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Can vaccine legacy explain the British pertussis resurgence?

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Abstract

Pertussis incidence has been rising in some countries, including the UK, despite sustained high vaccine coverage. We questioned whether it is possible to explain the resurgence without recourse to complex hypotheses about pathogen evolution, subclinical infections, or trends in surveillance efficiency. In particular, we investigated the possibility that the resurgence is a consequence of the legacy of incomplete pediatric immunization, in the context of cohort structure and age-dependent transmission. We constructed a model of pertussis transmission in England and Wales based on data on age-specific contact rates and historical vaccine coverage estimates. We evaluated the agreement between model-predicted and observed patterns of age-specific pertussis incidence under a variety of assumptions regarding the duration of immunity. Under the assumption that infection-derived immunity is complete and lifelong, and regardless of the duration of vaccine-induced immunity, the model consistently predicts a resurgence of pertussis incidence comparable to that which has been observed. Interestingly, no resurgence is predicted when infection- and vaccine-derived immunities wane at the same rate. These results were qualitatively insensitive to rates of primary vaccine failure. We conclude that the alarming resurgence of pertussis among adults and adolescents in Britain and elsewhere may simply be a legacy of historically inadequate coverage employing imperfect vaccines. Indeed, we argue that the absence of resurgence at this late date would be more surprising. Our analysis shows that careful accounting for age dependence in contact rates and susceptibility is prerequisite to the identification of which features of pertussis epidemiology want additional explanation.

Keywords

Epidemiology; Pertussis; Age-structure; Mathematical model

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PR and AAK developed the model framework. PR and MAR designed the study. MAR implemented the model, analyzed the results, and wrote the first draft of the report. AAK and PR contributed to the writing of the report.

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1. Introduction

The resurgence of pertussis in some highly-developed countries has caused a good deal of alarm [1]. In the United Kingdom, the unexpectedly large outbreak of 2012 - responsible for fourteen infant deaths - has prompted consideration of new prevention measures, including vaccination of pregnant women and a booster dose for adolescents [2–5]. Figure 1 depicts annual pertussis incidence against the background of vaccine uptake in England and Wales [4; 6]. Since 2000, a gradual increase in incidence among adults has been apparent. More recently, a sharp rise in incidence among infants and toddlers has become evident. This pattern of increasing incidence, especially among adults and adolescents, has emerged over the past two decades in a number of countries where pertussis had been considered under control [1;7–17].

A variety of mechanisms have been proposed to explain this phenomenon. Chief among these are the vaccine-driven evolution of *Bordetella pertussis* (the main aetiological agent) [15], improved surveillance [16], changes in diagnostic tests [17], cessation of natural immune boosting [18; 19], and the switch from whole-cell to acellular vaccines [20], with concomitant changes in the nature and duration of protection [17; 20]. Less attention has focused on the long-term consequences of inadequate coverage with an imperfect vaccine. Though effective vaccines have been widely used in England & Wales since 1957, their efficacy has never been perfect and vaccine coverage has only exceeded 90% since the 1990s. As we show here, the gradual accumulation within the population of individuals who have avoided both infection and vaccination and thus have escaped receiving protection sets the stage for a resurgence, even in the absence of the aforementioned complexities. Focusing squarely on the recent pertussis epidemiology in England and Wales, we developed a transmission model to determine the extent to which observed patterns of incidence are a predictable consequence of this legacy of imperfect vaccination.

2. Materials and Methods

We constructed an age-stratified compartmental model of pertussis transmission dynamics. Individuals are categorized by yearly age groups up to age 75, with an additional category for infants under five months of age (i.e. too young to have received at least two doses of pertussis vaccine under the pre-1990 vaccine schedule in the UK). For convenience, these age categories are labeled with indices starting from zero, so that N_0 designates the number of 0 – 6 month olds, N_1 is the number of 6 month – 1 year olds, N_2 is the number of 1 year olds, and so on up to N_{75} . The total population is designated by N .

All ages except for 0–5 month olds are tracked as yearly cohorts, with annual aging occurring at the start of each school year. Newborns are assumed to age continuously at rate $a = 12/5 \text{ yr}^{-1}$, corresponding to the assumption that a newborn spends on average 5 months in the 0 – 5mo age category. Susceptible newborns aging at time t have probability $u(t)e$ of being protected by vaccination, where $u(t)$ is the vaccine uptake at time t and e is the vaccine efficacy.

The model is initialized with conditions from the pre-vaccine era and proceeds by updating the numbers of individuals in each age category who are susceptible, latently infected, infectious, recovered, or vaccinated, respectively. Those in the recovered and vaccinated classes are protected from infection for a period, the duration of which is a random variable, as we detail below. The dynamics of susceptible (S_i), exposed (E_i), infectious (I_i), recovered (R_i and R'_i), and vaccinated (V_i and V'_i) individuals in age group i are given by:

$$\frac{dS_i}{dt} = w_V V_i' + w_R R_i' - \lambda_i(t) S_i + (bN - aS_0) \delta_{i,0} + a(1 - eu(t)) S_0 \delta_{i,1} \quad (1)$$

$$\frac{dE_i}{dt} = \lambda_i(t) S_i - \gamma E_i + aE_0(\delta_{i,1} - \delta_{i,0}) \quad (2)$$

$$\frac{dI_i}{dt} = \gamma E_i - r I_i + aI_0(\delta_{i,1} - \delta_{i,0}) \quad (3)$$

$$\frac{dR_i}{dt} = r I_i - w_R R_i + aR_0(\delta_{i,1} - \delta_{i,0}) \quad (4)$$

$$\frac{dR_i'}{dt} = w_R R_i - w_R R_i' + aR_0'(\delta_{i,1} - \delta_{i,0}) \quad (5)$$

$$\frac{dV_i}{dt} = eu(t) aS_0 \delta_{i,1} - w_V V_i + aV_0(\delta_{i,1} - \delta_{i,0}) \quad (6)$$

$$\frac{dV_i'}{dt} = w_V V_i - w_V V_i' + aV_0'(\delta_{i,1} - \delta_{i,0}) \quad (7)$$

where $\delta_{i,j}$ is the Kronecker delta, which is one if i and j are equal and zero otherwise.

The model described by these equations was implemented as a discrete, stochastic system. Specifically, we implemented a multinomial modification of Gillespie's τ -leap method [21–23]. This formulation allows us to quantify dynamic variability arising from small, random perturbations in our system and additionally helps to avoid conclusions resulting from unrealistic quantities (e.g. one ten-billionth of an infected person). The overall population used in our simulations (around 63 million people) is large enough that one might expect these effects to be relatively minor. However, we chose to use discrete, stochastic dynamics because our model includes a large number of age categories differing in incidence, immune history, and contact rates, and some events that are relatively rare (e.g. contact between infected 65 year olds and susceptible 15 year olds) could still be dynamically important.

Age group i gains susceptible members through immune waning and, if $i=1$ or $i=2$, births and the aging of susceptible newborns, respectively. The birth rate $b=1/75 \text{ yr}^{-1}$ is chosen to keep the population steady given the 75 year lifespan. Individuals leave the susceptible category by becoming exposed or, in the infant category, aging. The force of infection acting on age group i at time t is

$$\lambda_i(t) = q \sum_k F_{hk}(t) c_{hk} \frac{\tilde{I}_k}{\tilde{N}_k}$$

where c_{hk} is the average rate (in contacts per year) at which an individual who is between $5h$ and $5h+5$ years old makes contact with those between $5k$ and $5k+5$ years of age and q is

the probability of infection given exposure. The number of infected individuals and total individuals in the k^{th} five-year age block are denoted by

$$\tilde{I}_k = \sum_{5k < i \leq 5k+5} I_i \quad \text{and} \quad \tilde{N}_k = \sum_{5k < i \leq 5k+5} N_i$$

with I_0 and N_0 included in the calculation of $\tilde{N}_0$ and $\tilde{I}_0$, respectively.

Values of c_{ij} and q were adopted from an earlier study [24]. In particular, rates of daily contacts c_{ij} were obtained from the POLYMOD study [25] (see Figures S1D and 2A), and q was fixed at 4% as estimated in Ref. 24, leading to a pre-vaccine era mean age of first infection consistent with historical estimates (Fig. 2B). The necessary steps for obtaining contact rates c_{ij} from the data are described in detail in Section S1 of the supplementary material.

To capture the strong seasonality in children's social contacts [26], we incorporated an age-dependent seasonal forcing term $F_{hk}(t)$ based on school holidays. For $0 < h < 3$ or $0 < k < 3$ (i.e. when either party is 5–15 years old), $F_{hk}(t) = \kappa(1 \pm 0.2)$, with $+$ when school is in session and $-$ during school holidays. Because there are more school days than holidays, we use the normalization constant κ to ensure that $F_{hk}(t)$ has a mean of 1.0 over the whole year. The school holidays used in our simulations were July 19 September 8, October 28 November 3, December 21 January 10, and April 10 25. If neither party is 55 years old, $F_{hk}(t) = 1$, leaving the contact rate unaltered year round.

Beginning in 1957, we assume that infants are vaccinated at six months of age. From 1966, we used available estimates of vaccine uptake for the UK (Figure 1A) [6; 27]. Uptake data for the period prior to 1966 are unavailable; we assumed uptake ramped up linearly from 1957 to 1966. The results presented in the main text assume a value of 60% coverage in 1957. We explored other values; our results are qualitatively unaffected (see appendix S2). In the absence of a serological marker for protection, the efficacy of pertussis vaccines and the durations of infection- and vaccine-derived immunity are highly uncertain [28; 29]. The results presented in the main text assume a vaccine efficacy of 85%, biologically plausible for both the acellular and whole cell vaccines [30] though other efficacies produced qualitatively similar results (see appendix S3). In further tests of the robustness of our results, we similarly varied our assumptions regarding human lifespan and the shape of the contact matrix (see appendix S1 and S6).

In our simulations, individuals exposed to pertussis become infectious after an average of 8 days ($\gamma = 365/8 \text{ yr}^{-1}$) and the infectious period lasts 15 days on average ($r = 365/15 \text{ yr}^{-1}$), again as in the model of Ref. 24.

We model two stages of resistance, R_i and R'_i , so that the duration of immunity is gamma distributed with shape parameter two. The waning rate is given by $w_R = 2.0/d_R \text{ yr}^{-1}$ where d_R denotes the mean duration (in years) of infection derived immunity. Like infection-derived immunity, the duration of vaccine derived immunity is gamma distributed with shape parameter two. In simulations with lifelong natural (or vaccine derived) immunity, w_R (or w_V) is set to zero. We varied the assumed durations of vaccine- and infection derived immunity, respectively, between lifelong immunity and durations gamma-distributed with means of 70, 40, and 10 years (see Table 1).

For the initial conditions of our simulations, we used the population at the end of the 150th year of a run with lifelong immunity, no vaccination, and a total population of

approximately sixty- three million individuals. All simulations were run for 250 years, with vaccination beginning in the 157th year. At the end of each year, for each age category we recorded the population, number of susceptibles, number of successful vaccinations, and number of cases. The pre-vaccine behavior among runs with the same duration of natural immunity was very consistent (see Figure 3 and Figure S7).

Because of the computational cost of using Gillespie's direct algorithm with so many age-categories, we use a multinomial τ -leaping method [21–23], in which we move forward by a fixed time step τ and determine the set of events that occurred during that time step. All simulations presented in this paper use $\tau = 1/365$ yr.

At each step, we consider all the ways an individual can leave each category as a set of competing events. For a sufficiently small time step τ , we can approximate an individual's probability of leaving a category as the total rate at which individuals leave multiplied by the length of the time step. For example, susceptible newborns leave the category by aging at rate a or by becoming exposed at rate $\lambda_i(t)$, so each of the S_0 susceptible newborns has probability $(a + \lambda_0(t))\tau$ of leaving the category. We determine the total number who leave the category drawing from a binomial distribution, $X \sim B(S_0, p_0)$ in our example. The expected fraction of these individuals leaving via each event is proportional to that event's rate. Continuing our example, the X individuals leaving the susceptible newborn category are aging with probability $a/(a+\lambda_0(t))$ and have been exposed with probability $\lambda_0(t)/(a+\lambda_0(t))$, so we draw the numbers of aging and exposure events (X_a, X_E) from a multinomial distribution with X trials and probabilities $(a/(a+\lambda_0(t)), \lambda_0(t)/(a+\lambda_0(t)))$. For aging infants, we perform one more binomial draw with probability $u(t)e$ to determine how many aging infants are successfully vaccinated.

The number of births, which do not deplete any population categories, is determined by drawing from binomial distribution $B(N, b\tau)$, where b is the per capita annual birth rate. Because this is a discrete stochastic model, we also include an immigration rate of one infected individual per year, uniformly distributed among age categories to help distinguish between stable eradication and a chance extinction in an easily re-invaded population. Once the set of events taking place has been determined, the whole population is updated according to those events and the time t is incremented by τ .

3. Results

In Figure 2, we show a typical realization of the model, under the conservative assumption that infection-derived immunity is lifelong and that vaccination protects, on average, for 70 years (note that we did not take into account under-reporting, thus all cases are included in model incidences). Vaccine efficacy is assumed to be 85%, consistent with estimates from Ref. 31. Aggregate annual incidence, the estimated annual vaccine uptake and the percentage of the population susceptible to pertussis are shown in Figure 2B.

Consistent with observed patterns in England & Wales, incidence in our model declines with the onset of pediatric vaccination and rebounds during the early 1980s, after several years of low uptake due to the mid-1970s vaccine scare, before eventually returning to lower overall incidence and a long inter-epidemic period. Although high vaccine coverage is maintained, our model predicts a gradual increase in overall incidence beginning in the 1990s (Fig. 2B). In Figure 2C, we dissect these incidence data by age group, demonstrating that, as expected, in the pre-vaccine era, pertussis was most common in young children (with a mean age at infection in our model of 5 years). This figure also shows that the onset of immunization was accompanied by a rise in the age of cases and that, crucially, the increase in overall incidence over the past two decades appears to be primarily among adults. From the rollout

of the national infant vaccination programme in 1957 to the present day, the mean age of infection in our model climbed steadily, but for a dip following the vaccine scare of the mid-1970s.

This shift in age distribution was also apparent in the immunological profile of our simulated population (Fig 2D). In the pre-vaccine era, the proportion of susceptibles among the population fell sharply with age, as expected for a childhood infection. With the onset of pediatric vaccination, the fraction of susceptible children decreased substantially, but those who escaped protection (either due to incomplete coverage or primary vaccine failure) remained susceptible into adulthood. This effect is clearly visible in Figure 2D as a spillover of susceptibles into older age groups over time, with cohorts born at the start of the vaccine era on the leading edge of the wave.

Crucially, this rising incidence of pertussis in adults and adolescents occurred regardless of the assumed duration of vaccine-derived immunity. We provide support for this statement in Figure 3, which depicts the annual pertussis incidence in different age groups for varying durations of vaccine- and infection-derived immunity. When infection-derived immunity was lifelong, an increase in incidence among adolescents and adults was inevitable if vaccine-induced protection was not permanent (Fig. 3D). With long-lasting vaccine-derived immunity, there was also a notable increase in infant (<1 year old) cases (Fig. 3B).

4. Discussion

Our results suggest that rising pertussis incidence among adults and adolescents should not be surprising. Indeed, our simulations, even with the conservative assumptions of lifelong natural immunity, a 70-year mean duration of vaccine immunity and 85% efficacy predicted a long- lasting honeymoon period [32] followed by a resurgence among older age groups. This pattern is a legacy of incomplete vaccination with an imperfect vaccine: individuals born in the vaccine era are less likely to be infected as children and more likely to remain susceptible as teens and adults than their pre-vaccine predecessors. Thus, during the first few decades of vaccination, the population benefits both directly from vaccine protection of children and indirectly from herd immunity established by natural infection in the pre-vaccine era. As cohorts of children born in the vaccine era grow up, the latter effect diminishes and incidence among adults inevitably rises.

In view of the considerable uncertainty surrounding the nature and duration of acquired immunity to pertussis [33], it is important to assess the robustness of this conclusion. Accordingly, we varied model assumptions regarding the durations of natural and vaccine-induced immunity. When these were assumed equal, there was no resurgence. Rather, the model predicted substantially higher and steady incidence among all age groups (Fig S8), in contradiction with observation.

Our use of a model in which infection-derived immunity can be lifelong may at first glance appear to be at odds with studies documenting reinfection [29]. However, a number of population-level studies have found that incidence data are best explained by transmission models with long-lasting natural immunity [24; 34; 35]. Moreover, evidence suggesting that pertussis re-infections are frequently less transmissible than are primary infections [35; 36], goes some way toward resolving the apparent discrepancy between immune durations estimated from population-level data on the one hand and clinical studies on the other.

The demographics of our model are a rough caricature, with a constant birth rate and type I demographics (life expectancy of seventy five years). The observed slow rise in adult incidence driven by the aging of vaccine-era cohorts, however, is reasonably robust: the same trends emerge under a variety of demographic assumptions (Fig. S10), though the

cohort effects exhibited in Figure 3 are less sharply defined. In addition, incorporating immigration and population expansion would enhance the legacy effect described here. Similarly, the legacy of incomplete vaccination is still observed when alternative contact matrix structures are assumed (Fig. S2). However the detailed epidemiological picture, including the shape of the population's immunity profile and the timing and speed of the predicted resurgence, is affected by the precise structure of the contact network.

These caveats notwithstanding, the principal conclusion of our accounting should be clear. The legacies of infection and vaccination are visible in a population's immunity profile for decades and leave long-lived signatures on incidence dynamics. We submit that the recent resurgence in adult and adolescent pertussis cases may be best understood as the end of a long honey-moon period, during which infection-derived herd immunity and imperfect vaccine protection combined to greatly reduce incidence. In the years to come, as those who as children benefited from infection-induced immunity die, more effective vaccines and vaccination campaigns will likely be required if we are to regain the upper hand on this disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Pertussis incidence has been rising in several countries with sustained high vaccine coverage, including England and Wales.
- We parameterized an age-structured pertussis model with contact patterns and vaccine uptake data from England and Wales.
- The legacies of past vaccination rates and disease incidence remain in a population's immunological signature for decades.
- A history of incomplete vaccine coverage has the potential to generate a gradual resurgence in adult and adolescent cases.

Figure 1. Incidence of pertussis in England and Wales over time based on total notifications (panel A, solid line) and lab confirmed cases by age (panel B) [2; 12]. Incidences are plotted on a square root scale for clarity. Estimated vaccine uptake for each birth year is plotted in panel A (dashed line)[4]. Although the national immunization program began in 1957, uptake data is unavailable between 1957 and 1966.

Figure 2.

A. Age-specific pattern of contacts per day, normalized to run between 0 (white) and 1 (red). Infants, toddlers, and adults are involved in fewer contacts per day than school aged children. Furthermore, most contacts are between people of similar age (the strong, central diagonal). Of the remaining contacts, most appear to be inter-generational (the two weaker diagonals), largely composed of household contacts between parents and children. Panels B, C & D depict the results of a single realization of our transmission model with lifelong vaccine-derived immunity and 85% vaccine efficacy. B. Overall incidence (red), vaccine uptake (purple), and the overall fraction of the population susceptible to pertussis (cyan) by year. C. Incidence (in cases/100,000) by age during each year of a realization of the model. D. The fraction of each age group that is susceptible to pertussis, plotted over time.

Figure 3. Pertussis incidence through time for (A) the whole population, (B) infants under 1 year old, (C) toddlers 1–4 years old, and (D) adults and adolescents over 15 years old, plotted for model realizations assuming lifelong natural immunity. In each panel, different colored lines indicate predicted incidence when the duration of vaccine-derived immunity is varied from lifelong (black) to a mean of 10 years (lightest). For clarity, only one realization is plotted for each set of parameters, but other realizations matched closely (see Fig. S8). In the online supplementary materials, we present analogous figures under alternative assumptions of the durations of vaccine-derived and natural immunity.

Table 1

Biological interpretation of average immune durations

Mean Duration of Immunity	Probability of remaining immune after 10 years	Probability of remaining immune after 25 years	Probability of remaining immune after 50 years
70 years	0.97	0.84	0.58
40 years	0.91	0.64	0.29
10 years	0.41	0.04	0.0005