Parental Tdap Boosters and Infant Pertussis: A Case-Control Study

WHAT’S KNOWN ON THIS SUBJECT: Parental reduced antigen diphtheria-tetanus-acellular pertussis (Tdap) vaccination is difficult to implement, and empirical data on its impact is limited to a single hospital-based study in Texas, which found no reduction in infant pertussis hospitalization.

WHAT THIS STUDY ADDS: In New South Wales, Australia, a case-control study found both parents receiving Tdap 4 weeks before disease onset was associated with a significant reduction in risk of early infant pertussis and suggestive of persistent protection in subsequent pregnancies.

abstract

BACKGROUND: Although recommended for almost a decade, evidence for field effectiveness of vaccinating close adult contacts of newborn infants against pertussis (“cocooning”) is lacking. We evaluated the impact of a government-funded cocoon program during a pertussis epidemic in New South Wales, Australia.

METHODS: We matched all New South Wales laboratory-confirmed pertussis cases aged <4 months with onset between April 1, 2009, to March 30, 2011 to controls from the state birth register by date of birth and area of residence. Parental vaccine receipt was by self-report, with a subset verified. Parents were considered “immunized” if vaccinated <4 weeks before case symptom onset. The effectiveness of parental immunization (versus neither vaccinated) was quantified as (1 – odds ratio) × 100%.

RESULTS: Case households had fewer immunized mothers (22% vs 32%) or fathers (20% vs 31%) but were more likely to include additional and older children. After adjustment, when both parents met our definition of immunized, risk of pertussis at <4 months of age was reduced by 51% (95% confidence interval 10% to 73%). Maternal vaccination prepregnancy and an immunized father reduced the risk by 51% (95% confidence interval 0% to 76%).

CONCLUSIONS: Timely parental pertussis boosters provided significant protection. Evidence of protection from maternal vaccination prepregnancy is biologically plausible, and more precise data on the magnitude and duration of this is important for future policy recommendations. Pediatrics 2014;134:713–720
The strategy of vaccinating adults in close contact with infants too young to be fully immunized against pertussis (the "cocooning strategy") was first canvassed by the Global Pertussis Initiative in 2001. The cocooning strategy was recommended in the United States in 2006 and at differing time points in Germany, France, Italy, and Costa Rica and several other countries. Australia has had licensed reduced antigen content diphtheria-tetanus-acellular pertussis vaccine (Tdap) since 2000 and adopted the cocooning strategy as an unfunded recommendation in 2003. Australia has also had school-based delivery of a funded Tdap booster for adolescents since 2004.

Implementation of the cocooning strategy has proved difficult in the United States and other countries, with low uptake related to problems in both delivery and funding of the vaccine dose. Although transmission models predicted that cocooning should result in a >50% reduction in the incidence of severe pertussis in young infants, data on effectiveness in the field has been limited to a hospital-based study from Texas, which found no apparent reduction in infant pertussis hospitalizations despite good uptake of the vaccine among target mothers. In the context of a pertussis epidemic, the government of the Australian state of New South Wales (NSW) undertook in March 2009 to provide Tdap (Boostrix, GlaxoSmithKline, Belgium) free of charge for mothers, fathers, grandparents, and other close adult contacts of infants aged 4 months at onset and diagnosed between April 1, 2009, and March 31, 2011, the first 2 years of the funded cocoon program.

For each case, we identified eligible population controls who were born in NSW and matched to the case by date of birth (±7 days) and by statistical subdivision. Statistical subdivisions are defined by the Australian Bureau of Statistics as socially and economically homogeneous regions characterized by identifiable links between the inhabitants; there are 50 such regions in NSW. From the set of eligible controls for each case, 4 were randomly sampled for initial contact and invited participation. If none of the sampled controls could be contacted or agreed to participate, further controls were randomly sampled until there was at least 1 participating matched control for each case (further details can be found in the online Supplemental Information). Both case and control children who had died were excluded; this included 1 child who had died of pertussis.

**Enrollment and Data Collection**

In the first instance, parents of eligible cases and controls were mailed a letter introducing the study, together with a response form to decline participation or provide telephone contact details. After 2 weeks, if no declaration had been received and a telephone number was available for the case (either self-provided or from NCIMS) or control (either self-provided or from an electronic telephone directory that included cell phone numbers), contact for invitation to participate in an interview was initiated. Up to 15 attempts were made at varying times of the day on both weekdays and weekends to contact prospective participants.

Interviews were conducted by using a computer-assisted telephone interview system by trained interviewers, between January and June 2012. Information was collected about the infant’s day-care attendance, breastfeeding history, vaccination history, and, for cases, details of their pertussis illness. All household contacts of the infant were identified including their relationship to the infant and, for children, their date of birth. Additional information was collected regarding nonresident adult contacts of the infant including the frequency of contact. Demographic information, including educational attainment and health care safety-net scheme eligibility of the parent or guardian was obtained. All questions for a case referred to the period up until the onset of illness; for

**METHODS**

**Data Sources**

Notification of pertussis cases to public health authorities is required under the NSW Public Health Act. Cases are routinely recorded in the Notifiable Conditions Information Management System (NCIMS) administered by the NSW Ministry of Health. A notified case is classified as “confirmed” if there is definitive laboratory evidence (detection by nucleic acid testing or isolation by culture), or suggestive laboratory evidence (single point serology) together with a compatible clinical illness (coughing illness lasting 2 weeks associated with paroxysms, inspiratory whoop, or posttussive vomiting). Cases notified on clinical grounds alone are classified as “probable.” Since 1991, when notification of positive test results by laboratories was made mandatory in NSW, almost all cases have been classified as confirmed.

Control infants were identified by using the NSW perinatal data collection (PDC), a statutory register administered by the NSW Ministry of Health, which records information about pregnancy care, services, and outcomes for all births in NSW public and private hospitals as well as homebirths. Infant deaths were identified by using data from the NSW Registry of Births, Deaths and Marriages, which was linked to the NCIMS notification and PDC birth data sets.

**Study Population**

Eligible infants were those notified to NCIMS as confirmed pertussis cases, aged <4 months at onset and diagnosed between April 1, 2009, and March 31, 2011, the first 2 years of the funded cocoon program.

For each case, we identified eligible population controls who were born in NSW and matched to the case by date of birth (±7 days) and by statistical subdivision. Statistical subdivisions are defined by the Australian Bureau of Statistics as socially and economically homogeneous regions characterized by identifiable links between the inhabitants; there are 50 such regions in NSW. From the set of eligible controls for each case, 4 were randomly sampled for initial contact and invited participation. If none of the sampled controls could be contacted or agreed to participate, further controls were randomly sampled until there was at least 1 participating matched control for each case (further details can be found in the online Supplemental Information). Both case and control children who had died were excluded; this included 1 child who had died of pertussis.
controls, questions referred to the period up until onset date of illness in the case to which they are matched.

The receipt and timing of any Tdap vaccination doses since 2003 for the mother and other adult household contacts were ascertained by self-report, which may have been undocumented. Timing was asked in relation to the infant’s birth, as either years before the birth or as months after the birth. Consent was sought to contact nominated vaccine providers to verify maternal vaccination status using clinic records. Subject to parental consent, date of pertussis vaccine doses for all cases, controls, and their siblings were ascertained through the Australian Childhood Immunization Register (ACIR). The ACIR records immunizations provided to children aged <7 years who are enrolled in the Australian universal health insurance scheme, Medicare; it constitutes a nearly complete population register (~99% of the Australian birth cohort).13

Data Analysis
A multivariate conditional logistic regression model was used to estimate the adjusted odds ratio (OR) of maternal and paternal vaccination among cases versus controls after controlling for potential confounders. The fully adjusted model included households with both a resident mother and father: All measured confounders of the association between parental vaccination and infant pertussis were included in the adjusted model. For the primary analysis, maternal and paternal vaccination status were included in the model as separate categorical variables (immunized [vaccinated ≥4 weeks before disease onset], partially immunized [vaccinated <4 weeks before disease onset], or unimmunized [never vaccinated or vaccinated after disease onset]) with the last the referent status for all analyses. The effectiveness of maternal and paternal immunization for preventing infant infection was quantified using the adjusted OR: effectiveness = (1 – adjusted OR) × 100%. The combined effectiveness of both maternal and paternal immunization (versus neither vaccinated) was estimated from the linear combination of coefficients for the effects of maternal and paternal immunization. No interaction terms were included for the primary analysis. Secondary analyses were conducted making modifications to the primary model (additional details can be found in the Supplemental Information). Analyses were performed by using SAS version 9.3 and Stata version 12.1.

RESULTS
Study Population
The NCIMS database included 393 eligible pertussis cases. One infant who died of confirmed pertussis was excluded, as were 11 infants recorded as having probable rather than confirmed pertussis. Of 266 (68%) contactable cases, interviews were completed for 231 (87%; Fig 1). Of 4414 potential controls mailed an introduction letter, 883 (20%) were contactable and interviews completed for 605 (75%; Fig 1). At least 1 matched control was available for 217 (82%) of the contactable cases, yielding 217 cases and 585 controls in the final data set. Cases who could not be contacted were more likely to have disease onset in the first year of the study (61% vs 47%; P = .005) and to reside in a metropolitan area (61% vs 50%; P = .03). Included control parents were more likely to speak English at home and to have a university education than NSW residents of a similar age recorded in the 2011 national Census, but were similar with regard to the proportion of households with co-residing older children (Supplemental Table 3).

Compared with control households, case households had lower reported educational attainment of the primary caregiver, lower income as measured by eligibility for the national health care safety-net scheme, and mothers were less likely to have breastfed for >2 weeks (Table 1). Case households were more likely to include at least 1 co-resident child (81% vs 62% in control households; P < .001), and co-resident children were significantly more likely to be >5 years of age (Table 1). Case households were less likely to include a resident father, but case and control households did not differ with respect to resident adults who were not a parent (Table 1).

Household Vaccination
The overall proportion of mothers who reported receiving Tdap vaccine at any time did not differ significantly between cases (76%) and matched controls (79%). However, a significantly lower proportion of case mothers reported receiving Tdap at least 4 weeks before onset of disease in the index infant (22% vs 32%) or before pregnancy (12% vs 20%) than control mothers (Fig 2). Case fathers were also significantly less likely to report receiving Tdap vaccine at least 4 weeks before onset of disease in the index infant (20% vs 31%). Most vaccinated mothers (75% cases, 76% controls) and almost all vaccinated fathers (89% cases, 93% controls) reported receiving Tdap vaccine in a primary care setting rather than the delivery hospital.

A high and similar proportion of co-resident children, most of whom were siblings, in case and control households (92% and 93%) were confirmed by the ACIR to have had ≥3 doses of pertussis-containing vaccine. Similarly, 83% and 86% of eligible cocresiding child contacts among both case and control households were recorded on the ACIR as having received the booster dose scheduled at 4 to 5 years.

Effectiveness of Cocoon Doses
After adjusting for health care safety-net eligibility, educational attainment, and number and age of siblings, the estimated protective effect of immunizing
both parents (compared with vaccinating neither) for preventing infant pertussis was 51% (95% confidence interval [CI]: 10% to 73%; Table 2). The father's immunization status was the same as that for the mother in 73% of households (κ = 0.62; P < .001). The estimated independent protective effect of immunizing the mother alone, adjusted for the father's status, was 48% (95% CI: −2% to 74%). The protective effect of immunizing the father alone, adjusting for the mother's status, was 5% (95% CI: −79% to 50%). We also estimated the protective effect of self-reported pertussis vaccination of the mother at any time before pregnancy. After adjusting for health care safety-net eligibility, educational attainment, number and age of siblings, and paternal immunization status, the estimated vaccine effectiveness was 42% (95% CI: −24% to 73%) for the mother alone; if the father also reported receiving pertussis vaccine at least 4 weeks before the index date, the combined protective effect was 51% (95% CI: 0% to 76%; Supplemental Table 4).

**Adult Vaccination Status Verification**

We attempted to verify self-reported vaccination status of mothers in all cases and controls, but because written consent was required for us to contact providers, we were only able to obtain verification in a small subset of cases and controls, despite verbal consent usually being provided at the time of telephone interview. Provider verification of self-reported maternal vaccination status was obtained for 32 (94%) of 34 cases and 100 (92%) of 109 controls from whom we obtained written consent. The proportion for whom self-reported vaccination status was verified was higher among mothers who reported vaccination after delivery (24 [92%] of 26 cases and 63 [93%] of 68 controls) than among those who reported vaccination before pregnancy (3 [50%] of 6 cases and 13 [48%] of 27 controls).

**DISCUSSION**

Despite being widely recommended, until now there has been no evidence that vaccinating adults who are household
contacts of newborns after birth (the cocoon strategy) affords indirect protection against pertussis in early infancy. Our data support the findings of others that large household size (in particular, the presence of older siblings) is a significant risk factor for early infant pertussis; this association persisted even after adjusting for markers of socioeconomic disadvantage.14,15 We elected a priori to define an adult as immunized if he or she reported Tdap receipt at least 4 weeks before, reflecting the likely interval after which a booster response could be reasonably expected in all vaccinees.16 Here we provide evidence that infants of parents who met our definition of immunized are significantly less likely to be notified with pertussis before age 4 months, with a point estimate of 48% (95% CI: 6% to 71%). Previous household transmission studies suggest infected parents account for approximately half of cases of pertussis among young infants.17 We were not able to assess the source of infection among cases in this study, but the observed reduction in risk among infants of vaccinated parents indirectly supports the importance of parents, especially mothers, as a source of infection among young infants. Among all mothers who met our definition of immunized, our data suggest a greater protective effect in those who reported receiving vaccine before the current pregnancy than in those who reported receiving vaccine after delivery but at least 4 weeks before case disease onset. We did not have sufficient power to statistically distinguish protection in mothers who met our definition because of prepregnancy versus postdelivery vaccination; no women reported vaccination during pregnancy, which was not recommended during the study period.

The immunization status of the father was highly correlated with the mother; within these limitations, we did not find any evidence of an independent protective effect among immunized fathers. This is consistent with household transmission studies, which have consistently found that mothers are the most important source of infection for young infants.17 Among mothers, we did not find any evidence of protection of infants when the reported time of vaccine receipt was <4 weeks before the onset date for pertussis.

Given that delivery of the NSW cocoon program occurred predominantly in primary care, rather than maternity hospitals, it is not surprising that only 63% of the 300 mothers of control infants who reported receiving vaccine received it >4 weeks before disease onset in the matched case. An unanticipated finding was the significant minority of all mothers who reported receiving pertussis vaccine before the current pregnancy, 20% of control mothers and 12% of case mothers. This is likely due to the long-standing but unfunded recommendations for postpartum pertussis vaccination4 as well as mothers having had >1 pregnancy during the cocoon program. After adjustment, receipt of vaccine prepregnancy was associated with a lower pertussis risk (adjusted OR

FIGURE 2
Timing of maternal vaccination relative to date of pertussis diagnosis in cases and their matched controls.
We did not have sufficient numbers of women who had been immunized prepregnancy to assess the impact of increasing periods since vaccine receipt. Antibody titers are known to fall rapidly postvaccination, which has led the US Advisory Committee on Immunization Practice to recommend that mothers immunized during pregnancy should receive vaccine in the last trimester and have it repeated in subsequent pregnancies. However, there is suggestive evidence that the level of maternal antipertussis antibody remains significantly higher at a subsequent delivery after postnatal Tdap than it was in the previous pregnancy before Tdap receipt. The presence and degree of any such protection is an important issue for clarification because the requirement for repeat doses of Tdap with each pregnancy is likely to have an important impact on the acceptability and cost-effectiveness of maternal pertussis vaccination.

Most infant cases occurred in households where older siblings were fully immunized and the study was not powered to assess undervaccination of siblings as a separate risk factor. We note however that in the adjusted model, the presence of children >6 years of age in the household was associated with substantially higher point estimates of pertussis risk than was the presence of siblings aged 4 or 5 years. On further analysis, we were able to demonstrate a significant increase in risk associated with the presence of ≥1 children in the household who received their last vaccine dose ≥2 years previously. This is consistent with the waning of vaccine protection observed after the preschool booster.

Strengths of our study include use of whole-of-population case-ascertainment in a setting where almost all notified cases are laboratory-confirmed and

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Factors Associated With Early-Onset Pertussis and Its Prevention, Vaccination at Least 4 Weeks Before Disease Onset for Cases Compared With Age-Matched Controls</th>
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<tr>
<td>Factor</td>
<td>Cases, n (%)</td>
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<tr>
<td>Not vaccinated before disease onset</td>
<td>91 (42)</td>
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<td>≥4 wk before disease onset</td>
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<tr>
<td>Father residenta</td>
<td>195 (90)</td>
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<tr>
<td>Father vaccination status</td>
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<td>Not vaccinated before disease onset</td>
<td>89 (48)</td>
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<td>≥4 wk before disease onset</td>
<td>39 (20)</td>
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<td>Mother and father vaccination status</td>
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<td>Both ≥4 wk before disease onset</td>
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<td>Resident children ages, y</td>
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<td>Health care safety-net eligible</td>
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<td>Maternal education</td>
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<td>58 (27)</td>
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<td>Level 3</td>
<td>34 (16)</td>
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<td>Level 4</td>
<td>48 (22)</td>
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</tbody>
</table>

DTaP, diphtheria-tetanus-acellular pertussis; VE, vaccine effectiveness.

a The adjusted model was limited to households with a resident father.
sampling controls from a comprehensive population-based register of births, directly matching by date of birth and area of residence. We were able to further adjust for sociodemographic determinants and household composition by modeling the independent effects of mothers, fathers, and siblings across multiple age-based strata.

Our study also has important limitations. First, because of challenges with control recruitment, the socioeconomic status of recruited control households may have been higher than for case households, as reflected in higher levels of educational attainment and lower eligibility for subsidized health care compared with census data. The degree to which we failed to completely adjust for any differences could have biased the protective effect estimate. Second, we relied on self-report for parental vaccination status, which is prone to recall bias.23 Cocooning effects may have been falsely identified if mothers of infants who contracted pertussis were less likely to recall pertussis vaccination than mothers of control infants, or if mothers of control infants were more likely to falsely recall a vaccination that never occurred. When confirmation was attempted via the vaccine provider, we were able to verify vaccination for a high proportion of vaccinated mothers overall, although verification of timing was lower for Tdap reported to have been administered before pregnancy than for Tdap administered in the early postpartum period. Importantly, control households were comparable to census data with respect to presence of siblings and breastfeeding prevalence and verification data provided no evidence of differential misclassification of maternal vaccination status among cases versus controls. We therefore expect that any misclassification bias is more likely to have resulted in underestimation of any protective effect.

CONCLUSIONS

Our study provides evidence of a moderate reduction in the risk of laboratory-confirmed pertussis in infants aged <4 months whose parents have been booster immunized with acellular pertussis vaccine at least 4 weeks earlier. Despite being conducted in a setting where parental vaccine uptake was high and during a pertussis epidemic, we had limited power to address more specific questions such as the minimum latent period before which postnatal Tdap becomes protective and duration of protection for subsequent pregnancies. The presence and duration of any such protection is an important gap in knowledge needed to inform recommendations for programs for preventing infant pertussis.

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REFERENCES


(Continued from first page)

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