Infant Hospitalizations for Pertussis Before and After Tdap Recommendations for Adolescents

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ABSTRACT

OBJECTIVE: Recent universal vaccination efforts among children in the United States have markedly changed hospitalization patterns for many vaccine-preventable diseases. Infants with pertussis often require hospitalization to monitor for potentially life-threatening respiratory failure. In 2006, tetanus-diptheria-acellular pertussis (Tdap) vaccination was recommended for universal administration to adolescents, a known source of pertussis in infants. By 2011, 78% of adolescents in the United States had received Tdap. We sought to understand if patterns of pertussis hospitalization for infants changed with adoption of Tdap vaccination among adolescents.

METHODS: Infants (aged <1 year) diagnosed with pertussis were identified in the Nationwide Inpatient Sample by using diagnostic codes. We used variance-weighted least-squares regression over preimplementation years (2000–2005) to estimate pertussis hospitalization patterns if Tdap had not been available. We compared expected hospitalization rates with observed rates for 2008–2011. Two years (2006 and 2007) were excluded from analysis during early Tdap implementation.

RESULTS: The incidence of hospitalization for pertussis in 2000 was 5.82 (95% confidence interval: 4.51–7.13) discharges per 10,000 infants in the US population. The rate increased during pre-Tdap years by a mean of 0.64 pertussis discharges per 10,000 infants per year (P for trend = .004). Observed hospitalization rates for pertussis among infants were significantly lower than expected in 2008, 2009, and 2011, but in 2010 the observed and expected rates of hospitalization were not significantly different.

CONCLUSIONS: Adolescent Tdap vaccination appears to be partially effective in preventing pertussis hospitalizations among infants. However, broader Tdap immunization coverage may be necessary to achieve sustainable reductions in infant pertussis burden. Pediatrics 2013;132:e1149–e1155
Early childhood vaccination programs directly benefit young children by reducing hospitalization for severe illness and provide benefit to other populations (eg, adolescents and adults) by lowering overall disease burden.\textsuperscript{1,2} In contrast, the extent to which infants may benefit from vaccination among older individuals has not been established. The recommendation of universal pertussis vaccination for adolescents beginning in 2006\textsuperscript{3} presents an opportunity to examine this question. Although pertussis vaccine has been widely available in the United States since the 1940s and cases of pertussis among children reached a nadir in the 1970s, increasing rates of pertussis in the United States over the last 20 years have led to \textit{Bordetella pertussis} being one of the most prevalent vaccine-preventable infections in the United States.\textsuperscript{4,5} Newborns and young infants are more susceptible than other age groups to severe illness and even death from pertussis.\textsuperscript{6,7} Infants are known to acquire pertussis from adolescent and adult contacts,\textsuperscript{6,8,9} whose own early childhood vaccination against pertussis does not provide sustained immunity.\textsuperscript{8} In fact, older siblings have been implicated as the source of infection for as many as one-half of infant pertussis cases.\textsuperscript{10}

Initial analyses after implementation of adolescent vaccination suggested no change in infant pertussis prevalence.\textsuperscript{11} However, these analyses compared trends in pertussis illness during the tetanus-diphtheria-acellular pertussis (Tdap) period with patterns of pertussis incidence as far back as 1990, which differ in key respects from current circumstances. First, infant pertussis vaccination before 1997 was with whole-cell diphtheria-tetanus-pertussis (DTP) rather than diphtheria-tetanus-acellular pertussis (DtaP); the latter likely confers differing protection than the former.\textsuperscript{5,12,13} Second, vaccination coverage rates for children receiving at least 4 doses of DTP/DTaP did not consistently reach current levels (>80%) until 1996.\textsuperscript{14} Moreover, characterizing the burden of pertussis that causes morbidity severe enough to prompt hospitalization and even death is highly relevant to practitioners. The rates of clinically severe disease among infants in the context of increasing national pertussis incidence are unknown, and it is unclear if the introduction of the universal vaccine recommendations for adolescents is associated with a change in hospitalization rates for infants with pertussis.

We sought to (1) characterize hospitalization rates for infants with pertussis before and after universal recommendations for adolescent Tdap and (2) describe the clinical characteristics and hospital charges associated with infantile pertussis hospitalization.

\section*{METHODS}

\subsection*{Study Population}

We obtained data from the Nationwide Inpatient Sample (NIS)\textsuperscript{15} and the US Census Bureau. The NIS, developed by the Agency for Healthcare Research and Quality’s Healthcare Cost and Utilization Project, is the largest all-payer annual database including hospitalizations from across the United States, and has been used in multiple peer-reviewed studies to examine year-by-year hospital care patterns.\textsuperscript{1,16–19} We used the NIS rather than the Kids’ Inpatient Database, released every 3 years, to examine year-by-year trends. Infants (<1 year old) diagnosed with pertussis were identified in the NIS as having International Classification of Diseases, Ninth Revision, Clinical Modification, codes 033.0, 033.8, 033.9, or 484.3 as 1 of the first 15 diagnoses recorded (ie, principal diagnosis and as many as 14 secondary diagnoses). We calculated population-adjusted annual rates of pertussis hospitalization as hospital discharges per 10 000 infants in the US population in each calendar year by using data from the US Census Bureau for the denominator.\textsuperscript{20}

\subsection*{Primary Analyses}

Similar to methods published elsewhere,\textsuperscript{19} we used variance-weighted least-squares regression over the pre-recommendation years (2000–2005) to estimate expected population-adjusted pertussis hospitalization patterns in 2008 to 2011 for infants if Tdap vaccination had not been recommended for adolescents. Incidence estimates and 95% confidence intervals (CIs) were generated by using postregression marginal means. We then compared these expected estimates with pertussis hospitalization rates observed in national hospitalization data. We excluded 2 years (2006 and 2007) from analyses during initiation of Tdap vaccination for adolescents. By 2008, >40% of adolescents had been vaccinated with Tdap. We also performed a sensitivity analysis without excluding 2006 and 2007 by using interrupted time-series methods\textsuperscript{21} (see Supplemental Information for details).

We used sample-weighted data from the NIS throughout all analyses, to permit national inferences. Additionally, we compared NIS hospitalization data to surveillance data obtained from the Centers for Disease Control and Prevention (CDC) in the National Notifiable Disease Surveillance System\textsuperscript{22} over the study period to place our findings in the context of natural peak-and-trough cycles in pertussis illness.

We also examined aggregate hospital charges for infant pertussis cases over time, adjusting all dollars to 2011 by using the Consumer Price Index.\textsuperscript{23} To quantify charges associated with pertussis and mitigate the effects of rare cases with very high charges, we excluded outlier charges exceeding the 99th percentile of charge-per-discharge distribution in each year of data.
Supplementary Analyses

We performed supplementary analyses to examine the possibility that clinicians’ thresholds for hospitalizing infants with pertussis have changed during the study period. To determine if clinicians’ threshold for hospitalization changed during the study period, which could potentially have influenced patterns of hospital care for pertussis, we examined the proportion of infants with life-threatening illness over the study period. We defined life-threatening illness as any infant requiring intubation, extracorporeal membrane oxygen, or experiencing in-hospital mortality. We also examined the mean length of stay (LOS) over the study period as another proxy for potential differences in severity. In addition, if clinicians were increasingly comfortable observing older infants as outpatients during the study period, the mean age of hospitalized infants would be expected to decrease. We therefore examined the mean age of hospitalized infants with pertussis over time.

In addition, because pertussis is known to manifest in cyclic peak-and-trough patterns that present challenges for modeling incidence over time,24 we performed 2 analyses to explore the model effects of the high hospitalization rates in 2005. These analyses included “smoothing” the peak year incidence and removing the prevaccine peak year (2005) from the variance-weighted least-squares regression (see Supplemental Information for details).

All analyses were performed with Stata, version 12 (StataCorp, College Station, TX). As a study of deidentified data, our study was considered exempt from institutional review board approval by the University of Michigan Medical School.

RESULTS

Incidence of Pertussis Hospitalizations Among Infants

The annual frequency of infant pertussis hospitalizations ranged from ~1600 to >5000 cases nationally during the study period. Expressed in population-adjusted terms (Fig 1), from 2000 to 2005 the incidence of pertussis varied from a low in 2001 of 4.98 (95% CI: 3.57–6.38) hospitalizations per 10 000 infants to 12.89 (95% CI: 8.78–17.00) hospitalizations in 2005, increasing annually by a mean of 0.64 per 10 000 during this period (P for trend = .004). After implementation of Tdap vaccination among adolescents, the observed rates of pertussis were significantly lower than expected in 2008, 2009, and 2011 (2008 observed rate: 3.85 hospitalizations per 10 000 infants [95% CI: 2.90–4.81]; 2008 expected rate: 10.09 [95% CI: 7.41–12.76]; 2009 observed rate: 5.84 [95% CI: 4.41–7.27]; 2009 expected rate: 10.72 [95% CI: 7.63–13.82]; 2011 observed rate: 3.27 [95% CI: 2.37–4.16]; 2011 expected rate: 12.00 [95% CI: 8.06–15.94]). The observed rate of pertussis hospitalizations among infants in 2010 was not statistically significantly different than expected (observed rate: 7.78 [95% CI: 5.10–10.46]; expected rate: 11.36 [95% CI: 7.84–14.88]) (Fig 1).

Results of supplemental analyses (see Supplemental Information) revealed similar results as our primary analysis. For the time-series analysis, the incidence of infant pertussis hospitalization was significantly different after 2008. For the analyses in which we varied modeling assumptions about the cyclic nature of pertussis, rates of hospitalization among infants for pertussis were lower than expected in at least 3 of the years from 2008 to 2011.

Characteristics of Infants Hospitalized With Pertussis

In 2011, one-half of the infants with pertussis were female, 39% were white, and 61% had public coverage. The mean age at hospital discharge was 87 days. The proportion of children hospitalized with pertussis with life-threatening illness (composite measure: extracorporeal membrane oxygen, intubation, or death) was 5.7%. Infants with pertussis had a mean LOS of 5.4 days (Table 1).

During the study period, there were no significant differences in the proportion of infants hospitalized with pertussis who had life-threatening illness or in their mean age. However, there was a statistically significant decrease in mean LOS over time (Table 2).

![Observed incidence of hospitalizations for pertussis from NIS compared with the expected incidence had Tdap not been introduced to adolescents. United States, 2000–2011. The error bars and width of the expected incidence box represent a 1.4 standard error CI, so that overlapping CIs suggest that the difference is not statistically different (P > .05).](image-url)
Hospital Charges Associated With Pertussis Hospitalizations in Infants

The mean charges per discharge increased from $16,576 (95% CI: $13,259–$19,893) in 2000 to $26,954 (95% CI: $18,503–$35,405) in 2011 (P = .001; Table 2). Annual inflation-adjusted aggregate charges for pertussis-related care among hospitalized infants peaked in 2010 at $71.6 million; charges to Medicaid in 2010 were $51.8 million, or 72% of the national total. All charges are presented in 2011 US dollars.

Comparison of Infant Hospitalization for Pertussis With CDC Surveillance Data for Pertussis Disease In Infants

We compared the annual incidence of infant hospitalizations for pertussis with the same-year annual surveillance data reported by the CDC. Total annual infant hospitalizations ranged from 46% to 130% of the number of pertussis cases among infants reported to the CDC during the study period. Although in some years the number of hospitalizations exceeded the number of cases reported to the CDC and in other years the opposite was observed, the overall incidence pattern from both sources matches well in terms of the cyclic pattern of peaks and nadirs during the study period (Fig 2).

DISCUSSION

After the implementation of policy recommending universal Tdap vaccination for adolescents, pertussis hospitalization rates for infants were lower than expected in 3 out of 4 years in our study period. Our findings suggest the possibility of a reduced burden of pertussis severe enough to warrant hospitalization among infants but not consistent enough to mitigate hospitalizations for infantile pertussis in 2010, the first peak year of pertussis incidence after Tdap was first recommended.25

Our analysis, based on rates of hospitalization for infants with pertussis, contrasts somewhat with a recent report by Skoff et al11 that found no apparent impact of adolescent Tdap vaccination on overall infant pertussis incidence, as measured through CDC disease surveillance in the 1990–2009 period. The different findings may reflect the fact that we measured hospitalization, which is related to but distinct from overall disease incidence, and that we compared patterns of illness during the adolescent Tdap period versus patterns from 2000–2005 rather than using earlier years that included lower vaccination rates among infants and the use of DTP vaccine for infants. Additionally, over time, the relationship between the number of infantile hospitalizations and the CDC incidence evolved. Before 2006, the number of hospitalizations was actually above the overall incidence reported by the CDC. After 2007, the annual CDC incidence was above the number of hospitalizations. This trend may reflect increased reporting of pertussis to the CDC over the time period; importantly, an increase in reporting would bias an analysis using CDC surveillance data toward the null, making it more challenging to detect a decrease in incidence even if one existed.

Nonetheless, our findings and those of Skoff et al indicate that further Tdap vaccination efforts will be required to decrease the burden of severe pertussis illness in infants. National recommendations for Tdap have recently expanded beyond original recommendations issued in 2006 (Fig 3). Our findings of an inconsistent impact on infant pertussis hospitalizations in the Tdap era through 2011 indicate that infants may need further protection by 1 of 2 immunization efforts: improving vaccination rates among adolescents and implementing expanded vaccination recommendations among adults. The rates of Tdap vaccination among adolescents (aged 13–17 years) had increased to almost 78% by 2011.26

Certainly the rates of adolescents receiving Tdap could improve; however, clear barriers exist, including lack of parental knowledge about the vaccine, the perception that the vaccine is not necessary, and the lack of recommendations for the vaccine by clinicians.27
The expansion of vaccination recommendations to other populations may also prevent infantile pertussis. For mothers, postpartum vaccination alone may not be adequate in preventing infantile pertussis, and some data suggest that administration during pregnancy may be more effective in preventing infant infection. The Advisory Committee on Immunization Practices recommended Tdap vaccination during each pregnancy in 2012. A universal Tdap vaccination policy has also been suggested because the current vaccination rates among adults have remained <10%. Our study highlights the increase in the financial burden from pertussis over the past decade, on a per-discharge basis and in aggregate terms. The peak annual aggregate charge in 2010 of $71.6 million related to infant hospitalization for pertussis compares with ~1.4 million doses of Tdap vaccine that potentially could be used to target newborns’ unvaccinated adolescent and adult contacts (assuming an average Tdap vaccine cost of $50: $35 for Tdap vaccine as a mean of public- and private-sector acquisition prices plus $15 for administration per dose.) Given the predominance of public insurance among infants with pertussis, the burden of hospitalization costs falls disproportionately to state Medicaid programs. Of note, our charge estimates are conservative because we excluded outliers with very high charges.

In measuring hospitalization rates, it is essential to assess whether changes in the severity of illness in hospitalized infants changed during the study period. Neither mean age nor the percentage of hospitalized infants with life-threatening pertussis changed over time, suggesting that the threshold for hospitalization did not shift in clinically meaningful ways. Whereas mean LOS did decrease slightly during the study period, this finding is consistent with contemporary trends of shortening LOS for pediatric respiratory illnesses such as pneumonia and asthma.
This study must be considered in the context of several limitations. First, due to the observational deidentified nature of the study based on claims data, changes in infants’ hospitalization for pertussis cannot be causally linked to Tdap vaccine implementation. It was not possible to determine whether hospitalized infants had culture or polymerase chain reaction–confirmed pertussis. We also could not determine if an infant had been exposed to Tdap-vaccinated or unvaccinated adolescents, or whether the infants had received any DTaP vaccination themselves. Second, the NIS is sampled to ensure national representation of hospitalization; however, pertussis outbreaks can occur in smaller geographic areas. Coincidental over- or under-sampling from outbreak hotspots might affect national estimates year by year. Third, whereas costs would be a better estimation of economic impact, cost-to-charge conversion files are not available for the entire study period. Another limitation is that the use of diagnostic codes for the identification of pertussis cases has not been formally validated, although it has been used by other authors. We did not include the International Classification of Diseases, Ninth Revision, code for para-pertussis, because the vaccine does not prevent para-pertussis infections. As with any study based on discharge diagnoses, children with para-pertussis infection or a viral respiratory illness may be erroneously coded as pertussis and vice-versa.

Finally, pertussis incidence follows a naturally cyclic pattern, which makes predicting the expected incidence challenging. Therefore, a linear regression model may not fully capture trends in pertussis. We have thus presented sensitivity analyses in the Supplemental Information that reveal findings similar to our main analysis. Furthermore, both descriptive statistics and linear regression have been previously used to model annual incidence of pertussis. In addition, the use of variance-weighted least-squares regression allowed us to account for the annual variance in each year of the NIS.

CONCLUSIONS

Infection with pertussis can result in life-threatening and sometimes fatal illness for young infants. The implementation of policy for universal vaccination among adolescents against pertussis appears to have been partially effective in decreasing the rates of hospitalization for pertussis among infants. However, the observed rates of infant hospitalization during the peak year of 2010 were no different than expected. Further Tdap vaccination efforts among adolescents, and likely adults as well, are needed to prevent infant hospitalization on a more consistent basis.

REFERENCES

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