Rethinking the efficacy of acellular pertussis vaccines for primary immunization

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Abstract

Background The US has experienced a nationwide resurgence of pertussis since the mid-1970s, despite high 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. However, the duration of protection conferred by DTaP vaccines remains incompletely quantified.

Methods and Findings We employed a rigorously validated, age-structured model of pertussis transmission to explore a range of hypotheses regarding the degree of waning DTaP-derived immunity. For every hypothesis, we calculated the vaccine effectiveness and the relative increase in the odds of acquiring pertussis (or odds ratio) in children aged 5 to 9 years. We then assessed the simulated DTaP vaccine traits that best reproduced the empirical values of odds ratios from recent US epidemiological studies. We found a marked association between the degree of waning immunity, the vaccine effectiveness, and the odds ratio. Unexpectedly, the odds ratio was positively associated with the vaccine effectiveness, as a consequence of non-linear, age-assortative dynamics. Based on the empirical odds ratios, we estimated that vaccine effectiveness exceeded 75% and that more than 65% of children remained immune to pertussis 5 years after the last DTaP dose.

Conclusions Our results show that temporal trends in the odds of acquiring pertussis are a seriously flawed measure of the durability of vaccine-induced protection. They further demonstrate that DTaP vaccines confer imperfect, but long-lived protection. We argue that control strategies should be based upon the best available estimates of vaccine properties and the age-structure of the transmission network.

Pertussis, or whooping cough, is an acute respiratory disease, caused by a bacterial infection and typically characterized by a prolonged cough [1]. Despite the availability of prophylactic vaccines since the 1930s [2], recent epidemiological data indicate that the control of pertussis remains incomplete and problematic. Indeed, the disease continues to exact a heavy toll worldwide, with an estimated 24.1 [7–40] million cases and 161 [38–671] thousand deaths in 2014 in children younger than 5 yr, for the most part in low-income countries [3]. Despite large reductions in reported cases after the start of routine vaccination with Diphtheria–Tetanus–whole-cell Pertussis (DTwP, also known as DTP) vaccines, pertussis has re-emerged in several high-income countries that maintained high vaccination coverage [4, 5]. Prominently, the US has experienced a nationwide resurgence of pertussis since the mid-1970s [6, 7], with incidence highest in infants but increasing disproportionately in adolescents and adults [8, 9]. Most recent US estimates indicate that 15,737 individuals contracted pertussis in 2016, including 1,793 cases and 6 deaths in infants [10]. Additional control measures were implemented in response to this growing burden, which have met with mixed success (e.g., [11], but also [12, 13]). These difficulties illustrate both the complexity of, and knowledge gaps in, our understanding of pertussis biology and epidemiology [14, 15]. Foremost among the latter are uncertainties surrounding the nature of vaccinal immunity, which make the evaluation of vaccine efficacy in the field challenging [16].

Waning immunity following vaccination with Diphtheria–Tetanus–acellular Pertussis (DTaP) vaccines is widely believed to be responsible for the growing burden of pertussis in the US [17, 18, 19]. These subunit vaccines, based on a subset of purified antigens of *Bordetella pertussis*, were developed in response to concerns over the safety of DTwP vaccines [1]. Vaccine trials demonstrated the safety and the efficacy of DTaP vaccines [20], which progressively replaced DTwP in most high-income countries, including the US which switch to the acellular vaccines in the mid-1990s [21, 22]. However, concerns over the population-level impacts of these vaccines soon surfaced [18]. In a recent meta-analysis that included 2 case-control studies [23, 24] and 1 cohort study [25] in the US, McGirr et al. [26] estimated that the odds of acquiring pertussis increased 1.33[1.23–1.43]-fold each year since receipt of the last dose of DTaP. Similar results were obtained in another, more recent, case-control study [27]. 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 [28, 17, 18] and new vaccines [29, 30]. However, it has not been established that this is a valid interpretation. Here, we demonstrate that this interpretation is in fact invalid by showing that the observed odds ratio is more consistent with much more durable vaccinal protection.

To this end, we used an empirically validated population-based model of pertussis transmission, structured according to age and parametrized using high-quality age-specific incidence data from Massachusetts [31].

As previously reported, this model successfully captured key features of pertussis epidemiology in the US (Fig. 1), chiefly the resurgence from the mid-1970s (Fig. 1B) and the concomitant shift of cases to adolescents and adults (Fig. 1C) [31]. According to this model, these changes are an end-of-honeymoon effect [32]—that is, they are the slowly manifesting but predictable consequences of incomplete historical coverage with imperfect, but nevertheless efficacious, vaccines that confer slowly waning protection and generate strong herd immunity. The underlying mechanism of this effect is illustrated in the immunological profile presented in Fig. 1A, and further explained in the legend of Fig. 1.

Unexpectedly, we also found that our model-based estimates of the increase in the odds of pertussis were consistent with those that have been obtained in the aforementioned case-control and cohort studies commonly interpreted as evidence for rapidly waning DTaP immunity (Fig. 3F in Ref. [31] and Refs. [23, 24, 25, 26, 27]). To fully resolve the apparent paradox, we took advantage of the validated model, adapting it to incorporate known changes in immunization practices in the US (including the switch to DTaP [21, 22] and the introduction of booster vaccination with Tdap in adolescents [33]) and using it to systematically compare different measures of DTaP efficacy. Specifically, we performed extensive simulations to contrast 3 measures of DTaP efficacy in 5 simulated cohorts of children born between 2001 and 2005. First, we varied the degree of waning immunity following DTaP vaccination, here quantified as the probability that DTaP-induced immunity wanes within 5 yr (p_5). Second, we estimated the resulting vaccine effectiveness (VE) using standard methods. Finally, we computed the average relative yearly change in the odds of acquiring pertussis (or odds ratio, OR) after last DTaP vaccination. By comparing our model-based OR estimates with those of empirical studies [23, 24, 25, 26, 27], we sought to determine the vaccinal traits of DTaP that best explained recent epidemiological data in the US.

Figure 1: Resurgence of pertussis in the US as an end-of-honeymoon effect. This figure shows a typical simulation of a stochastic model of pertussis transmission [31], under a US-like scenario of immunization, assuming that 95% of infants are immunized with vaccines that wane slowly on average (average waning rate, 0.011 per yr, 5% probability that immunity wanes within 5 yr). A: Variations of the fraction susceptible to pertussis infection over time (x -axis), and according to age (y -axis). The top x -axis indicates changes in immunization practices assumed in the model: 1940, start of mass vaccination with DTwP; 1967, start of booster doses in children aged 15–18 mo (4th dose) and 4–6 yr (5th dose); 1992, start of DTaP for booster doses; 1997, start of DTaP for all doses. B: Total incidence of pertussis. The vertical dashed line indicates the assumed start time of mass vaccination with DTwP. C: Incidence of cases over age (x -axis) and over time (color). Each line represents a distinct year. The 3 panels illustrate the end-of-honeymoon effect, as follows. In the prevaccine era, cases are concentrated in young children who, upon 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 in whom vaccinal protection did not initially take) 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 susceptibles visible in panel A, which leads to a gradual resurgence. See Text S1 for complete details on the model formulation, parametrization, and implementation.

The results, presented in Fig. 2A, revealed a marked association between the 3 measures of vaccine efficacy. As expected, the estimated vaccine effectiveness increased as the degree of waning decreased, exceeding 90% when immunity waned in less than 15% within 5 yr. Counterintuitively, an equally strong, but *positive*, association was found between the vaccine effectiveness and the yearly increase in the odds ratio.

To understand this result, we show in Fig. 2B the simulated incidence rates in children aged 5 to 9 yr (i.e., 0 to 4 yr following the last DTaP vaccination), for a range of assumptions regarding DTaP efficacy. Assuming a slowly waning, highly efficacious DTaP ($p_5 = 0.05$, $VE = 0.96$), pertussis incidence was predicted to increase almost linearly over age, on average by 43% after every year since last DTaP vaccination (Fig. 2B, top panel). This result is best interpreted as a consequence of the high transmissibility of pertussis (estimated Basic Reproduction Ratio, $R_0 \approx 10$ in MA [31], see also Refs. [34, 35]): 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 (Fig. S2). In contrast, the incidence profile differed markedly in the high-waning, low-efficacy DTaP scenario (Fig. 2B, lower panel). Here the incidence was predicted to peak 1–3 yr after last receipt of DTaP, resulting on average in a *decrease* in the risk of pertussis (i.e., $OR \leq 1$). 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 [36]. Hence, these results demonstrate an intricate relationship between the degree of waning and the odds ratios, making their interpretation difficult and their validity as a measure of vaccine efficacy and the durability of immunity questionable.

Based on the meta-analysis estimate in Ref. [26] ($OR=1.33$ [1.23–1.43]), we predict that the effectiveness of DTaP in children aged 5 to 9 yr exceeds $\approx 75\%$ (Fig. 2A). We also predict that more than 65% of children remain immune to pertussis 5 yr after the last dose of DTaP, or, equivalently, that the duration of protection exceeds approximately 12 yr. Of note, we find that the odds ratio estimates become more variable when the vaccine effectiveness exceeds 90%, as post-vaccine cases become increasingly rare and their dynamics increasingly stochastic. We propose that this finding might qualitatively explain the large estimation uncertainty found in some empirical studies [24, 25, 26], although we acknowledge other potential sources of uncertainty not incorporated into our model. To further quantify the predicted efficacy of DTaP, we also calculated the *vaccine impact*, a population-level measure of the overall reduction in transmission caused by vaccination [37, 38]. We found comparable results based on this measure, with empirical estimates of odds ratios more consistent with a vaccine impact exceeding about 50% (Fig. S4). We also found these results to be robust to alternative assumptions regarding the level of vaccine coverage, the simulation protocol, and the inclusion of demographic trends (Figs. S7–S9). Critically, these results were also insensitive to the assumed efficacy of Tdap in teenagers (Fig. S6). Altogether, we conclude from these experiments that, in stark opposition to recent claims [17, 18], recent epidemiological data in the US are actually more consistent with efficacious DTaP vaccines that confer long-term protection, reduce overall transmission, and induce herd immunity. It would be a mistake to conclude, however, that routine vaccination with DTaP alone will be sufficient to eradicate the disease [31].

Figure 2: Comparison of DTaP efficacy measures. A: Association between odds ratios (x -axis) and vaccine effectiveness (y -axis), based on 10^4 simulations with varying degrees of waning (color scale). The empirical range of odds ratios is based on the meta-analysis estimate in Ref. [26]. 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 0 to 4 yr after receipt of the last dose of DTaP (that is, during ages 5 to 9 yr). The y -axis values differ between panels, for visual clarity. See Text S1 for information on how the quantities in this figure were estimated.

With serological correlates of vaccinal protection still obscure [29], the efficacy of pertussis vaccines has been regularly debated [16]. A major point of contention remains the ability of pertussis vaccines to prevent transmission, in addition to disease [39, 40, 41, 42]. Regarding DTwP vaccines, a large body of evidence (reviewed in Ref. [15]) has shown that they can successfully reduce transmission. In contrast, there is a growing consensus that DTaP vaccines do not reduce transmission, and therefore might be inadequate to control pertussis [17, 18]. This view is partly based on evidence that DTaP generates an immune response different from that of DTwP or natural infection [43], though the immunological 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, 41]. We have previously argued that such results cannot be straightforwardly extrapolated to human populations inasmuch as they are inconsistent with the clear-cut signatures of herd immunity following DTaP vaccination observed

in several countries [42, 15] The present findings entirely confirm this view, as they point to efficacious DTaP vaccines that confer an admittedly imperfect, but slowly waning immunity.

Our results have policy implications. First, the rationale behind future control strategies should incorporate the fact that, despite widespread belief, DTaP vaccines are actually efficacious and able to cause indirect effects via herd immunity. Second, we propose that control objectives should take into account the epidemiological dynamics of pertussis, in particular its high transmissibility. Indeed, our results suggest that a relatively high burden of pertussis—including periodic outbreaks in school-aged children—may be the norm, even with efficacious 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 impact of current control measures, and predict the effect of new control strategies. Finally, our results emphasize the complexity of pertussis epidemiology and the fact that seemingly intuitive measures of vaccine efficacy can be misleading in the face of this complexity.

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Author contributions

Study conception: MDdC, PR, AAK; model development and implementation: MDdC; results analysis: MDdC, PR, AAK; writing: MDdC, PR, AAK.

Competing interests

The authors declare they have no competing interests related to this manuscript.

Data and code availability

All simulated data and computer codes will be deposited in a Dryad digital repository and are available upon request of the reviewers.

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