Waning Immunity to Pertussis Following 5 Doses of DTaP

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KEY WORDS

Pertussis, DTaP, immunity, Immunization Information Systems, vaccines

ABBREVIATIONS

CDC—Centers for Disease Control and Prevention
CI—confidence interval
DTaP—acellular pertussis vaccines combined with diphtheria and tetanus toxoids
IIS—Immunization Information System
PCR—polymerase chain reaction
Tdap—tetanus toxoid-reduced diphtheria toxoid-acellular pertussis

Dr Tartof conceptualized and designed the study and analyses, drafted the initial manuscript, and finalized and approved the final draft. Ms Lewis carried out analyses, reviewed the manuscript, and approved the final manuscript. Ms Kenyon coordinated and supervised surveillance data collection at 1 of the sites, reviewed the manuscript, and approved the final manuscript. Ms White coordinated and supervised immunization data collection at 1 of the sites, reviewed the manuscript, and approved the final manuscript. Mr Osborn coordinated and supervised immunization data collection at 1 of the sites, reviewed the manuscript, and approved the final manuscript. Dr Liko coordinated and supervised surveillance data collection at 1 of the sites, reviewed the manuscript, and approved the final manuscript. Dr Zell supervised analyses, reviewed the manuscript, and approved the final manuscript. Ms Martin collaborated in conceptualization and design of the study and analyses, reviewed the manuscript, and approved the final manuscript. Dr Messonnier collaborated in conceptualization and design of the study and analyses, reviewed the manuscript, and approved the final manuscript. Dr Clark collaborated in conceptualization and design of the study and analyses, reviewed the manuscript, and approved the final manuscript. Ms Skoff supervised in conceptualization and design of the study and analyses, reviewed the manuscript, and approved the final manuscript.

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WHAT'S KNOWN ON THIS SUBJECT: Despite high coverage with acellular pertussis vaccine (DTaP), rates of pertussis have increased substantially in 7- to 10-year-olds in recent years. Duration of protection with 5 doses of DTaP may wane earlier than expected and is currently not well described.

WHAT THIS STUDY ADDS: This evaluation reports increasing risk of pertussis in the 6 years after receipt of the fifth DTaP dose, suggesting that waning of vaccine-induced immunity is occurring before the recommended adolescent booster dose at 11 to 12 years of age.

abstract

FREE

OBJECTIVE: To assess the risk of pertussis by time since vaccination in children in Minnesota and Oregon who received 5 doses of acellular pertussis vaccines (DTaP).

METHODS: These cohort analyses included Minnesota and Oregon children born between 1998 and 2003 who had 5 DTaP doses recorded in state Immunization Information Systems. Immunization records and statewide pertussis surveillance data were combined. Incidence rates and risk ratios for pertussis were calculated for the 6 years after receipt of the fifth DTaP dose.

RESULTS: The cohorts included 224 378 Minnesota children and 179 011 from Oregon; 458 and 89 pertussis cases were identified in Minnesota and Oregon, respectively. Pertussis incidence rates rose each year of follow-up: 15.6/100 000 (95% confidence interval [CI]: 11.1–21.4) at year 1 to 138.4/100 000 (CI: 113.3–166.9) at year 6 (Minnesota); 6.2/100 000 (CI: 3.3–10.6) in year 1 to 24.4/100 000 (CI: 15.0–37.8) in year 6 (Oregon). Risk ratios increased from 1.9 (CI: 1.3–2.9) in year 2 to 8.9 (CI: 6.0–13.0) in year 6 (Minnesota) and from 1.3 (CI: 0.6–2.8) in year 2 to 4.0 (CI: 1.9–8.4) in year 6 (Oregon).

CONCLUSIONS: This evaluation reports steady increase in risk of pertussis in the years after completion of the 5-dose DTaP series. This rise is likely attributable in part to waning immunity from DTaP vaccines. Continuing to monitor disease burden and vaccine effectiveness in fully vaccinated children in coming years will be important to assess ongoing risk as additional cohorts vaccinated solely with acellular pertussis vaccines are introduced. *Pediatrics* 2013;131:e1047–e1052

The incidence of pertussis has increased in the United States since the 1980s despite high coverage with pertussis childhood vaccines.[1,2] Whole-cell pertussis vaccines were first introduced for widespread use in the United States in the 1940s. However, safety concerns over whole-cell vaccines[3–5] prompted the development and licensure of acellular pertussis vaccines combined with diphtheria and tetanus toxoids (DTaP) for use in the United States.[6,7] DTaP was recommended for the fourth and fifth doses of the 5-dose childhood series beginning in 1992 and for all 5 doses of the series in 1997.[6] The risk of pertussis among fully vaccinated children and the duration of protection of the current DTaP series of doses given at 2, 4, 6, 15 to 18 months, and 4 to 6 years are not well described. However, immunity after the acellular vaccination series has been generally considered durable.[8–11]

Although infants aged <6 months continue to be at greatest risk for severe disease and death, pertussis can occur in individuals of all ages. Adolescents accounted for an increasing burden of reported pertussis cases during the 1990s and early 2000s. With implementation of the tetanus toxoid-reduced diphtheria toxoid-acellular pertussis (Tdap) vaccination program beginning in 2005, the burden of disease in adolescents has been reduced.[12] Recently, the burden of disease in 7- to 10-year-olds, a group that had previously had a low risk of disease, has increased. From 2007 to 2009, the proportion of overall reported pertussis cases that occurred among 7- to 10-year-olds nearly doubled from 13% to 23% (Centers for Disease Control and Prevention [CDC] unpublished data).

Children who had recently completed the 5-dose vaccine series in 2005 were among the first birth cohorts to receive acellular pertussis vaccines for all 5 doses. The rise in reported pertussis incidence among this age group may represent earlier waning of immunity after the fifth dose in children who received acellular vaccines for all doses of the childhood vaccination series compared with those cohorts of children who were partially or fully vaccinated with whole-cell vaccines. The objective of this evaluation was to assess the risk of pertussis by time since vaccination in children who received the complete acellular childhood series.

METHODS

We compared incidence rates and risk of pertussis in children from Minnesota and Oregon born between January 1, 1998, and December 31, 2003 for each of the 6 years after completion of the 5-dose DTaP series. We also compared statewide all-ages pertussis incidence and incidence of cases in 7- to 10-year-olds in Oregon and Minnesota from 2000 to 2010 using surveillance data from the National Notifiable Diseases Surveillance System.

Participating sites were selected based on the quality of statewide pertussis surveillance data and the strength of state Immunization Information Systems (IISs). The Minnesota Department of Health and the Oregon Health Authority are supported by the CDC Emerging Infection Program Network to conduct enhanced pertussis surveillance. Furthermore, Minnesota and Oregon are 2 of 8 grantee sites that receive funding through CDC's Sentinel Site Immunization Information Systems Program to achieve higher standards of data quality in their state IISs (http://www.cdc.gov/vaccines/programs/iis/activities/sentinel-sites.htm).

Pertussis cases were identified from statewide surveillance and included cases in children aged ≤15 years with cough onset before November 1, 2010, in Minnesota and December 31, 2010, in Oregon. Cases were classified according to the Council of State and Territorial Epidemiologists case definition[13] and analyses included only confirmed cases. Clinical cases are defined as cough of >2 weeks' duration with paroxysms, inspiratory whoop, or posttussive vomiting. Confirmed cases are defined as isolation of *Bordetella pertussis* from culture with a cough of any duration or those persons meeting the clinical case definition who are either positive by polymerase chain reaction (PCR) or are epidemiologically linked to a laboratory-confirmed case.

Immunization data were obtained from the Minnesota and Oregon IISs. In both databases, all children born in-state are uploaded into the system by birth certificate. Data included all immunization records for children born between January 1, 1998, and December 31, 2003. The data set included demographic variables (sex, race, county, date of birth, ethnicity), provider information (provider enrolled in Vaccines for Children, type of practice), and vaccination data (date of each vaccination, vaccine manufacturer, lot number).

Records from IISs and surveillance data were combined using matching algorithms based on first and last name, date of birth, mother's last name, last known address, and county of residence. Records that did not match on all variables were individually reviewed and hand-matched if additional data in the IISs or surveillance databases demonstrated that the 2 records represented the same child. All matched records for cases identified in the IISs were assigned a unique identifier, and immunization records for noncases were added back into the combined dataset.

The final cohort included all children born between 1998 and 2003 who had 5 recorded doses of DTaP with the fifth dose received between the ages of 4 and 6 years. Our analyses were limited to

fully vaccinated children because we were unable to confirm nonreceipt of doses that were missing from the IISs in eligible children. Children were excluded if they received a DTaP dose before 6 weeks of age. We also excluded children who developed pertussis <14 days after receipt of their fifth DTaP dose to eliminate bias associated with insufficient time to develop a full immune response.

Incidence rates of pertussis were calculated for each of the 6 years after receipt of the fifth DTaP dose, where receipt of the fifth dose was defined as day 0, that is, the beginning of follow-up time. The first year was from day 0 through day 365. Person-time was assessed monthly. Cohort members were censored at the time of illness onset, when they reached November 1, 2010, in Minnesota or December 31, 2010, in Oregon ("timed out"), on the date of receipt of Tdap booster vaccine, or when they reached the end of 6 years of follow-up from the time of their last DTaP dose, whichever came first. Incidence rates were calculated as the total number of children who developed pertussis during each of years 1 to 6 of follow-up, divided by the total number of months of person-time contributed by the cohort for that year, divided by 12, to estimate the average annual incidence rate. We calculated 95% confidence interval (CI) estimates under the Jeffrey's prior distribution for each estimate.[14]

A log binomial model was used to calculate risk ratios and corresponding 95% CIs for years 2 through 6 after the fifth DTaP dose, using year 1 as the referent group. All statistical analyses in this evaluation were performed by using SAS, version 9.3 (SAS Institute, Cary, NC).

RESULTS

From 2000 to 2010, the overall reported pertussis incidence ranged from 10.4 to 18.6 cases per 100 000 population in Minnesota compared with 3.2 to 7.5 cases per 100 000 population in Oregon. Minnesota was in the first quartile of states ranked by pertussis incidence in 2010, and Oregon was in the third quartile. In 2010, the overall incidence of reported pertussis was 2.5 times higher in Minnesota than in Oregon. The incidence in children aged 7 to 10 years in Minnesota increased more than sixfold from 2007 to 2009 (Fig 1). From 2006 to 2010, cases among 7- to 10-year-olds also rose in Oregon but to a much lesser degree. From 2006 to 2010, Minnesota reported 6.5 times the number of cases in 7- to 10-year-olds compared with Oregon.

A total of 432 613 and 305 984 children born between 1998 and 2003 were identified in the Minnesota and Oregon IISs, respectively. Of these children, 224 378 (51.9%) Minnesota children and 179 011 (58.5%) children in Oregon had 5 documented doses of DTaP with the fifth dose received between the ages of 4 and 6 years. From these fully vaccinated cohorts, 458 confirmed cases of pertussis occurred in Minnesota and 89 cases occurred in Oregon in the 6 years after receipt of the fifth DTaP dose. Among Minnesota children with 5 DTaP doses, 12%, 72%, and 16% received the fifth DTaP dose at age 4, 5, and 6 years, respectively, compared with 25%, 57%, and 18%, respectively, in Oregon. Age at receipt of fifth dose did not differ between cases and noncases within each state; we were not able to assess race and ethnicity because of a high proportion of missing data. Manufacturer and lot number information were missing for a large proportion of the 7 143 303 recorded DTaP doses administered in both states. In Minnesota, lot number and manufacturer data were missing for 94% and 94% of doses, respectively; in Oregon, 69% of doses were missing lot number, and manufacturer data were missing for 71% of doses.

Risk ratios increased from 1.9 (1.3–2.9) in year 2 to 8.9 (6.0–13.0) in year 6 in Minnesota, and from 1.3 (0.6–2.8) in year 2, to 4.0 (1.9–8.4) in year 6 in Oregon (Table 1). In Minnesota, the incidence rates of pertussis during the follow-up period ranged from 15.6 cases per 100 000 population (95% CI: 11.1–21.4) in year 1, to 138.4 cases per 100 000 population (95% CI: 113.3–166.9) in year 6 (Fig 2). In Oregon, incidence rates ranged from 6.2 cases per 100 000 population (95% CI: 3.3–10.6) in year 1 to 24.4 cases per 100 000 population (95% CI: 15.0–37.8) in year 6 (Fig 2).

DISCUSSION

This evaluation identified an increase in incidence rates and risk ratios of reported pertussis in the 6 years after receipt of the fifth DTaP dose, strongly suggesting waning of vaccine-induced immunity. Despite considerably different rates of pertussis in Minnesota and Oregon during the period of investigation, similar trends of increase in risk ratios were observed in both states.

The level of protection immediately after completion of the childhood DTaP series is high, with postlicensure vaccine effectiveness estimates ranging from 88.7% to 97%.[15,16] However, recent studies as well as our investigation demonstrate that protection from the DTaP series begins to wane after vaccination, contributing to the accumulation of vaccinated individuals who are still susceptible to disease.[15,17–19] Assuming a constant attack rate of pertussis across age groups, this growing pool of susceptible persons helps to explain the emergence of an increased burden of disease among 7- to 10-year-olds, a group that previously had a low risk of disease, presumably due to partial or complete vaccination with whole-cell vaccines. Pertussis is highly contagious, and in years of increased circulation, even modest waning of vaccine-induced

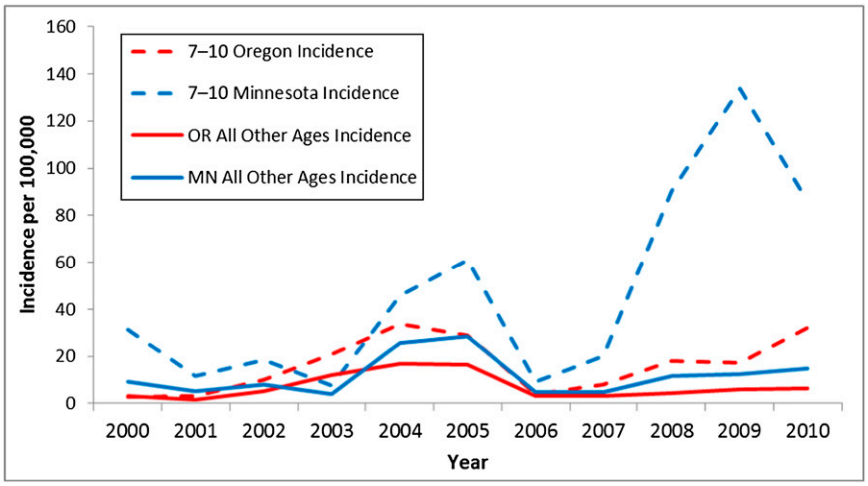

FIGURE 1

Statewide pertussis incidence and incidence of cases in 7- to 10-year-olds, Oregon (OR) and Minnesota (MN), 2000–2010. Based on National Notifiable Diseases Surveillance System data, confirmed cases only.

TABLE 1 Risk of Pertussis in Years 2–6 After Fifth Dose of DTaP, Minnesota and Oregon, 2010

Year	Minnesota RR (95% CI)	Oregon RR (95% CI)
1	Reference	Reference
2	1.9 (1.3–2.9)	1.3 (0.6–2.8)
3	2.6 (1.7–3.8)	1.5 (0.7–3.7)
4	3.2 (2.1–4.8)	1.7 (0.8–3.7)
5	6.1 (4.1–8.9)	2.6 (1.2–5.6)
6	8.9 (6.0–13.0)	4.0 (1.9–8.4)

RR, relative risk.

immunity can result in a large number of cases.

Our evaluation compared 2 geographically and epidemiologically diverse states. Although we observed similar increasing trends in pertussis incidence and risk ratios after receipt of the fifth DTaP dose between Minnesota and Oregon, the magnitude of estimates varied. Different intensity of pertussis incidence between the 2 states likely influenced our observed point estimates. National surveillance data demonstrate that reported pertussis incidence rises and falls in cyclic patterns that differ from state to state, so these results are not unexpected.[20] However, the observed variation may have also been affected by differing surveillance and testing practices. Ascertainment of cases in Minnesota was influenced by several pertussis outbreaks in schools, and by an overall emphasis on increasing recognition and confirmation of cases in adolescents and older children (Minnesota Department of Health, personal communication with Cynthia Kenyon). In contrast, pertussis prevention and control strategies shifted in 2005 in Oregon to emphasize targeted prophylaxis for infants and pregnant women in their third trimester; this change may have had an impact on case finding efforts.[21] Additionally, although PCR was added to the Council of State and Territorial Epidemiologists case definition in 1997, there is variability by state in the availability and use of PCR for the diagnosis of pertussis. Differences in surveillance and testing practices between the 2 states may have contributed to more intensive case finding and the identification of more cases in Minnesota compared with Oregon.

The national resurgence in pertussis, including the increase among 7- to 10-year-olds, is likely being driven by a number of factors such as a true increase in disease, increased recognition and reporting by physicians, improved laboratory diagnostics, and waning of immunity. Although it has also been hypothesized that changes in the organism may be contributing to the resurgence by increasing vaccine failures,[22,23] a recent study evaluating historical pertussis strains in the United States demonstrated that antigen drift away from pertussis vaccine targets had been occurring many years before the transition to acellular vaccines.[24] Furthermore, DTaP vaccines have been shown to be effective at preventing pertussis in the short-term supporting their effectiveness against circulating strains. Although multiple factors can explain the overall increase in pertussis, the striking and sudden increase in disease among 7- to 10-year-olds beginning in 2005 and the strong cohort effect that is observed in national surveillance data are likely being driven by earlier waning of immunity from acellular vaccines.

Existing data from state IISs served as the foundation for our evaluation. Using IISs to evaluate vaccines is an emerging concept, but recognition of the value of IISs for epidemiologic studies is growing.[25–32] Compared with field studies, the use of existing data are more efficient in terms of time and cost. Additionally, using IISs allowed us to obtain data to evaluate disease over a long risk period and with the inclusion of multiple birth cohorts. This is particularly important when studying a disease such as pertussis, where cases can increase or decrease fourfold from one year to another in the same location. Being able to average incidence data over several years helps minimize the effect of annual fluctuations on disease estimates. However, the adoption of IISs by most states has been only in the past 10 years, limiting the availability of data and affecting the extent of provider participation. Although our participating sites were early adopters of IISs, length of follow-up time was limited. IIS analyses are also affected by variability

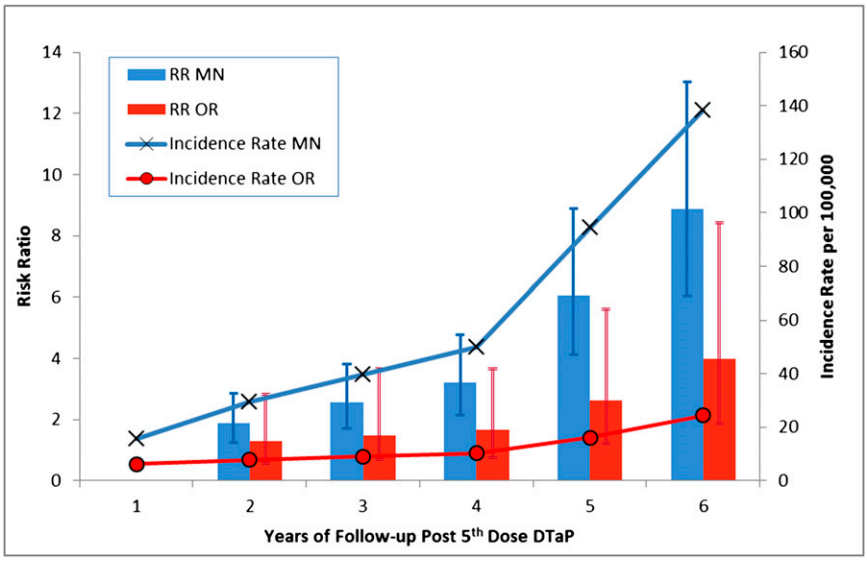

FIGURE 2
Risk ratios and incidence rates for pertussis by year of follow-up post fifth-dose DTaP, Minnesota (MN) and Oregon (OR), 2010.

in data completeness between states and over time. Because a high proportion of missing lot and vaccine manufacturer data, we were unable to evaluate the role of vaccine formulation on duration of protection. Finally, missing vaccination information in IISs may not always be an indication of nonvaccination. Because it was not possible to determine why age-appropriate doses were unavailable for some members of our cohort, we restricted our analyses to children fully vaccinated with DTaP. Without unvaccinated children, we were not able to calculate a traditional measure of vaccine effectiveness for DTaP. Fortunately, new federal goals to improve health information technology place priority on expanding IISs and current limitations will likely diminish over time.[33–35]

CONCLUSION

In this evaluation, existing data allowed us to rapidly assess the increasing burden of pertussis among 7- to 10-year-old children in the United States. Pertussis continues to be the most poorly controlled bacterial vaccine-preventable disease in this country, despite high rates of DTaP coverage.[2] Continuing to monitor disease burden and vaccine effectiveness in fully vaccinated children in the coming years will be important to assess ongoing risk as additional cohorts vaccinated solely with acellular pertussis vaccines are introduced, and to estimate vaccine effectiveness and duration of protection of Tdap booster vaccination as acellular vaccine recipients age. Additionally, as we explore options regarding improved vaccine formulations for the future, it will be important to generate further immunologic and epidemiologic data to investigate determinants of waning immunity with acellular vaccines. Because new vaccines remain distant on the horizon, leveraging current best practices such as vaccination education and achieving high coverage are still the best protections available against pertussis. Maintaining strong DTaP and Tdap immunization programs is critical to control of pertussis in this period of increased circulation of disease.

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