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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.

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]. Fig. 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

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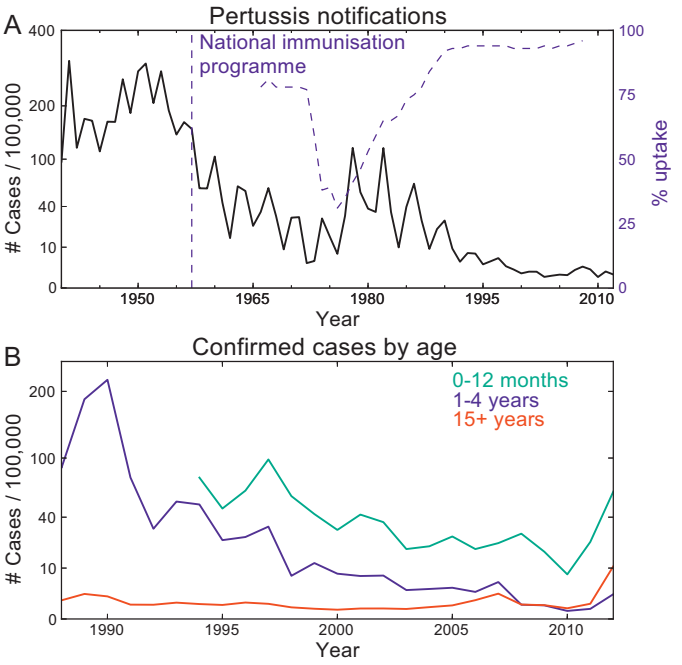

Fig. 1. Incidence of pertussis in England and Wales over time based on total notifications (panel A, solid line) and lab confirmed cases by age (panel B) [2,12]. Incidences are plotted on a square root scale for clarity. Estimated vaccine uptake for each birth year is plotted in panel A (dashed line)[4].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

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 to 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 $a = 12/5\,\text{year}^{-1}$, corresponding to the assumption that a newborn spends on average 5 months in the 0–5 month 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:

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

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

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

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

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

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

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

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 $i = 0$ or $i = 1$, births and the aging of susceptible newborns, respectively. The birth rate $b = 1/75\ \text{year}^{-1}$ 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

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

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 kth five-year age block are denoted by

$$\widetilde{I}_k = \sum_{5k<i\le 5k+5} I_i \text{ and } \widetilde{N}_k = \sum_{5k<i\le 5k+5} N_i$$

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 Figs. 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 (Fig. 1A) [6,27]. Uptake data for the period