlying medical conditions were more likely to get vaccinated. This was not likely to be a significant source of confounding in VE estimates in our study because adjusting for the presence of an underlying medical condition in multivariate modeling did not substantively change the estimates, nor did the inclusion of any other covariate. There were differences in the age distribution between cases and controls, which we addressed by adjusting for age in months and conducting analyses stratified by age. However, the possibility of residual confounding remains.

Conclusions

U.S. children age 6 to 59 months experience a substantial number of hospitalizations, ED visits, and outpatient visits for influenza each year. Our results suggest that even in an influenza season (2004–2005) with suboptimal vaccine match, more than one half of these visits could be prevented with recommended influenza vaccination. Partial vaccination did not appear to be effective. These results offer additional evidence in support of recommendations for vaccinating children against influenza and highlight importance of children receiving the recommended number of influenza vaccinations.

Acknowledgments

KAP received support from the Robert Wood Johnson Generalist Physician Faculty Scholar Program and NIH K23 AI065805. Dr. Edwards received support from the NIH N01 AI25462 and the Centers for Disease Control and Prevention (CDC 200-2002-00732 and grant CDC U01 IP000022).

We thank A. Curns, C. Brown, R. Seither, J. Copeland, F. Walker, and L. Finelli, CDC, Atlanta; D. Kent, A. Clay, E. Keckley, A. Khan, P. Sacket, N. Crowder, Y. Tang, A. Blackman, J. Peters, J. Doersam, and N. Whitehead, Vanderbilt University Medical Center, Nashville; Y. Zhu, R. Hornung, S. Sexton, and M. Holloway, Cincinnati Children's Hospital Medical Center, Cincinnati; C. Freundlich, University of Rochester School of Medicine and Dentistry, Rochester, N.Y.; and all the study nurses for their work in support of this research.

The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention.

Abbreviations

ED	Emergency Department
ACIP	Advisory Committee on Immunization Practices
VE	Vaccine Effectiveness

NVSN	New Vaccine Surveillance Network
ARI	acute respiratory illness
RT-PCR	reverse transcription-PCR
aHRR	adjusted hazard rate ratios

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Figure 1.

Vaccine effectiveness (VE) using multivariate conditional logistic regression to estimate laboratory-confirmed influenza-related visits by risk status for fully vaccinated children compared to unvaccinated children, adjusting for age in months and insurance type according to influenza season. High-risk conditions included asthma, cancer, diabetes, heart disease, immune deficiency, kidney disease, sickle cell disease, cystic fibrosis, and chronic lung disease.

Figure 2.

Vaccine effectiveness (VE) using multivariate conditional logistic regression to estimate laboratory-confirmed influenza-related visits by visit setting for fully vaccinated children compared to unvaccinated children, adjusting for age in months and insurance type according to influenza season. High-risk conditions included asthma, cancer, diabetes, heart disease, immune deficiency, kidney disease, sickle cell disease, cystic fibrosis, and chronic lung disease.

Table 1

Characteristics of Influenza-Positive Cases and Influenza-Negative Controls by Influenza Season (N = 2,474)

Characteristics, <i>n</i> (%)	2003–2004 Influenza Season		2004–2005 Influenza Season			
	Cases (N = 228)	Controls (N = 744)	<i>P</i>	Cases (n = 197)	Controls (n = 1,305)	<i>P</i>
Age group			.002			.491
6 to 23 months	106 (46.5)	432 (58.1)		109 (55.3)	756 (57.9)	
24 to 59 months	122 (53.5)	312 (41.9)		88 (44.7)	549 (42.1)	
Vaccination status			.001			.028
Fully vaccinated	8 (3.5)	54 (7.3)		24 (12.2)	263 (20.2)	
Partially vaccinated	22 (9.7)	134 (18.0)		43 (21.8)	272 (20.8)	
Unvaccinated	198 (86.8)	556 (74.7)		130 (66.0)	770 (59.0)	
Male gender	120 (52.6)	414 (55.7)	.424	121 (61.4)	690 (52.9)	.025
Insurance type			.920			.405
Private	69 (30.3)	229 (30.8)		61 (31.0)	466 (35.7)	
Public	149 (65.4)	486 (65.3)		130 (66.0)	790 (60.5)	
None	10 (4.4)	28 (3.8)		5 (2.5)	46 (3.5)	
Unknown	0 (0.0)	1 (0.1)		1 (0.5)	3 (0.2)	
ARI visit setting			.142			.243
Inpatient	42 (18.4)	154 (20.7)		35 (17.8)	294 (22.5)	
ED	110 (48.3)	304 (40.9)		54 (27.4)	367 (28.1)	
Outpatient	76 (33.3)	286 (38.4)		108 (54.8)	644 (49.4)	
Geographic area			<.001			<.001
Cincinnati	66 (29.0)	351 (47.2)		38 (19.3)	437 (33.5)	
Nashville	92 (40.4)	112 (15.1)		76 (38.6)	446 (34.2)	
Rochester	70 (30.7)	281 (37.8)		83 (42.1)	422 (32.3)	
High-risk condition ^a	59 (25.9)	242 (32.5)	.057	50 (25.4)	359 (27.5)	.532

^a High-risk conditions included asthma, cancer, diabetes, heart disease, immune deficiency, kidney disease, sickle cell disease, cystic fibrosis, and chronic lung disease.

Table 2
Influenza Vaccination Status of Influenza-Positive Cases and Influenza-Negative Controls by Child Characteristics and Influenza Season

Characteristics, <i>n</i> (%)	2003-2004 Influenza Season			2004-2005 Influenza Season			<i>P</i>
	Vaccination Status			Vaccination Status			
	Full (N = 62)	Partial (N = 156)	None (N = 754)	Full (N = 287)	Partial (N = 315)	None (N = 900)	
Age group							<.001
6 to 23 months	36 (58.1)	107 (68.6)	395 (52.4)	185 (64.5)	264 (83.8)	416 (46.2)	
24 to 59 months	26 (41.9)	49 (31.4)	359 (47.6)	102 (35.5)	51 (16.2)	484 (53.8)	
Gender							.529
Male	36 (58.1)	85 (54.5)	413 (54.8)	163 (56.8)	165 (52.4)	483 (53.7)	
Female	26 (41.9)	71 (45.5)	341 (45.2)	124 (43.2)	150 (47.6)	417 (46.3)	
Insurance type							<.001
Private	33 (53.2)	49 (31.4)	216 (28.7)	153 (53.3)	105 (33.3)	269 (29.9)	
Public	28 (45.2)	103 (66.0)	504 (66.8)	130 (45.3)	195 (61.9)	595 (66.1)	
None	1 (1.6)	4 (2.6)	33 (4.4)	3 (1.1)	14 (4.4)	34 (3.8)	
Unknown	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.4)	1 (0.3)	2 (0.2)	
ARI visit setting							<.001
Inpatient	19 (30.7)	21 (13.5)	156 (20.7)	71 (24.7)	66 (21.0)	192 (21.3)	
ED	25 (40.3)	59 (37.8)	330 (43.8)	54 (18.8)	79 (25.1)	288 (32.0)	
Outpatient	18 (29.0)	76 (48.7)	268 (35.5)	162 (56.5)	170 (54.0)	420 (46.7)	
Geographic area							<.001
Cincinnati	24 (38.7)	49 (31.4)	344 (45.6)	67 (23.3)	87 (27.6)	321 (35.7)	
Nashville	8 (12.9)	28 (18.0)	168 (22.3)	105 (36.6)	107 (34.0)	310 (34.4)	
Rochester	30 (48.4)	79 (50.6)	242 (32.1)	115 (40.1)	121 (38.4)	269 (29.9)	
High-risk condition ^a							<.001
Yes	29 (46.8)	63 (40.4)	209 (27.7)	108 (37.6)	82 (26.0)	219 (24.3)	
No	33 (53.2)	93 (59.6)	545 (72.3)	179 (62.4)	233 (74.0)	681 (75.7)	

^aHigh-risk conditions included asthma, cancer, diabetes, heart disease, immune deficiency, kidney disease, sickle cell disease, cystic fibrosis, and chronic lung disease.

Table 3

Vaccine Effectiveness (VE) Using Conditional Logistic Regression^a to Estimate Laboratory-Confirmed Influenza-Related Visits by Vaccination Status, Age Group, and Influenza Season

Vaccination Status	aOR (95% CI)	VE (%) (95% CI)	aOR (95% CI)	VE (%) (95% CI)	aOR (95% CI)	VE (%) (95% CI)
2003-2004						
Aged 6-59 mo (N = 971)						
Aged 6-23 mo (N = 537)						
Fully vaccinated ^b	0.56 (0.22-1.42)	44 (-42-78)	0.72 (0.23-2.30)	28 (-130-77)	0.34 (0.06-2.06)	66 (-106-94)
Partially vaccinated ^b	0.57 (0.32-1.03)	43 (-3-68)	0.58 (0.27-1.22)	42 (-22-73)	0.67 (0.22-2.09)	33 (-109-78)
Age (months) ^c	1.01 ^d (1.00-1.03)		1.05 (1.00-1.11)		0.98 (0.96-1.01)	
Public/no insurance ^f	1.05 (0.70-1.59)		1.00 (0.55-1.83)		1.02 (0.54-1.91)	
Underlying medical condition	0.84 (0.55-1.29)		1.18 (0.62-2.25)		0.62 (0.34-1.13)	
2004-2005						
Aged 6-59 mo (N = 1,493)						
Aged 6-23 mo (N = 860)						
Fully vaccinated ^b	0.43^d (0.26-0.72)	57 (28-74)	0.45^e (0.23-0.87)	55 (13-77)	0.37^e (0.16-0.84)	63 (16-84)
Partially vaccinated ^b	0.89 (0.59-1.35)	11 (-35-41)	1.03 (0.62-1.70)	-3 (-70-38)	0.62 (0.25-1.53)	38 (-53-75)
Age (months) ^c	1.00 (0.99-1.02)		1.03 (0.99-1.08)		1.00 (0.98-1.03)	
Public/no insurance ^f	1.43 ^d (0.99-2.06)		1.86^e (1.07-3.22)		1.23 (0.73-2.07)	
Underlying medical condition	1.03 (0.70-1.51)		0.97 (0.55-1.72)		1.10 (0.63-1.93)	

^aControls were frequency matched to cases on site (Cincinnati, Nashville, or Rochester), visit setting (Inpatient/ED or Clinic), and date of enrollment (controls)/date of influenza symptom onset (cases).

^bReference = unvaccinated.

^cIndicates unit increase for each additional month of age.

^d $P < .01$

^e $P < .05$; otherwise not significant.

^fReference = private insurance.