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Duration of Immunity and Effectiveness of Diphtheria-Tetanus–Acellular Pertussis Vaccines in Children

Matthieu Domenech de Cellès, PhD; Pejman Rohani, PhD; Aaron A. King, PhD

IMPORTANCE The United States has experienced a nationwide resurgence of pertussis since the mid-1970s, despite high estimated vaccine coverage. Short-lived immunity induced by diphtheria-tetanus–acellular pertussis (DTaP) vaccines in young children is widely believed to be responsible for this growing burden, but the duration of protection conferred by DTaP vaccines remains incompletely quantified.

OBJECTIVE To assess the duration of immunity and the effectiveness of DTaP vaccines in US children.

DESIGN, SETTING, AND PARTICIPANTS A mathematical, age-structured model of pertussis transmission, previously validated empirically on incidence data in Massachusetts, was used in this simulation study to assess the duration of DTaP immunity most consistent with the empirical values of the relative increase in the odds of acquiring pertussis from recent epidemiologic studies in the United States. The study included 5 simulated cohorts of children born between January 1, 2001, and December 31, 2005, followed up between the ages of 5 and 9 years (study period, January 1, 2006, to December 31, 2014). Statistical analysis was performed from May 1 to December 1, 2017.

INTERVENTIONS Vaccination with DTaP according to the US immunization schedule, with a range of assumptions regarding the degree of waning immunity.

MAIN OUTCOMES AND MEASURES Vaccine effectiveness and relative change in the odds of acquiring pertussis (odds ratio) in children aged 5 to 9 years, duration of DTaP immunity, and vaccine population-level impact.

RESULTS This study found a marked association between the degree of waning immunity, vaccine effectiveness, and the odds ratio. Counterintuitively, the odds ratio was positively associated with vaccine effectiveness, as a consequence of nonlinear, age-assortative transmission dynamics. Based on the empirical odds ratios (1.33; 95% CI, 1.23-1.43), it was estimated that vaccine effectiveness exceeded 75% in children aged 5 to 9 years and that more than 65% of children remained immune to pertussis 5 years after the last DTaP dose.

CONCLUSIONS AND RELEVANCE The results of this study suggest that temporal trends in the odds of acquiring pertussis are an unreliable measure of the durability of vaccine-induced protection. They further demonstrate that DTaP vaccines confer imperfect, but long-lived protection. Control strategies should be based on the best available estimates of vaccine properties and the age structure of the transmission network.

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Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Matthieu Domenech de Cellès, PhD, Biostatistics, Biomathematics, Pharmacoepidemiology, and Infectious Diseases Unit, Institut Pasteur, Inserm U1181, University of Versailles St-Quentin-en-Yvelines, 25 rue du Dr Roux, 75015 Paris, France (matthieu.domenech-de-celles@pasteur.fr).

Pertussis, or whooping cough, is an acute respiratory disease, mainly caused by the bacterium *Bordetella pertussis* and typically characterized by a prolonged cough.[1,2] Despite the availability of prophylactic vaccines since the 1930s,[2,3] recent epidemiologic data indicate that the control of pertussis remains incomplete and problematic. The disease continues to exact a heavy toll worldwide, with an estimated 24.1 million (uncertainty range, 7 million-40 million) cases and 161 000 (range, 38 000-671 000) deaths in 2014 in children younger than 5 years, for the most part in low-income countries.[4] Despite large reductions in reported cases of pertussis after the start of routine vaccination with diphtheria-tetanus-whole-cell pertussis (DTwP, also known as DTP) vaccines, pertussis has reemerged in several high-income countries that maintained high vaccination coverage.[5,6] Prominently, the United States has experienced a nationwide resurgence of pertussis since the mid-1970s,[7,8] with the incidence highest in infants but increasing disproportionately in adolescents and adults.[9,10] Most recent US estimates indicate that 18 975 individuals contracted pertussis in 2017, including 2276 cases and 9 deaths in infants.[11] Additional control measures were implemented in response to this growing burden, which have met with mixed success.[12-14] These difficulties illustrate both the complexity of, and knowledge gaps in, the biology and epidemiologic features of pertussis.[15,16] Foremost among the latter are uncertainties surrounding the nature of immunity, which make the evaluation of vaccine effectiveness in the field challenging.[17]

Waning immunity after vaccination with diphtheria-tetanus-acellular pertussis (DTaP) vaccines is widely believed to be responsible for the growing burden of pertussis in the United States.[18-20] These subunit vaccines, based on a subset of purified antigens of *B pertussis*, were developed in response to concerns about the safety and the heterogeneous efficacy of DTwP vaccines.[1] Clinical trials demonstrated the safety and the efficacy of DTaP vaccines,[21] which progressively replaced DTwP in most high-income countries, including the United States, which switched to the acellular vaccines in the mid-1990s.[22,23] However, concerns about the population-level effectiveness of these vaccines soon surfaced.[19] In a meta-analysis that included 2 case-control studies[24,25] and 1 cohort study[26] in the United States, McGirr and Fisman[27] estimated that the odds of acquiring pertussis increased 1.33-fold (95% CI, 1.23-fold to 1.43-fold) each year since receipt of the last dose of the DTaP vaccine. Similar results were obtained in another, more recent, case-control study.[28] These results have been interpreted as evidence for widespread and rapid waning of protection conferred by DTaP vaccines, casting doubt on the vaccine's ability to control pertussis and sparking debate on the need for other control strategies[18,19,29] and for new vaccines.[30,31] However, the validity of this interpretation has been questioned.[32] We demonstrate that this interpretation is in fact invalid by showing that the range of the observed relative change in the odds of acquiring pertussis (or odds ratio [OR]) is more consistent with much more durable vaccinal protection.

Key Points

Question How are trends in the odds of acquiring pertussis related to the effectiveness and durability of vaccine protection?

Findings This simulation study used a previously validated mathematical model of pertussis transmission to systematically explore a range of hypotheses about the degree of waning immunity conferred by the diphtheria-tetanus–acellular pertussis vaccine. Based on metrics documented in epidemiologic studies in the United States, it was estimated that vaccine effectiveness exceeded 75% in children aged 5 to 9 years.

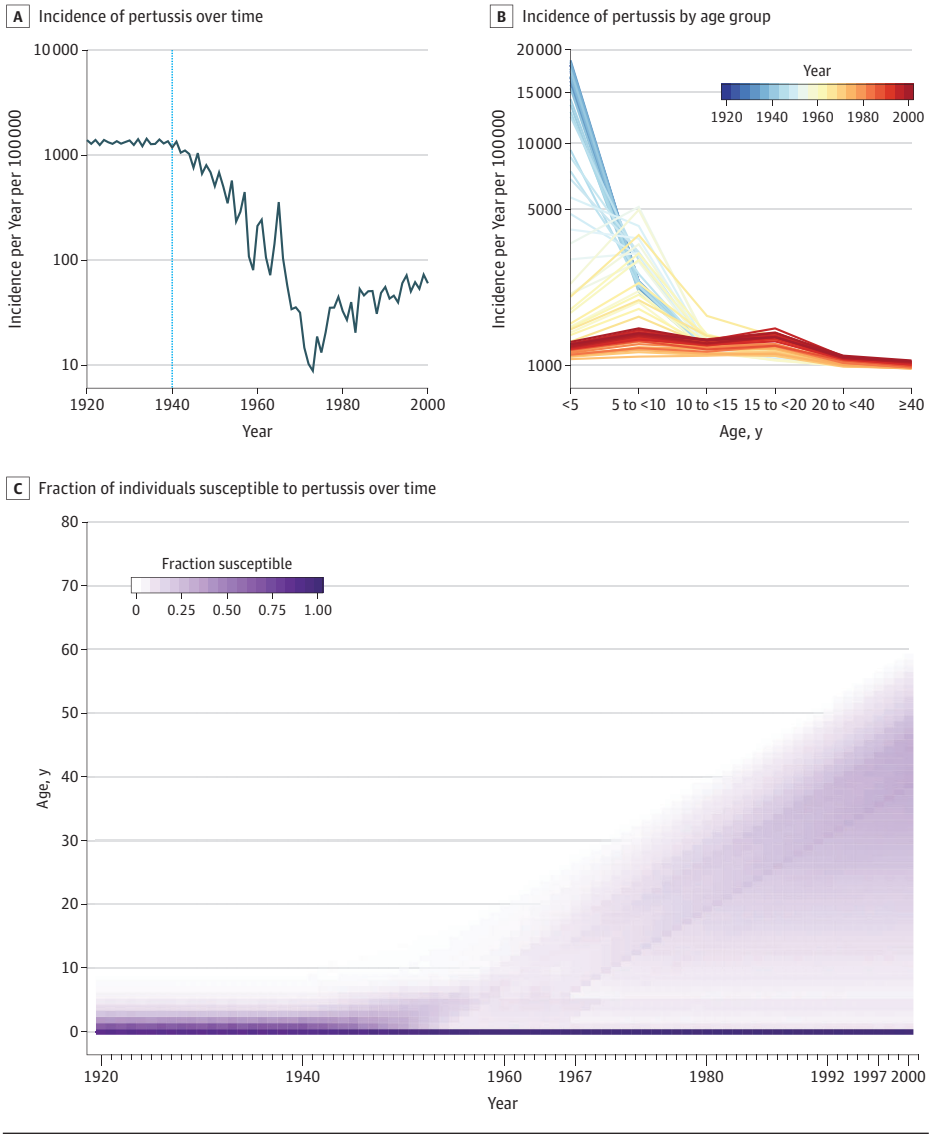
Meaning These results suggest that the diphtheria-tetanus–acellular pertussis vaccine confers imperfect, but long-lived, protection.

Methods

Transmission Model

We used an empirically validated population-based model of pertussis transmission, structured according to age and previously parametrized using high-quality age-specific incidence data from Massachusetts[33] (eTable 1 and eFigures 1-3 in the Supplement). The model allows for postvaccine infections in previously vaccinated individuals, caused by primary vaccine failure and failure in vaccine duration (ie, waning vaccinal immunity). Using statistical inference methods, a previous study showed that both DTwP and DTaP vaccines conferred imperfect, but slowly waning, immunity.[33] This model also successfully captured key features of pertussis epidemiologic characteristics in the United States (**Figure 1**), chiefly the resurgence from the mid-1970s (Figure 1A) and the concomitant shift of cases to adolescents and adults (Figure 1B). According to this model, these changes are an "end-of-honeymoon" effect—that is, they are the slowly manifesting but predictable consequences of incomplete historical coverage with imperfect, but nevertheless effective, vaccines that confer slowly waning protection and generate strong herd immunity. This effect, first explored in the case of measles,[34] is associated with a transient phase of very low incidence after the start of mass vaccination, followed by a rebound of cases as a new equilibrium is reached. The mechanism underlying this effect is illustrated in the immunologic profile presented in Figure 1C.[33] In the prevaccine era, cases are concentrated in young children who, on recovery, develop long-lived immunity against reinfection, resulting in strong herd immunity in older individuals. The inception of mass vaccination leads to an overall reduction in transmission in those vaccinated and in the population at large. Hence, children who were not vaccinated (or who experienced primary vaccine failure) are increasingly likely to reach adulthood having avoided natural infection. Concomitantly, older cohorts, with their long-lived immunity derived from natural infection during the prevaccine era, gradually die out. The result is the gradual buildup of susceptible individuals (Figure 1C), which leads to a gradual resurgence. See eAppendix 1 in the Supplement for complete

Figure 1. Resurgence of Pertussis in the United States as an "End-of-Honeymoon" Effect



A, Incidence of pertussis over time. The vertical dashed line indicates the start time of mass vaccination with the diphtheria-tetanus–whole-cell pertussis (DTwP) vaccine. B, Incidence of pertussis by age group and the accompanying shift of cases to adolescents and adults. C, Variations of the fraction of individuals susceptible to pertussis infection (colored scale) over time (x-axis), and according to age (y-axis). Dates on the x-axis indicate changes in immunization practices assumed in the model: 1940, start of mass vaccination with DTwP vaccine; 1967, start of booster doses in children 15 to 18 months of age (fourth dose) and 4 to 6 years of age (fifth dose); 1992, start of diphtheria-tetanus–acellular pertussis (DTaP) vaccine for booster doses; 1997, start of DTaP vaccine for all doses. This figure shows a typical simulation of a stochastic model of pertussis transmission,[33] under a US-like scenario of immunization and assuming that 95% of infants are immunized with vaccines that wane slowly on average (mean waning rate, 0.011 per year, 5% probability that immunity wanes within 5 years). The model correctly estimates the resurgence of pertussis from the 1970s (see Methods for more information).

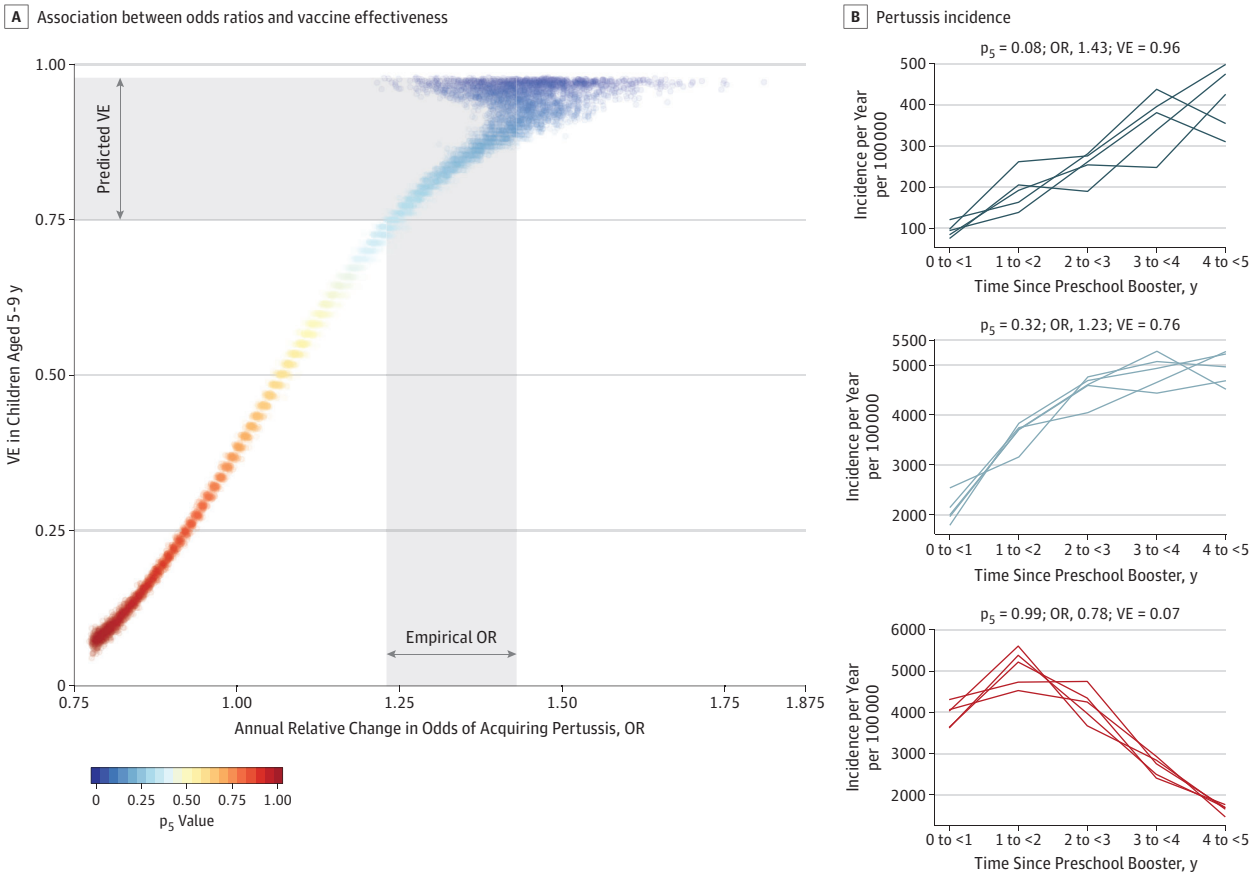
details on the model formulation, parametrization, and implementation.

Given that one of our key findings was that, on average, DTaP-derived immunity is long lasting, although highly variable,[33] we reported surprising agreement between our model-based estimates of the increase in the odds of acquiring pertussis and those estimated in the aforementioned case-control and cohort studies.[24-28,33] These empirical values have been routinely interpreted as evidence for rapidly waning DTaP immunity.[24-28] To fully resolve this apparent paradox, we took advantage of the validated model, adapting it to incorporate known changes in immunization practices in the United States (Figure 1A). These changes included the introduction of DTwP in the 1940s, the switch to DTaP (first recommended for the fourth and fifth vaccine doses,[22] then for the full 5-dose course[23]), and the introduction of booster vaccination with the adult tetanus-diphtheria-pertussis (Tdap) vaccine in adolescents.[35] The model was run to examine the dynamics of pertussis in 5 simulated cohorts of children born between January 1, 2001, and December 31, 2005, tracked from age 5 to 9 years (simulated study period, January 1, 2006, to December 31, 2014) (eTable 2 in the Supplement). Complete model details and specifications are given in eAppendix 1 in the Supplement. Because this was a simulation study, no approval by an ethics committee was required.

Measures of DTaP Protectiveness

Statistical analysis was performed from May 1 to December 1, 2017. Because the relative change in the odds of acquiring pertussis (OR) is not an intuitive metric, we aimed to examine its association with 2 more standard measures of DTaP protectiveness (eAppendix 1 in the Supplement). First, we varied the rate of waning immunity after DTaP vaccination, here quantified as the probability that DTaP-induced immunity wanes within 5 years. Second, we used regression models to estimate, from model simulations, the vaccine effectiveness and

Figure 2. Comparison of Diphtheria-Tetanus–Acellular Pertussis (DTaP) Protectiveness Measures



A, Association between odds ratios (ORs; x-axis) and vaccine effectiveness (y-axis), based on 10 000 simulations with varying degrees of waning DTaP immunity (color scale). The empirical range of ORs is based on a meta-analysis estimate.[27] B, Pertussis incidence as a function of time since last receipt of DTaP for 3 values of DTaP-induced immunity waning. In each panel, the 5 lines represent 5 cohorts of children born between 2001 and 2005, tracked for ≤4 years after receipt of the last dose of DTaP (ie, from 5 to 9 years of age). The y-axis values differ between panels, for visual clarity. See eAppendix 1 in the Supplement for full details on how the quantities in this Figure were estimated. p_5 indicates probability that DTap-induced immunity wanes within 5 years; and VE, vaccine effectiveness.

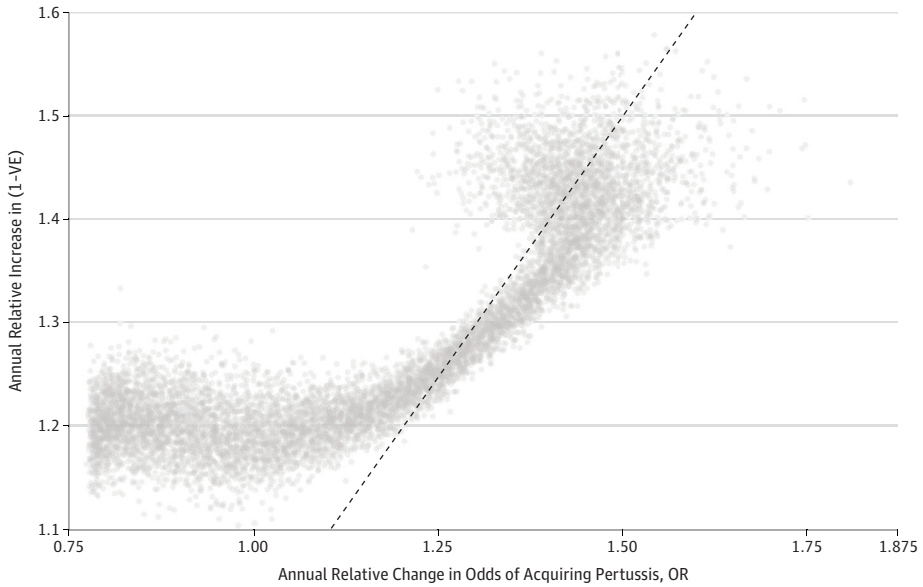
the mean OR in the 5 simulated cohorts of children aged 5 to 9 years. By comparing our model-based OR estimates with those of empirical studies,[24-28] we also sought to determine the vaccinal traits of DTaP that best explained recent epidemiologic data in the United States.

Results

Association Between Measures of Vaccine Protectiveness

The results revealed a marked association between the 3 measures of vaccine protectiveness (**Figure 2**A).[27] As expected, the estimated vaccine effectiveness increased as the degree of waning decreased, exceeding 90% when immunity waned in less than 15% of individuals within 5 years. An equally strong, but counterintuitively positive, association was found between vaccine effectiveness and the yearly change in the odds of acquiring pertussis. To understand this result, we show in Figure 2B the simulated incidence rates in children aged 5 to 9 years (ie, 0-4 years after the last DTaP vaccination), for a range of assumptions regarding DTaP protectiveness. Assuming a slowly waning, highly effective DTaP vaccine (8% probability that immunity wanes within 5 years, vaccine effectiveness of 0.96), pertussis incidence was estimated to increase almost linearly with age, on average by 43% after every year since the last DTaP vaccination (Figure 2B).[27] This result is best interpreted as a consequence of the high transmissibility of pertussis (estimated basic reproduction ratio, R_O approximately 10 in Massachusetts[33])[36,37]: at vaccine coverage below the critical threshold, circulation persists and the risk of disease remains relatively high in groups with high contact rates, such as schoolchildren (eFigure 2 in the Supplement). In contrast, the incidence profile differed markedly in the high-waning, low-effectiveness DTaP scenario (Figure 2B). Here the incidence was estimated to peak 1 to 3 years after last receipt of DTaP, resulting on average in a decrease in the risk of pertussis (ie, OR<1). Under this scenario, transmissibility is so high that the pool of susceptible children—including those for whom vaccinal immunity has waned—is rapidly depleted, limiting further transmission.[38] Hence, these results demonstrate an intri-

Figure 3. Association Between the Odds Ratio (OR) and the Degree of Waning Vaccine Effectiveness (VE)



The figure compares the relative change in the odds of acquiring pertussis (OR; x-axis) with the relative increase of 1 − VE (a measure of waning VE; y-axis) in children aged 5 to 9 years, based on 10 000 model simulations. The dashed gray line is the identity line.[24] For ORs in the range of 1.23 to 1.43,[27] it can be seen that the OR typically exceeds the relative increase in 1 − VE. Hence, assuming equality leads to the erroneous conclusion that diphtheria-tetanus-acellular pertussis immunity wanes too fast.

cate association between the degree of waning vaccinal immunity and the OR, making their interpretation difficult and their validity as a measure of vaccine protectiveness and of the durability of vaccinal immunity questionable.

Estimated Effectiveness of DTaP Vaccines

Based on a meta-analysis estimate[27] (OR, 1.33; 95% CI, 1.23-1.43), we estimate that the effectiveness of DTaP in children aged 5 to 9 years exceeds approximately 75% (Figure 2A).[27] We also estimate that more than 65% of children remain immune to pertussis 5 years after the last dose of DTaP. We find that the OR estimates become more variable when the vaccine effectiveness exceeds 90%, as postvaccine cases of pertussis become increasingly rare and their dynamics become increasingly random. We propose that this finding might qualitatively explain the large estimation uncertainty found in some empirical studies,[25-27] although we acknowledge other potential sources of uncertainty not incorporated into our model. To further quantify the estimated protectiveness of the DTaP vaccine, we also calculated the vaccine impact, a population-level measure of the overall reduction in transmission caused by vaccination.[39,40] We found comparable results based on this measure, with empirical estimates of ORs more consistent with a vaccine impact exceeding about 50% (eFigure 4 in the Supplement). These results were insensitive to the assumed value of Tdap protectiveness in teens (eFigure 5 in the Supplement). Finally, we also found these results to be robust to alternative assumptions regarding the level of vaccine coverage, to the simulation protocol, to the inclusion of demographic trends, and to the duration of infection-derived immunity (eFigures 6-9 in the Supplement). Altogether, we conclude from these experiments that, in stark opposition to recent claims,[18,19] current epidemiologic data in the United States are actually more consistent with effective DTaP vaccines that confer long-term protection, reduce overall transmission, and induce herd immunity.

Association Between the OR and Waning Vaccine Effectiveness

To further help interpret the results of recent epidemiologic studies, we estimated the annual relative increase in 1 − vaccine effectiveness seen 4 years or less after the last DTaP vaccination, a measure quantifying the degree of waning vaccine effectiveness (eAppendix 2 in the Supplement). In a previous study,[24] this quantity was assumed to equal the OR, such that, for example, an OR of 1.42 implied that the DTaP vaccine was 42% less effective each year. As shown in **Figure 3**, we found that, in fact, these 2 quantities were generally not equal. The OR typically exceeded the degree of waning vaccine effectiveness in the range of ORs reported in the literature (1.23-1.43).[27] In other words, assuming equality leads to the erroneous conclusion that DTaP immunity wanes too quickly. We propose that this finding can resolve the apparent disagreement between a previous study[33] and several other previous epidemiologic studies in the United States.[24-28]

Discussion

With serologic correlates of vaccinal protection still obscure,[31] the efficacy of pertussis vaccines has been regularly debated.[17] A major point of contention remains the ability of pertussis vaccines to prevent transmission, in addition to preventing disease.[41-44] Regarding DTwP vaccines, a large body of evidence[15] has shown that they can successfully reduce transmission of pertussis. In contrast, there is a growing consensus that DTaP vaccines do not reduce transmission of pertussis, and therefore might be inadequate to control pertussis.[18,19]

This view is based partly on evidence that the DTaP vaccine generates an immune response different from that of the DTwP vaccine or natural infection,[45] although the immunologic mechanisms of vaccinal protection remain incompletely understood. Furthermore, experimental studies in animal models have suggested that vaccination with DTaP prevents symptomatic disease, but not transmissible infection.[44,46] Previous studies have argued that such results cannot be straightforwardly extrapolated to human populations inasmuch as they are inconsistent with the clear-cut signatures of herd immunity after DTaP vaccination observed in several countries.[15,41] The present findings confirm this view, as they point to effective DTaP vaccines that confer an admittedly imperfect, but slowly waning, immunity.

Limitations

Our study has several limitations. First, although we found that the effectiveness of the 5-dose course of DTaP was high, it is unclear if these results extrapolate to the booster dose of Tdap. Previous evidence (not based on ORs in previously vaccinated children) has suggested that Tdap immunity wanes substantially over time.[47] Applying the method presented here, or more formal statistical inference methods,[33] will be helpful to get an estimate of the waning rate of Tdap immunity. Second, for simplicity we assumed that each dose of the DTaP vaccine acted similarly, by removing a fraction of children from the pool of susceptible individuals. Nevertheless, more complex mechanisms may be at play. For example, it is likely that vaccine immunity evolves after each new dose of the DTaP vaccine, so that our results may only be valid for the full 5-dose course of the DTaP vaccine. To test this hypothesis, our model could be extended to consider a progressive change of DTaP immunity with the number of doses received.

Our results have policy implications. First, the rationale behind future control strategies should incorporate the fact that, despite widespread belief, DTaP vaccines are actually effective and able to induce indirect protection (herd immunity). Second, we propose that control objectives should take into account the epidemiologic dynamics of pertussis, in particular its high transmissibility. Our results suggest that a relatively high burden of pertussis—including periodic outbreaks in school-aged children—may be the norm, even with effective but imperfect vaccines. In view of the high transmissibility of pertussis, current DTaP vaccines are likely insufficient to eradicate the disease on their own, but they nevertheless remain an important part of effective control strategies. Empirically validated models of pertussis transmission, such as those presented here, will prove useful to define achievable control objectives, assess the effectiveness of current control measures, and estimate the effect of new control strategies.

Conclusions

Our results show that temporal trends in the odds of acquiring pertussis are a flawed measure of the durability of vaccine-induced protection. They further demonstrate that DTaP vaccines confer imperfect, but long-lived, protection. Finally, our findings emphasize the complexity of the epidemiologic characteristics of pertussis and the fact that seemingly intuitive measures of vaccine protectiveness can be misleading in the face of this complexity.

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Author Affiliations: Biostatistics, Biomathematics, Pharmacoepidemiology, and Infectious Diseases Unit, Institut Pasteur, Inserm U1181, University of Versailles St-Quentin-en-Yvelines, Versailles, France (Domenech de Cellès); Odum School of Ecology, University of Georgia, Athens (Rohani); Department of Infectious Diseases, University of Georgia, Athens (Rohani); Center for the Ecology of Infectious Diseases, University of Georgia, Athens (Rohani); Department of Ecology and Evolutionary Biology, University of Michigan, Ann Arbor (King); Department of Mathematics, University of Michigan, Ann Arbor (King); Center for the Study of Complex Systems, University of Michigan, Ann Arbor (King).

Author Contributions: Dr Domenech de Cellès had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Rohani and King contributed equally to this work.
Concept and design: All authors.
Acquisition, analysis, or interpretation of data: Domenech de Cellès, King.
Drafting of the manuscript: Domenech de Cellès.
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Supervision: Rohani, King.

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