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Modelling the effect of changes in vaccine effectiveness and transmission contact rates on pertussis epidemiology

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ABSTRACT

The incidence of the highly infectious respiratory disease named pertussis or whooping cough has been increasing for the past two decades in different countries, as in much of the highly vaccinated world. A decrease in vaccine effectiveness over time, especially when acellular vaccines were used for primary doses and boosters, and pathogen adaptation to the immunity conferred by vaccines have been proposed as possible causes of the resurgence. The contributions of these factors are not expected to be the same in different communities, and this could lead to different epidemiological trends. In fact, differences in the magnitude and dynamics of pertussis outbreaks as well as in the distribution of notified cases by age have been reported in various regions.

Using an age-structured mathematical model designed by us, we evaluated how the changes in some of the parameters that could be related to the above proposed causes of disease resurgence – vaccine effectiveness and effective transmission rates – may impact on pertussis transmission.

When a linear decrease in vaccine effectiveness (VE) was assayed, a sustained increase in pertussis incidence was detected mainly in infants and children. On the other hand, when changes in effective transmission rates (β_{ij}) were made, a dynamic effect evidenced by the presence of large peaks followed by deep valleys was detected. In this case, greater incidence in adolescents than in children was observed. These different trends in the disease dynamics due to modifications in VE or β_{ij} were verified in 18 possible scenarios that represent different epidemiological situations. Interestingly we found that both incidence trends produced by the model and their age distribution resemble the profiles obtained from data reported in several regions. The implications of these correlations are discussed.

Introduction

After the introduction of vaccination programs, the morbidity and mortality associated with the respiratory disease called pertussis or whooping cough decreased substantially. However, pertussis-related hospital admissions and fatalities are still evident, particularly in young infants. Most reported deaths occur in unvaccinated or incompletely vaccinated infants who are younger than 12 months. Nevertheless, the disease also affects adolescents and adults (de Melker et al., 2006).

During the last two years large outbreaks have been detected in Australia, the Netherlands, the UK and the US (Spokes et al., 2010; DeBolt et al., 2012; Public Health, 2013; Winter et al., 2012). The possible causes for this disease outbreaks and resurgence are still under debate and include a decrease in vaccine effectiveness over time (waning immunity) and pathogen adaptation (Mooi, 2010; Klein et al., 2012; Misegades et al., 2012; Sheridan et al., 2012).

Since pertussis vaccination is the best strategy to control pertussis disease cases, it is possible to suspect that some of the recent epidemiological features could be the consequence of failures in current vaccine effectiveness. In fact, there is recent evidence showing that acellular vaccines (aP) induce protection for less time than the whole-cell vaccines (wP) (McCarthy, 2013). Acellular vaccines were developed because of concerns that the whole-cell vaccines caused neurological and other reactions in children. Because of such concerns in the 1980s and 1990s wP vaccines were gradually replaced with aP in some countries. As an example of the failure of acellular vaccines, in a case–control study designed to assess the risk of pertussis among 10–17 year olds during the 2010–2011 outbreak in northern California, the researchers found that teenagers

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who had received four whole-cell vaccines were nearly six times less likely to have been given a diagnosis of pertussis than those who had received all acellular vaccines and nearly four times less likely than those who had received a mix of vaccines (Klein et al., 2013). It is proposed that the switch to the acellular vaccine may partly explain the resurgence of pertussis. Beyond the fact that the effectiveness of the vaccines may be reduced by the change from cellular to acellular vaccines, it can also be altered by the divergence between circulating bacterial strains and those used in vaccine production. It was proposed that the selection pressure exerted by vaccines has selected circulating bacteria. It is expected that the predominance of a particular geno/phenotypic bacterial background is not the same everywhere because of the different formulations and vaccination schemes used (i.e prn minus strains, see below).

Regarding pathogen adaptation, antigenic divergence detected initially involved mutations affecting the *B. pertussis* proteins included in the acellular vaccines. This divergence could affect pertussis transmissibility. In the 1990s, strains emerged with a novel allele for the Ptx promoter, ptxP3 strains produce more Ptx in vitro (Mooi et al., 2009). The ptxP3 strains have risen to predominance replacing the resident ptxP1 strains in many European countries, the US and Australia (Mooi et al., 2009; Advani et al., 2011; Lam et al., 2012; Petersen et al., 2012; Schmidtke et al., 2012) and also in Argentina. Van Gent et al. reported that the detected variation in the promoter for pertussis toxin (ptxP) and Prn contribute significantly to differences in colonization (van Gent et al., 2011). Regarding pertactin, the analysis of a subset of strains with the same ptxP allele revealed that the ability to colonize mice increased in the order Prn1 < Prn2 and Prn3. The increased colonization of strains containing Prn2 could also involve greater transmissibility.

More recently, strains that do not express one or more components of pertussis vaccines, in particular Prn, have emerged (Barkoff et al., 2012; Hegerle et al., 2012; Otsuka et al., 2012). In particular in US it was reported that pertactin-deficient isolates increased substantially over 50% in 2012 (Pawloski et al., 2014). PRN is a surface protein, which contains a RGD motif (Arg-Gly-Asp) involved in the attachment of *B. pertussis* to mammalian cells. Using animal (mice) models it was observed that PRN-deficient isolates are able to multiply in the respiratory tract of young mice but not in the respiratory tract of adult mice, suggesting a decrease in virulence in adults (Bouchez et al., 2009). Taking into account these results and the known role of pertactin as an adhesin, it is possible to suggest that this deficiency in protein that in principle helps the bacteria to subvert the immune response conferred by vaccines, especially those of the acellular vaccine, would also have an impact on pertussis transmission. Thus, an infectious individual carrying a pertactin-negative isolate may lead to a lower infective contact than that produced by an individual carrying a pertactin-positive isolate. At this point it is important to note that the effective contact can be modified differently depending on which geno-phenotype of bacteria in bacterial population prevails: if strains not expressing pertactin prevail, the contact rate decreases; whereas if Prn2 strains prevail, colonization increases and transmission might be greater.

Moreover, effective contact rates can be affected by other factors independent of pathogen adaptation, e.g., use of acellular vaccines. It has recently been demonstrated in a non-human animal model that acellular vaccines fail to prevent colonization and transmission, increasing the infectivity of contact rates (β_{ij})(Warfel et al., 2014). Another reason that may produce a global change in β_{ij} is a health campaign conducted against pertussis or other diseases that indirectly affect pertussis transmission (i.e., during pandemic flu). This could cause a transient reduction of β_{ij}, assuming that health care is strong for a limited period of time, usually when public health problems are very evident, and then, when the risks decrease the population becomes more relaxed in the implementation of such health cares.

All the aforementioned data show the relevance of analyzing the effect of changes in vaccine effectiveness and transmission contact rates on pertussis epidemiology.

In this work we use our previously designed mathematical model for pertussis transmission to evaluate possible changes in the effectiveness of the vaccine and in β_{ij} in 18 different possible epidemiological scenarios. These scenarios consider different contact patterns among individuals, different duration of natural or vaccine-induced immunity and different vaccination coverage. With our model we observed that the impact on pertussis epidemiological profile caused by the change in the effectiveness of the vaccine differs from that produced by global changes in β_{ij}. Beyond the intrinsic relevance of our findings, interestingly we could correlate our results with epidemiological profiles obtained from data reported in different regions.

Materials and methods

In this work we used our previously designed age-structured compartmental model with 9 epidemiological classes (Fabricius et al., 2013). The schema of the model is presented in Fig. 1. The 9 epidemiological classes shown in the figure are divided into 30 age groups. Thus, for fully susceptible individuals, for example, we define $S_i(t)$ as the fraction of individuals in class S, at time t, with age in the interval (a_i, a_{i+1}). The force of infection λ_i is the rate at which susceptible or partially immune individuals of age group i acquire infection. This is the only rate in our model that is not constant through time and depends on the fractions of infected individuals (which are dynamical variables of the model) through the expression:

$$\lambda_i = \sum_j \beta_{ij} I_j^* \quad ; \quad I_j^* = I_{1j} + \rho_1 I_{2j} + \rho_2 I_{3j} \tag{1}$$

where β_{ij} is the contact parameter matrix and I_j^* is the effective fraction of individuals of age j in the population that is infective. Factors ρ_1 and ρ_2 are taken smaller than one to consider that infected individuals in classes I_2 and I_3 are less infective than the ones in I_1 class

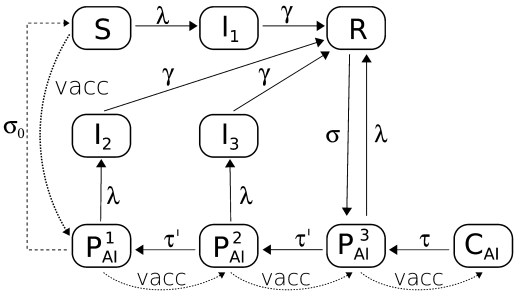

Fig. 1. Schematic representation of the mathematical model. Individuals are in the susceptible epidemiological class S when born, and remain there except when they become infectious through contact with an infected individual and enter the full symptomatic infective class I_1, or they acquire the lowest level of immunity through the first vaccine dose and enter P^1_{AI} (P_{AI}: Partial Acquired Immunity). When receiving successive vaccination doses (dotted lines), individuals go through classes of increasing immunity and eventually reach the C_{AI} (Complete Acquired Immunity) class. Individuals in classes P^1_{AI} and P^2_{AI} develop a less symptomatic illness when they get infectious, entering class I_2 (mild infection) or I_3 (weak infection), respectively. In this model, infection fades in a time$1/\gamma$. After this time, individuals in infective classes I_1, I_2 or I_3 recover and enter class R. Individuals in P^3_{AI} class acquire an extremely weak infection, thus they do not become infective and directly enter R class. Individuals in partial or complete immunity classes decrease in their immunity levels at rates σ, τ and τ' and they eventually become completely susceptible at a very slow rate τ_0.

For details see ref. (Fabricius et al., 2013).