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On the Role of Different Age Groups and Pertussis Vaccines During the 2012 Outbreak in Wisconsin

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Background. There is limited information on the roles of different age groups in propagating pertussis outbreaks, and on the impact of vaccination on pertussis transmission in the community.

Methods. The relative roles of different age groups in propagating the 2012 pertussis outbreak in Wisconsin were evaluated using the relative risk (RR) statistic that measures the change in the group's proportion among all detected cases before vs after the epidemic peak. The impact of vaccination in different age groups against infection (that is potentially different from the protective effect against detectable disease) was evaluated using the odds ratios (ORs), within each age group, for being vaccinated vs undervaccinated before vs after the outbreak's peak.

Results. The RR statistic suggests that children aged 13–14 years played the largest relative role during the outbreak's ascent (with estimates consistent across the 3 regions in Wisconsin that were studied), followed by children aged 7–8, 9–10, and 11–12 years. Young children and older teenagers and adults played more limited relative roles during the outbreak. Results of the vaccination status analysis for the fifth dose of DTaP (for children aged 7–8 years: OR, 0.44; 95% confidence interval [CI], 0.23–0.86; for children aged 9–10 years: OR, 0.51; 95% CI, 0.27–0.95); and for Tdap for children aged 13–14 years (OR, 0.38, 95% CI, 0.16–0.89) are consistent with protective effect against infection.

Conclusions. While our epidemiological findings for the fifth dose of DTaP and for Tdap are consistent with protective effect against infection, further studies, including those estimating vaccine effectiveness against infection/transmission to others particularly for pertussis vaccines for adolescents, are needed to evaluate the impact of vaccination on the spread of pertussis in the community.

Keywords. age groups; DTaP; pertussis; Tdap.

The reported incidence of pertussis in the United States is on the increase, with major outbreaks reported during 2010, 2012, and 2014 [1]. While several factors behind the increase in reported pertussis incidence, such as waning effectiveness of acellular vaccines [2–6], improved testing and reporting, and the possible impact of genetic changes to *Bordetella pertussis* have been studied [7, 8], there is uncertainty about the specific contributions and importance of different population groups in propagating pertussis outbreaks. In particular, it is unclear which age groups play the leading roles in propagating pertussis outbreaks and what impact vaccination has on pertussis transmission in the community, including transmission to infants [9]. Additionally, vaccine effectiveness against infection and transmission to others is potentially different from effectiveness

against symptomatic disease episodes, as suggested by transmission studies in baboons [10]. Moreover, that effectiveness might depend on the type of vaccine employed, with a series of 5 doses of diphtheria, tetanus, and acellular pertussis (DTaP) administered to younger children, and a Tdap booster recommended for routine use among adolescents aged 11–12 years [11].

In a recent paper by Worby et al. [12] (see also [13, 14]), a method was introduced for assessing the roles of different population groups during pertussis outbreaks. That method compares population groups, usually defined by age, or age and vaccination status in terms of their proportion among incident cases of infection before vs after the outbreak's peak. Groups that play a more prominent role in perpetuating outbreaks due to either increased contact rates or increased susceptibility to infection, or both, are overrepresented among incident cases of infection occurring during the ascent of the outbreak. Such groups experience a disproportionate depletion of the pool of susceptible individuals during the outbreak's early stages and represent a relatively smaller proportion of all cases of infection in the population during the outbreak's later stages. Importantly, this comparison of the relative roles of different age groups is valid if one uses data on detected (reported) pertussis cases for the inference (see [12], Appendix 2). The method, when applied to data from the 2012 pertussis outbreak in Minnesota, points

to the key role played by the adolescents aged 11–14 years in propagating that outbreak. Additionally, the findings in Worby et al. [12] were consistent with the protective effect of the fifth dose of DTaP against pertussis infection, with the corresponding results for Tdap in Worby et al. [12] being inconclusive.

The issues considered in Worby et al. [12], particularly the protective effect of pertussis vaccines against infection, have received limited attention in the literature. On the other hand, vaccine effectiveness against pertussis disease, including its temporal waning, and the potential benefit of replacing pertussis vaccines with the aim of protecting recipients against pertussis disease have been studied extensively in the literature (eg, [2–6, 15, 16]). Those two aspects of vaccine effectiveness are related to different goals of vaccination policies, namely protecting recipients against disease outcomes vs mitigating the spread of pertussis in the community. Further work, including study of vaccine effectiveness against infection/transmission, may inform future vaccination efforts and vaccine development.

In this paper, we apply the methodology in Worby et al. [12] to assess the relative roles of different age groups in propagating the 2012 pertussis outbreak in Wisconsin. Here, quantification of the relative role for an age group according to the methodology in Worby et al. [12] is related to the impact of vaccination of an individual in that age group with an effective vaccine on reducing the epidemic's initial growth rate/reproductive number (see [12], Appendices 6 and 8, as well as [17]). Additionally, we examine the effect of both DTaP and Tdap vaccination on pertussis infection during that outbreak, evaluating, for each vaccine, the consistency of the epidemic data with the hypotheses of either a having protective effect against infection or having no such effect. We hope that studies such as this one or Worby et al. [12] can exhibit epidemiological evidence that contributes to our understanding of the effect of pertussis vaccines on infection/transmission.

METHODS

Data
We considered pertussis case reporting data from 2011–2013, routinely collected by the Division of Public Health, Wisconsin Department of Health Services, with confirmed and probable cases included in our analyses [18]. Upon publication, the authors will destroy the data, in accordance with the Data Use Agreement. We restricted our analysis to the main outbreak wave, which we visually ascertained to extend from week 35 of 2011 through week 6 of 2013, peaking during week 19 of 2012 (Figure 1). During this period, a total of 7481 cases were reported, 75% of which were children under the age of 17 years.

The outbreak in each region may comprise multiple local outbreaks, with peaks potentially occurring at different times than the regional peak. To mitigate the potential effect of this phenomenon on our inference method, we only considered Wisconsin public health regions [19] with outbreak curves of reported pertussis cases that had pronounced major peaks.
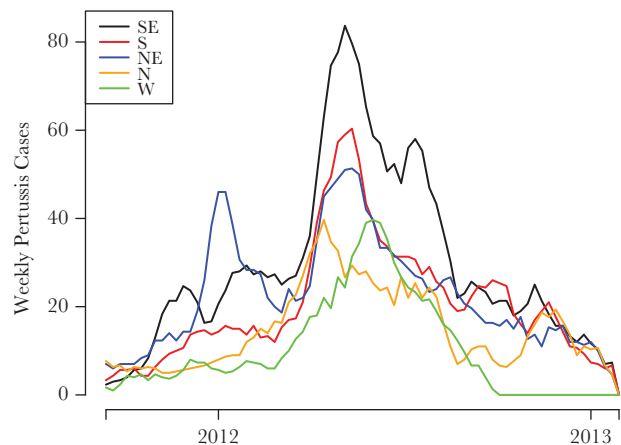

Figure 1. The number of reported cases of pertussis by week of onset by Wisconsin Division of Public Health Region: Southeastern, Southern, Northeastern, Northern, Western [19], 2011–2013. Incidence curves were smoothed using a 3-week moving average.

Thus, only outbreaks in the Southeastern Region (Figure 1, black curve, 2176 cases), Southern Region (Figure 1, red curve, 1525 cases), and Western Region (Figure 1, green curve, 762 cases) were included in all the analyses. For the Western region, only the first epidemic wave (up to week 38, 2012, before the beginning of the second wave) was considered.

Data on vaccination history of reported pertussis cases were provided to us by the Division of Public Health, Wisconsin Department of Health Services. The covariates included time of vaccine administration and vaccine type (DTaP, Tdap, whole cell, etc.) for each administered pertussis vaccine dose.

Age Group Analysis
We categorized cases into 11 age groups (at onset of illness; <1, 1–2, 3–4, 5–6, 7–8, 9–10, 11–12, 13–14, 15–16, 17–19, 20+ years). We used the region-specific outbreak peak times to determine whether reported cases occurred before or after the peak. The region-specific peak week t for reported cases may not correspond to the peak week for the incidence of pertussis infection in the community because only a fraction of cases of pertussis infection are reported to the Division of Public Health. Therefore, to diminish the possibility of misclassification of the periods before and after the peak of the incidence of infection, we defined the before-the-peak period to be the period up to week $t - 2$ (inclusive), and the after-the-peak period to be the period starting at week $t + 2$. Cases occurring during weeks $t - 1$ through $t + 1$ were excluded. We note that excluding longer intervals centered at the peak week is also possible (Supplementary Data, Section S3).

For the joint analysis for the 3 regions, for each age group, g, cases occurring before the outbreak peak in each region were combined for the three regions, with their total number denoted by $B(g)$, and the same applies to cases occurring after the peak, with their number denoted by $A(g)$. The estimated relative risk

for each age group g is the ratio of the proportion of cases in the group g among all reported cases in the population before the peak and the corresponding proportion for cases after the peak, as in Eq. 1 (here h in the sum runs over all age groups):

$$RR_E(g) = \frac{B(g)}{\sum_h B(h)} / \frac{A(g)}{\sum_h A(h)} \qquad (1)$$

The proportions of reported cases among all cases of pertussis infection in each age group are age-specific, and generally low [20]. The numbers of reported cases $B(g)$ and $A(g)$ in group g before and after the peak are then binomially distributed, and the logarithm ln ($RR(g)$) of the relative risk in group g is approximately normally distributed [21]. Under this approximation, the 95% confidence interval for $R(g)$ is $exp(\ln(RR_E(g)) \pm 1.96 \cdot SE)$, where ln ($RR_E(g)$) is estimated via Eq. 1, and the standard error is

$$SE = \sqrt{\frac{1}{B(g)} + \frac{1}{A(g)} - \left(\frac{1}{\sum_h B(h)} + \frac{1}{\sum_h A(h)}\right)} \qquad (2)$$

Vaccination Status Analyses

Similarly, we explored the effect of pertussis vaccination on pertussis infection. It is recommended that children receive 5 doses of the DTaP vaccine, administered at ages 2, 4, and 6 months, between 15–18 months, and 4–6 years [11]. Additionally, administration of the Tdap booster vaccine is recommended when the child is aged 11–12 years [11]. We used a different definition of age groups compared with the age group analysis, namely for each age group, eg, 7–8 years, we considered children aged between 7 and 8 years at the beginning of the inference period, week 35, 2011, for the vaccination status analysis. Selection criteria for the analysis of the effect of vaccination on pertussis infection are described in Section S1 of the Supplementary Data. Briefly, we excluded cases who were vaccinated after the beginning of the inference period (week 35, 2011) prior to symptom onset, cases with out-of-schedule/uncertain vaccination history, and cases who received whole-cell vaccines.

To diminish the biases resulting from vaccine distribution during the course of the outbreak (see "Discussion"), we considered age groups that do not overlap with the age ranges recommended for pertussis vaccine administration that are indicated by the US CDC Advisory Committee on Immunization Practices [11]. We considered the effect of the fifth dose of DTaP for age groups 7–8 years and 9–10 years, as well as the effect of Tdap for age groups 13–14 years and 15–16 years. For an age group g, we performed logistic regression for cases within that age group that met the inclusion criteria described in the previous paragraph, with the binary outcome being the receipt of the corresponding vaccine dose (eg, the fifth dose of DTaP for age 7–8 years) and the 3 (binary) covariates representing whether the case occurred before or after the outbreak peak, whether the child was African American, and whether the child was of Hispanic ethnicity. The regression coefficient for the first covariate corresponds to the logarithm of the odds ratio $OR(g)$ for being vaccinated with the corresponding vaccine dose vs unvaccinated, namely not having received the corresponding vaccine dose, though possibly being vaccinated with the earlier doses, for the prepeak vs postpeak periods. If a vaccine had no effect, one would expect the pool of susceptible individuals in both groups (vaccinated and unvaccinated individuals) to be depleted at the same rate, resulting in an odds ratio of 1. Odds ratios below 1 suggest a greater depletion of the pool of susceptibles in the unvaccinated group during the prepeak period. Such estimates would be consistent with a protective effect against infection for the vaccine in question [12, 14], though other interpretations, including residual confounding, are also possible (see "Discussion").

RESULTS

Age Group Analysis

The total number of reported cases in each age group for children under the age of 17 years for the 3 regions utilized in our analyses is presented in Figure 2. The highest rate for the reported cases belongs to children aged 13–14 years (434.8 per 100 000), followed by children aged <1 years (418.2/100 000) and 9–10 years (383/100 000).

For pertussis epidemics in each of the 3 Wisconsin regions included in our study, as well as for the combined epidemic in those 3 regions, we estimated the relative risk for each of the age groups, as described in the Methods (Eq. 1). Table 1 provides both the regional estimates for the Southeastern, the Southern, and the Western regions and the estimates for the 3 regions combined. The highest relative risk (RR) estimates were in children aged 13–14 years; their magnitude was similar across the 3 regions. The estimates for other age groups varied somewhat by region, with children aged 11–12 years having the second
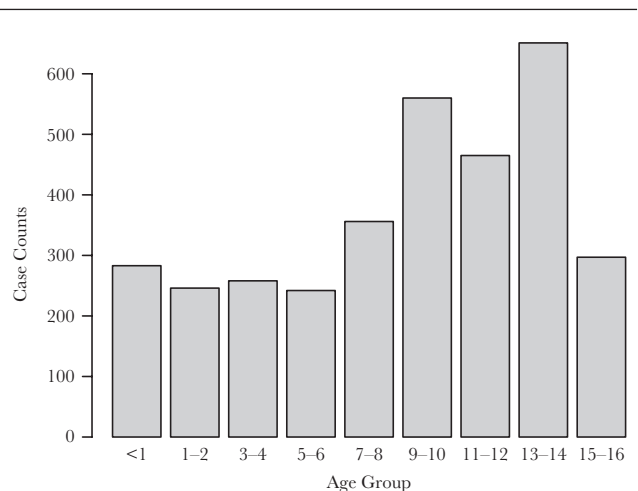

Figure 2. Total number of reported cases in each age group for children under the age of 17 years.

Table 1. Relative Risk Estimates for SE Wisconsin, S Wisconsin, W Wisconsin, and the Combined Estimates for the Outbreak in the 3 Regions

Age Group/Region, y	SE Wisconsin (n = 2176)	S Wisconsin (n = 1525)	W Wisconsin (n = 762)	3 Regions Combined
<1	0.69 (0.48–0.98)	1.16 (0.77–1.76)	1.09 (0.65–1.84)	0.91 (0.72–1.16)
1–2	0.62 (0.41–0.93)	0.73 (0.47–1.13)	0.77 (0.42–1.4)	0.68 (0.52–0.88)
3–4	0.69 (0.47–1.03)	0.68 (0.43–1.1)	1.0 (0.62–1.62)	0.79 (0.61–1.01)
5–6	0.96 (0.66–1.39)	0.73 (0.46–1.15)	0.79 (0.41–1.51)	0.84 (0.65–1.09)
7–8	0.96 (0.71–1.3)	1.44 (0.98–2.11)	1.15 (0.67–1.98)	1.13 (0.91–1.4)
9–10	1.06 (0.85–1.34)	1.06 (0.78–1.44)	0.87 (0.57–1.32)	1.03 (0.87–1.22)
11–12	1.1 (0.86–1.41)	1.13 (0.76–1.68)	1.33 (0.86–2.05)	1.19 (0.99–1.44)
13–14	1.74 (1.43–2.13)	1.7 (1.25–2.31)	1.67 (1.08–2.59)	1.74 (1.49–2.04)
15–16	0.76 (0.55–1.04)	0.9 (0.56–1.45)	0.76 (0.41–1.41)	0.81 (0.63–1.03)
17–19	0.85 (0.56–1.29)	0.9 (0.5–1.64)	0.5 (0.21–1.16)	0.81 (0.59–1.11)
20+	0.9 (0.73–1.12)	0.86 (0.72–1.03)	0.88 (0.63–1.21)	0.84 (0.74–0.95)

The estimates are derived using Eq. 1, with confidence bounds calculated from Eq. 2.

highest RR estimates in 2 of the 3 regions and children aged 7–8 years having the second highest RR estimate in Southern Wisconsin. The RR estimates in individuals over the age of 15 years were lower than the ones in children aged 7–14 years; estimates in children younger than age 7 years were generally lower than the ones in children aged 7–8 years and 11–14 years.

Vaccination Status Analysis

We investigated the effect of DTaP and Tdap vaccination in various age groups. Our results for the fifth dose of DTaP in children aged 7–8 years and 9–10 years, and for Tdap in adolescents aged 13–14 years, are consistent with protective effects against pertussis infection (see more on this in the "Discussion") (Table 2). The estimate for the effect of Tdap in children aged 15–16 years (odds ratio [OR], 1.97; 95% confidence interval, 0.70–5.56) was inconclusive due to the small sample size.

DISCUSSION

A good deal of uncertainty exists about the roles of individuals in different age groups in propagating pertussis outbreaks. Such roles can be measured by examining the effect of the distribution of a fixed quantity of a highly efficacious pertussis vaccine to members of a given age group on the growth rate/reproductive number of the outbreak in the whole community, and comparing those effects for vaccine distribution in the different age groups. Another quantity important for the control

Table 2. Combined Estimates for SE Wisconsin, S Wisconsin, and W Wisconsin of the Odds Ratio for Being Vaccinated vs Unvaccinated Before vs After the Outbreak Peak for Different Combinations of Vaccine Dose/Age Group

Vaccine Dose	3 Regions Combined
DTaP 5, age 7–8 y (n = 236)	0.44 (0.23–0.86)
DTaP 5, age 9–10 y (n = 296)	0.51 (0.27–0.95)
Tdap, age 13–14 y (n = 288)	0.38 (0.16–0.89)
Tdap, age 15–16 y (n = 79)	1.97 (0.70–5.56)

Inclusion criteria for this analysis are described in Section S3 of the Supplementary Data.

of pertussis epidemics is the effectiveness of pertussis vaccines against infection and transmission to others. Vaccine effectiveness against detectable pertussis disease is commonly studied in the literature, but the latter effectiveness might be different from the former. Moreover, vaccine effectiveness against infection rather than disease is relevant to the impact of vaccination on transmission dynamics in the whole community.

In our previous work [12–14], we have devised a methodology for examining those questions for infectious disease outbreaks. That methodology is based on the evaluation of the temporal changes in the distribution of reported cases for a chosen disease outcome in different population groups using certain summary statistics [12–14], for example, the $RR(g)$ and the $OR(g)$ statistics utilized in this paper. Here, we apply this methodology to data on pertussis cases during the 2012 outbreak in Wisconsin. Our estimates suggest that adolescents aged 13–14 years had the most prominent role during the Wisconsin outbreak, compared with the prominence of children aged 11–12 years during the 2012 pertussis outbreak in Minnesota [12]. Receipt of whole-cell vaccines during early childhood is protective against pertussis disease compared with receipt of acellular vaccines alone [22]. It might be that a difference in the timing of the switch from whole-cell to acellular pertussis vaccines in Wisconsin compared to Minnesota contributed to the fact that children aged 13–14 years played a less prominent role during the Minnesota epidemic compared to the Wisconsin one. We also note that, for the more recent (particularly the 2014) outbreaks in the United States, when even older children were covered entirely by acellular pertussis vaccines, the role of older children appears to have increased even further [23]. Older adolescents are expected to play a prominent role during future pertussis outbreaks as well, while the effectiveness of the Tdap vaccine, usually administered at age 11–12 years, wanes rapidly with time [4]. Further studies are needed to evaluate the potential impact of booster vaccination for older adolescents, including the use of more efficacious vaccines than Tdap, on pertussis epidemics in the community.

Pertussis vaccines are known to be effective against disease outcomes such as reported episodes or hospitalizations, though that effectiveness wanes with time [2–6, 15]. The less-studied quantity that is more relevant to the impact of vaccination on pertussis transmission in the community is vaccine effectiveness against infection. For example, adolescents were the leading drivers of the recent pertussis outbreaks, as suggested, for example, by the results of this paper, as well as Worby et al. [12]. Correspondingly, preventing pertussis infection in adolescents, rather than just pertussis disease, which represents a small fraction of all cases of pertussis infection in adolescents [20], could potentially mitigate the outbreak in whole community, reducing disease burden in other age groups as well [24], including infants. We have found that for children aged 7–8 years or 9–10 years, as well as for adolescents aged 13–14 years (but not 15–16 years), the proportion of those children/adolescents who didn't receive the fifth dose of DTaP/Tdap, respectively, was lower during the descent of the Wisconsin outbreak compared to the ascent period of that outbreak. This suggests that children/adolescents who didn't receive the corresponding vaccine dose experienced a larger depletion of the pool of susceptible individuals during the outbreak's ascent compared to the population of children/adolescents who received that vaccine dose. One possible explanation for this is that the corresponding vaccines reduces the likelihood of pertussis infection, resulting in higher infection rates in unvaccinated children/adolescents compared to vaccinated ones during the outbreak's ascent. Other explanations for this estimate are also possible. For example, unvaccinated children/adolescents could be more susceptible to infection due to a combination of economic or behavioral reasons, and the effect could be increased by assortative mixing, in which people with similar susceptibilities preferentially contact one another. The only covariates available to us were race/ethnicity, which we included in the logistic regression model, but residual confounding remains a possibility. It is also possible that vaccine effectiveness against infection wanes during the course of the outbreak, with rising susceptibility to infection among vaccinated children/adolescents resulting in the increase in their proportion among all detected cases in in a given age group with time. We also note that our finding about the consistency of the data with the protective effect of Tdap against infection for adolescents aged 13–14 years is different from the results in Worby et al. [12], where the corresponding analyses were inconclusive. There were methodological differences in the selection criteria for the analysis in this paper compared to the study by Worby et al. [12]. In particular, the availability of data on the exact age for reported cases in this study, but not in Worby et al. [12], allowed us to define the cohorts used in the analyses of vaccine effect by the age range for reported cases (eg, 13–14 years) at the beginning of the epidemic rather than at symptom onset, as in Worby et al. [12]. It is difficult to estimate to what extent methodological differences, vaccine administration during the two epidemics, differences in population/mixing patterns between Wisconsin and Minnesota, and the statistical noise contributed to the differences in the estimates for Tdap. Further studies that assess the effectiveness of pertussis vaccines against infection/transmission to others are needed to evaluate the findings in this paper and regarding the fifth dose of DTaP and Tdap [12].

Our paper has some limitations. The relation between the RR statistic and the role played by individuals in a given age group during the outbreak is not entirely clear. Our earlier work [12, 13, 17] attempted to address this issue through simulations of transmission dynamics, finding an association between the RR statistic and the impact of vaccination on the epidemic's initial growth rate/reproductive number, though this association could be affected by differences in the distribution of susceptibility to infection in different age groups [17]. Vaccine administration during the course of an outbreak may introduce a bias for the OR statistic. Indeed, let VO be the population of children who received pertussis vaccination during the outbreak. Cases of infection in individuals in VO before the vaccination date resulting in reported disease are included in the analysis. For our analyses of the vaccine effect, this left-censoring of the time of infection makes cases in VO earlier compared to cases not in VO that have the same vaccination status. Thus reported cases in VO who were unvaccinated at the start of the outbreak would, on average, bias the odds ratio downward, while reported cases in VO who were vaccinated at the start of the outbreak would, on average, bias the odds ratio upward. Our analyses in Section S2 of the Supplementary Data suggest that the magnitude of the potential bias in the OR estimates for DTaP is likely small. The magnitude of the corresponding bias for Tdap is less certain. Finally, changes in case reporting rates during the course of the outbreak due to increased awareness could affect the RR estimates. We note that awareness about the high rates of pertussis disease in adolescents, particularly those aged 13–14 years (Figure 2), would likely result in a disproportionate increase in the number of reported cases in that age group after the epidemic peak compared to other age groups, which would bias the RR statistic for adolescents aged 13–14 years downward (Eq. 1). At the same time, the RR estimate for adolescents aged 13–14 years was highest in each of the 3 Wisconsin regions included in our study.

In summary, our results suggest the prominent role of adolescents in propagating the 2012 pertussis outbreak in Wisconsin and are consistent with the protective effect of the fifth dose of the DTaP vaccine and of the Tdap vaccine against pertussis infection in grade school children and adolescents aged 13–14 years, respectively. The results are mostly analogous to the earlier findings in Minnesota [12], except that the protective effect of Tdap against infection could not be ascertained in that study. We believe that despite some limitations, the issues considered in this paper, and in Worby et al. [12, reflect some of the basic aspects of pertussis epidemiology and the related public

health policies, such as the potential impact of vaccination of adolescents, possibly including booster vaccination for older adolescents, with Tdap, or perhaps with vaccines of higher efficacy against infection, on pertussis epidemics in the community. We hope that further studies, including those that assess the efficacy of pertussis vaccines against infection/transmission to others, will advance our understanding of those issues further and help inform the corresponding vaccination policies and vaccine development efforts.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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