Competition, coinfection and strain replacement in models of *Bordetella Pertussis*

Emily J. Nicoli[1], Diepreye Ayabina[2], Caroline L. Trotter[3], Katherine M. E. Turner[1], Caroline Colijn[2]

[1] *School of Social and Community Medicine, University of Bristol, Canynge Hall, 39 Whatley Road, Bristol, BS8 2PS, UK*
[2] *Department of Mathematics, Imperial College London, South Kensington Campus, London SW7 2AZ, UK. c.colijn@imperial.ac.uk*
[3] *Department of Veterinary Medicine, University of Cambridge, UK*

Abstract

Pertussis, or whooping cough, is an important respiratory infection causing considerable infant mortality worldwide. Recently, incidence has risen in countries with strong vaccine programmes and there are concerns about antigenic shift resulting in vaccine evasion. Interactions between pertussis and non-vaccine-preventable strains will play an important role in the evolution and population dynamics of pertussis. In particular, if we are to understand the role strain replacement plays in vaccinated settings, it will be essential to understand how strains or variants of pertussis interact. Here we explore under what conditions we would expect strain replacement to be of concern in pertussis. We develop a dynamic transmission model that allows for coinfection between *Bordetella pertussis* (the main causative agent of pertussis) and a strain or variant unaffected by the vaccine. We incorporate both neutrality (in the sense of ecological/population genetic neutrality) and immunity into the model, leaving the specificity of the immune response flexible. We find that strain replacement may be considerable when immunity is non-specific. This is in contrast to previous findings where neutrality was not considered. We conclude that the extent to which models reflect ecological neutrality can have a large impact on conclusions regarding strain replacement. This will likely have onward consequences for estimates of vaccine efficacy and cost-effectiveness.
Keywords: *Bordetella pertussis*, strain replacement, coinfection, competition, epidemic, specific immunity

1 Introduction

Whooping cough, or pertussis, is an important respiratory infection. Approximately 16 million cases and 195,000 deaths among children occur annually worldwide [39]. Pertussis is caused predominantly by the bacteria *Bordetella pertussis* that resides in the upper respiratory tract and is commonly spread through the secretion of small droplets from a host being transmitted to a susceptible individual. Typical symptoms include the classic paroxysmal cough preceding the 'whooping' intake of

breath, sometimes followed by vomiting; this cough can last for up to 8 weeks and in some cases even longer. Household studies have found that there are high levels of mild symptoms and asymptomatic carriage, particularly in adolescents and adults [13, 24, 31]. This leads to under-reporting and poses a risk to younger children and infants who are unknowingly exposed and who are more susceptible to severe symptoms and increased risk of mortality.

Incidence of pertussis has recently seen a marked rise in developed countries with long-running, high-coverage vaccine programmes [8, 23]. There is also evidence that the age profile of the cases has changed [6, 41], with higher incidence in teenagers and adults, for what was previously thought of as a childhood disease. Tests into the efficacy of the acellular vaccine have produced variable results [19, 38, 43], and there have been suggestions that the increases in incidence are the result of antigenic shift in *B. pertussis*, allowing evasion of vaccine-acquired immunity [35, 36]. However, there are also other sources of genetic variation [17, 21].

The related bacterial strain *Bordetella parapertussis* causes similar symptoms to *B. pertussis*, though parapertussis symptoms are generally less severe. The relationship between *B. pertussis* and *B. parapertussis* is not clear [18, 14]. As differential diagnosis has no effect on clinical treatment, clinicians rarely specifically test for *B. parapertussis*, and the reported percentage of pertussis cases caused by *B. parapertussis* varies, with studies in Europe suggesting it ranges from 2% to 36% [4, 20, 27, 33] and a large study in the US reporting 14% of pertussis cases identified as *B. parapertussis* [9]. There is considerable debate on the level of immunity that infection with one of these strains confers against the other. A range of studies have found that the acellular and whole-cell vaccines protect against pertussis more strongly than they do against parapertussis [44, 12, 22]. Watanabe and Nagai [42] found that mice infected with either strain were able to clear both, when re-infected with both strains six weeks after their initial infection. More recent work found that acellular vaccination cleared *B. pertussis*, but led to a large increase in *B. parapertussis* colony-forming units in co-infected rodents, suggesting strong inter-strain competition [30] within hosts. In 2008, Restif *et al.* [40] developed a mathematical model of *B. pertussis* and *B. parapertussis* allowing for coinfection, to analyse the effect of asymmetric cross-immunity between the strains. Their model suggested that the pertussis vaccine would have little effect on the prevalence of *B. parapertussis*.

Similar strains of a pathogen can be expected to compete for hosts and/or to compete for resources within hosts. When strains are competing for resources, we would expect that selectively reducing the prevalence of one of them would lead to rises in the other one, as more resources become available (as was found, *within* hosts, in the rodent study [30] mentioned above). Inter-strain competition *for* hosts is modulated by immunity: a vaccine can lead to strain replacement by selectively protecting hosts from a primary strain, allowing a non-vaccine strain to access more hosts than it would otherwise. This can undermine the efficacy and cost-effectiveness of vaccination programmes. Accordingly, in using models to explore whether strain replacement is a concern in a particular setting, it is helpful to determine the likely mechanisms by which the strains may be in competition with each other and explore how these play out using mathematical models.

Some of us have previously argued that models exploring inter-strain interactions should behave in a sensible way in the limit when the strains are identical [28, 11]. In particular, a rare strain should not have a reproductive advantage simply by virtue of being rare. If it has such an advantage, there is so-called "coexistence for free" – in the limit in which strains are identical, rare strains are given a competitive advantage in the model, despite being identical to the more common strain. This

reproductive advantage is nonsensical, as each identical individual in a population should have the same number of descendants on average. Models that permit this "identical behaviour of identical strains" (and do not feature coexistence for free) can be called "neutral null models" (or, here, simply "neutral"). Many mathematical models of multiple circulating strains do not allow identical behaviour of identical strains [28]; the resulting implicit assumptions about competition in these models have potentially large consequences for conclusions about vaccine-induced strain replacement (compared to models that do allow neutral interactions). For example, the *B. pertussis*/*B. parapertussis* model by Restif *et al.* [40] does not meet the neutral null criterion, and so may promote the coexistence of both *B. pertussis* and *B. parapertussis*, reducing the model's inter-strain competition.

It is challenging to incorporate immunity and vaccination into the neutral framework, because if immunity is entirely non-specific, then the strains are not meaningfully different from the point of view of vaccination, but if immunity is specific, a model will fail the neutral test. Furthermore, including immunity in the neutral framework in a compartmental, SIR-type, model requires adding a number of compartments reflecting individuals who are susceptible, infected or recovered with one strain and immune to the other. Accordingly, we set out to construct the simplest model with the following ingredients: (1) satisfies the neutral null criteria when strains are identical; (2) contains vaccination specific to one strain (when they are not identical); (3) contains immunity, which, reflecting the uncertainty around specificity in pertussis, can be more or less specific to each strain (when they are not identical). We develop a neutral model of *B. pertussis* interacting with a non-vaccine strain (which could be *B. parapertussis*, if the model is parameterised appropriately). We include vaccination and immunity, where the immune specificity is parameterized such that the model is neutral when the strains are indistinguishable. We allow neutrality to be broken by the introduction of strain-specific immunity, and we explore the relationship between the specificity of immunity and the extent of strain replacement due to vaccination.

2 Methods

Modeling strategy

We developed a compartmental SIR-type model, allowing for coinfection and immunity. Both our model and the model by Restif *et al.* [40] incorporate coinfection, and we note that if coinfecion is not included, this amounts to an assumption that strains are competing strongly for hosts. This assumption would drive models towards strain replacement because under strong competition for hosts, reducing the prevalence of one strain makes hosts available to the other. Consequently, our model is based on the neutral null model proposed by Lipsitch *et al.* [28], in which individuals can become coinfected with both strains, or dually infected with the same strain. Neutrality requires that coinfected individuals can have one strain "knocked out" by the other (strain replacement). Otherwise, a rare strain has an advantage by virtue of being rare [11, 28]. In our model, infection with a second strain results in coinfection rather than super-infection, because super-infection (one strain entirely and instantly displacing the other) is a strong assumption about inter-strain competition. We also add a 'recovered' compartment, R, representing individuals who have acquired immunity to both strains (Figure 1a).

Specific immunity cannot be included when verifying whether a model meets the neutral null criteria for identical strains, as immunity to one strain and not the other requires a difference between the strains. Furthermore, if there is specific

immunity, then a rare strain will have an advantage over a prevalent strain due to the population's partial immunity (only) to the prevalent strain. When a rare strain has an advantage due to being rare, this will promote stable coexistence of the two strains. To explore this spectrum of competition, we begin with a neutral null model and build specific immunity on top of it. The result is a model that reduces to a neutral null model when strains are indistinguishable. To do this, we make the assumption that when individuals gain specific immunity to one strain, they can still become either singly or dually infected with the other. Therefore we require compartments to represent individuals who have recovered from one of the strains and are now: 1) susceptible to the other strain, 2) infected with the other strain or 3) dually infected with the other strain. This introduces six additional compartments to the model (compared to the six-state model with coinfection in [28]) and gives the structure shown in Figure 1b.

Neither a neutral model nor a model requiring specific immunity can be used to study the interplay between neutrality, specific immunity and strain replacement, as the neutral null model has no specific immunity and the model with specific immunity is not neutral. We therefore introduce a parameter s to smoothly interpolate: $s \in [0, 1]$ is a parameter that shows the extent of strain specific immunity present in the model (Figure 2). When $s = 1$ there is specific immunity and the model reduces to the model in Figure 1b, which is not neutral. When $s = 0$ there is no specific immunity and the model reduces to the model in Figure 1a, which is neutral. When $0 < s < 1$, the model reflects the presence of some strain-specific immunity as well as some non-specific immunity. For simplicity, we assume symmetric inter-strain interactions except for the asymmetry in the transmission and response to vaccination. As a result, s appears to have a number of distinct effects in the model, but these are all one effect: smoothly interpolating between a neutral model and a non-neutral one with specific immunity.

We make the following assumption about immunity: when individuals are singly or dually infected with one strain, on recovery, they are either fully protected against reinfection with the same strain (specific immunity) or fully protected against both strains (non-specific immunity). As a result, the recovery rate r is multiplied by s when immunity is specific and by $1 - s$ when immunity is non-specific. The same also applies to the loss of immunity. We model the proportions of hosts in different epidemiological classes.

Model equations

The differential equations are:

$$\begin{aligned}
\frac{dS}{dt} &= \mu(1-\nu-S) - (\lambda_p+\lambda_n)S + \gamma_p S_{Rp} + \gamma_n S_{Rn} + (1-s)\gamma R \\
\frac{dI_p}{dt} &= -\mu I_p + \lambda_p S - rI_p - k_{sp}\lambda_p I_p - k_{cp}\lambda_n I_p + \gamma_n I_{pRn} \\
\frac{dI_n}{dt} &= -\mu I_n + \lambda_n S - rI_n - k_{sn}\lambda_n I_n - k_{cn}\lambda_p I_n + \gamma_p I_{nRp} \\
\frac{dI_{pn}}{dt} &= -\mu I_{pn} + k_{cp}\lambda_n(I_p - cI_{pn}) + k_{cn}\lambda_p(I_n - cI_{pn}) - rI_{pn} + \\
&\qquad 2ck_{cp}\lambda_n I_{pp} + 2ck_{cn}\lambda_p I_{nn} \\
\frac{dI_{pp}}{dt} &= -\mu I_{pp} + k_{sp}\lambda_p I_p + ck_{cn}\lambda_p I_{pn} - 2ck_{cp}\lambda_n I_{pp} - rI_{pp} + \gamma_n I_{ppRn} \\
\frac{dI_{nn}}{dt} &= -\mu I_{nn} + k_{sn}\lambda_n I_n + ck_{cp}\lambda_n I_{pn} - 2ck_{cn}\lambda_p I_{nn} - rI_{nn} + \gamma_p I_{nnRp} \\
\frac{dS_{Rp}}{dt} &= \mu(\nu - S_{Rp}) + sr(I_p + I_{pp}) - k_{cp}\lambda_n S_{Rp} - \gamma_p S_{Rp} + s\gamma_n R \\
\frac{dI_{nRp}}{dt} &= -\mu I_{nRp} + k_{cp}\lambda_n S_{Rp} - k_{sn}\lambda_n I_{nRp} - \gamma_p I_{nRp} - rI_{nRp} \\
\frac{dI_{nnRp}}{dt} &= -\mu I_{nnRp} + k_{sn}\lambda_n I_{nRp} - rI_{nnRp} - \gamma_p I_{nnRp} \\
\frac{dS_{Rn}}{dt} &= -\mu S_{Rn} + sr(I_n + I_{nn}) - k_{cn}\lambda_p S_{Rn} - \gamma_n S_{Rn} + s\gamma_p R \\
\frac{dI_{pRn}}{dt} &= -\mu I_{pRn} + k_{cn}\lambda_p S_{Rn} - k_{sp}\lambda_p I_{pRn} - \gamma_n I_{pRn} - rI_{pRn} \\
\frac{dI_{ppRn}}{dt} &= -\mu I_{ppRn} + k_{sp}\lambda_p I_{pRn} - rI_{ppRn} - \gamma_n I_{ppRn} \\
\frac{dR}{dt} &= -\mu R + r(I_{pn} + I_{pRn} + I_{ppRn} + I_{nRp} + I_{nnRp}) - s(\gamma_p + \gamma_n)R \\
&\qquad -(1-s)\gamma R + (1-s)r(I_p + I_{pp} + I_n + I_{nn})
\end{aligned}$$

where:

$$\begin{aligned}
\lambda_p &= \beta_p(I_p + I_{pRn} + qI_{pn} + 2q(I_{pp} + I_{ppRn})) \\
\lambda_n &= \beta_n(I_n + I_{nRp} + qI_{pn} + 2q(I_{nn} + I_{nnRp}))
\end{aligned}$$

The states and variables are defined in full in Table 1.

Parameters and simulation

Due to the high dimensionality of the model, little algebraic analysis is feasible and we take a simulation approach. Prevalences reported in figures are numerically-determined equilibria of the model except for the trajectories in Figure 3. The model was parameterised according to the literature wherever possible. All programming and analysis was performed using MATLAB [34], while XPPAUT [15] was used to solve the differential equations. We introduce a small amount of the non-vaccine strain at the time at which vaccine is introduced in the simulations, mimicking the introduction of small amounts of diverse strains in real populations through mutation, acquisition of genetic material, immigration of hosts carrying diverse strains and so on (these are not explicitly modeled).

Our parameters are based on limited available information from clinical data and previous modeling works. We set the average infectious period $\frac{1}{r}$, where r is the

recovery rate, for both strains to be 20 days [2]. Infection-induced immunity may often be longer-lasting than vaccine-induced immunity [3, 5], but Cherry [7] argued that both vaccination- and infection-induced immunity are of similar duration. We follow this latter assumption for simplicity and clarity. We set the average duration of immunity $\frac{1}{\gamma}$ (where γ is the rate of loss of immunity) to be 20 years, which Aguas et al [1] report is consistent with empirically-determined rates of waning immunity. Pertussis is a highly contagious disease with very large reproductive number R_0 of $12 - 17$ [29]. We choose values of R_0 from this range for both strains. We also explore values of R_0 that are well below these high estimates to see the effect on our results. The relationship between the basic reproduction number of a strain, R_{0i} and its transmission rate, β_i is $R_{0i} = \frac{\beta_i}{\mu+r}$, where $1/\mu + r$ is the average duration of infection (taking the lifespan $1/\mu$ into account.

No estimates of the inter-strain interactions k_c and k_n are available; these were varied between 0 and 1. We impose symmetry on all rates of secondary infection i.e. $k_{cn} = k_{sn} = k_{sp} = k_{cp}$. We also assume that at time $t = 0$, most of the individuals in the population are susceptible to both strains i.e. in the class (S), a small but equal fraction of individuals are singly infected with either strain (I_p or I_n), and no individuals in all other classes i.e. initial condtions are, $I_p = I_n = 0.003$, $S = 0.994$ and $I_{nn} = I_{pp} = I_{pn} = S_{Rp} = S_{Rn} = I_{pRn} = I_{ppRn} = I_{nRn} = I_{nnRn} = 0$ at $t = 0$.

3 Results

We find that the specificity of the immune response can shift the model from a regime in which there is no strain replacement and the strains' population dynamics are independent of each other to one in which vaccination leads to complete strain replacement, i.e. where there is no significant change in pre- and post-vaccine prevalence of both strains combined. Figure 3 shows the prevalence of *B. pertussis* and *B. parapertussis* in our model with $s = 0$, $s = 0.5$ and $s = 1$, and in the model proposed by Restif *et al.* [40]. When immunity is not strain-specific ($s = 0$), pertussis vaccination can eliminate pertussis, but the prevalence of the non-vaccine strain increases to compensate. The result is that the vaccine has no significant impact on the overall number of cases. In contrast, when immunity is specific, vaccination has no significant impact on the prevalence of the non-vaccine strain. Intermediate values of specificity result in outcomes between these two extremes, with moderate increases in the non-vaccine strain after vaccination. In addition, the extent of immunity to one strain conferred by infection with the other has consequences for the level of vaccination required to eliminate infection. For example, when $s = 0.5$ (Figure 3b with $s = 0.5$), the effect of vaccination on *B. pertussis* is reduced compared to its effect when $s = 0$, and a vaccine coverage of 0.95 no longer eliminates *B. pertussis*.

Under parameters where non-specific immunity is asymmetric, ie where *B. parapertussis* infection confers some immunity to *B. pertussis* but not vice versa [40, 44], we found that the prevalence of *B. parapertussis* is slightly higher than with the parameters of Table 1. This is due to the advantage that the asymmetry confers – those who have prior infection with *B. pertussis* remain more susceptible to *B. parapertussis* than vice versa. However, the bifurcation diagrams are very similar to those reported here and do not indicate that *B. parapertussis* would have the ability to replace *B. pertussis* following a vaccination programme.

We compared our results to those of Restif *et al.* [40], who modeled *B. pertussis* and *B. parapertussis*, allowing for coinfection. In their model, rather than interacting neutrally, identical strains reach a 50/50 equilibrium prevalence independent of their

initial relative frequencies, meaning that an initially rare (but otherwise identical) strain has far more descendants than the initially prevalent one. Their model is similar to our model when $s = 1$ (specific immunity). Figure 3a shows that both their model and ours with $s = 1$ find no strain replacement, as Restif *et al.* concluded. However, when immunity is less specific we find considerable strain replacement. Furthermore, we obtain the same result – higher specificity means less competition and less replacement – even if we adjust the effect of s in the model to only modify some of the terms (for example, if the s terms leaving the dually-infected classes are removed so that s only affects the singly-infected classes, we still find that $s = 0$ results in strain replacement and that replacement is reduced when $s > 0$).

We explore the interplay between s, vaccination levels, and the relationship between the prevalence of the two strains (Figure 4) under parameters reflective of *B. pertussis* and *B. parapertussis*. The steady state prevalences of the two strains are shown over a range of values of vaccine coverage. As vaccine coverage increases for the neutral model ($s = 0$), the prevalence of *B. pertussis* decreases, but the prevalence of *B. parapertussis* increases, and the overall (total) prevalence remains essentially unchanged. Conversely, in the case where $s = 1$, vaccination leads to decreasing *B. pertussis* prevalence while *B. parapertussis* prevalence remains constant. These results are not specific to *B. parapertussis* but would apply generically to a non-vaccine strain.

The bifurcation diagrams in Figure 5 show the equilibrium steady states for the models, with navy blue indicating no disease, yellow indicating that only *B. pertussis* persists, blue indicating that only *B. parapertussis* persists, and red showing where both strains stably coexist. When $s = 0$ (Figure 5a), there is very little coexistence and the model exhibits competitive exclusion (the strain with the higher R_0 value out-competes the other strain). If $s = 0.5$ there is generic coexistence; only if the R_0 of one of the strains is low will the other strain persist alone. This is also the case when $s = 1$. In addition when $s = 1$ the two strains are independent, such that the R_0 of one strain has no effect on the prevalence of the other, shown in Figure 5c by the horizontal and vertical boundaries between the single strain and coexistence steady states. The model proposed by Restif *et al.* shows similar horizontal and vertical boundaries between the single strain and coexistence steady states.

Figure 6 shows how the value of the non-vaccine-strain R_0 (*B. parapertussis*; R_{0n} in the figure) affects the prevalence of both strains over varying vaccine coverages and for $s = 0$, 0.5 and 1. When $s = 0$ (top left panel) there is a trade-off such that when one strain's prevalence is high, the other's is low. This is an intuitive reflection of the inter-strain competition. When $s = 1$, vaccine coverage has little or no effect on the prevalence of *B. parapertussis* (bottom right panel). Conversely (top right panel), the R_0 of parapertussis has essentially no effect on pertussis prevalence when $s = 1$.

4 Discussion

In any vaccination programme in which there is antigenic diversity of the pathogen, strain replacement should be of concern. We have illustrated in a mathematical model that how much of a concern it is depends strongly on the specificity of the immune response; this shapes the inter-strain interactions. In using models to determine whether or not strain replacement is probable, modelers must carefully consider their assumptions about these interactions. Neutral models allow identical strains to behave identically (independent of their relative prevalence); a consequence of this is that the relative frequencies of indistinguishable strains should be constant

in time [28]. This in turn means that if there were more infections of one group, there would be fewer of another (as relative frequencies sum to 1) – the embodiment of competition. Models that have "coexistence for free", i.e. models that contain some implicit mechanism promoting the long-term stable coexistence of different strains, also have reduced inter-strain competition. Generally speaking, the more coexistence-promoting a model is, the less competition exists between its strains. This has consequences when it comes to making predictions about strain replacement.

Strain replacement is rooted in inter-strain competition. If strains are competing for hosts and some hosts are protected from one strain but not another by vaccination, the stage is set for strain replacement. Strain replacement can also occur (in models) where vaccination targets each strain equally but one has an advantage in super-infecting or re-infecting hosts with the other strain [32]. In contrast, if infection with a strain is entirely unrelated to current or past infection with another strain then concern about strain replacement would be unnecessary. But this is unlikely to be the case for very closely related pathogens.

The fundamental effect underlying our results is that the extent of strain replacement depends on whether the underlying model is neutral. This result can be obtained in a wide range of models. With reference to Figure 5, imagine an intervention that only targets the strain whose R_0 is on the horizontal axis as a horizontal, left-pointing arrow moving R_0 from a higher point to a lower one. In the neutral null case (top left panel), this arrow can easily move the model from a point in one single strain region (light blue) to the other single strain region (yellow), i.e. causing strain replacement. Whether it does so depends on the strength of the intervention, i.e. how much does it reduce R_0, and how much higher R_0 of the vaccine preventable strain is than that of the escape strain initially. In the non-neutral cases where coexistence is generic, such an arrow will generally not move the system across the bifurcation boundary. Nicoli [37] illustrated these diagrams for a wide range of neutral and non-neutral models; neutral models generically show the competitive exclusion-type bifurcation diagram (similar to that shown in [11]) in which the only prevalent strain is the one with a higher R_0.

Recently, Flasche et al [16] also stressed that strain replacement will occur when immunity is not strain-specific. They note that if a strain limits its own transmission to the same extent it limits the spread of a competing strain (non-specific immunity), then coexistence is unlikely. In the same way, in our model, for strain replacement to occur, there must be some non-specific immunity. It is likely that the true level of competition between *B. pertussis* and *B.parapertussis* lies somewhere between the competing and independent regimes.

Cross-immunity compared to strain-specific immunity is not the only mechanism for epidemiologically relevant interaction between strains or infections. For example, differential susceptibility, co-treatment of different infections, differential symptomaticity (ie differences in virulence and transmissibility) and enhancement effects such as one strain resulting in increased transmission of the other, would all affect the interactions between strains. While model structures can be developed which account for these effects, strain interactions are affected by subtle modeling choices, and models may inadvertently make strong assumptions that bias conclusions that depend on inter-strain interactions. We suggest that clearly elucidating how strains interact and why, considering the extent of competition and the nature of coexistence-promoting mechanisms, should be a fundamental part of model development in this field.

The parameter s moves our model between two extremes, neutrality (competi-

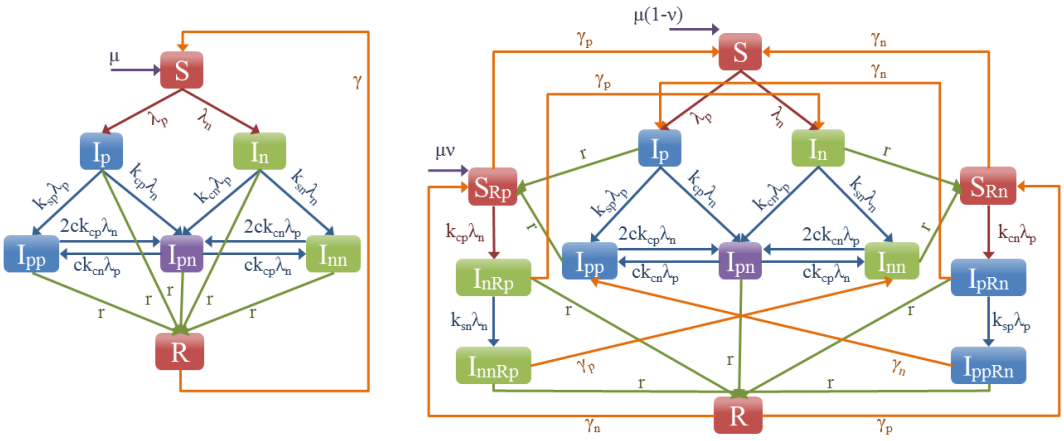
tion) and strain specific immunity (independence). However, it would be difficult to infer s from epidemiological data. Vaccination would be a natural experiment to see what happens and potentially to infer s, but the other complexities and heterogeneities in such hypothetical studies would make this very challenging. An alternative approach would be to conduct experiments in animal models to guide inference on the degree of specific and non-specific immunity [31], but such studies would have difficulty capturing the long-term and population-level effects of inter-strain competition. In addition to the difficulty in inferring s from data, limitations of this work include simplifying assumptions in the model: homogeneous population mixing, deterministic dynamics, lack of age structure, and so on. Including these complexities would be expected to change the details of the model trajectories, and in particular the high-frequency oscillations are likely an artefact of these simplifying assumptions. In addition, at low prevalence, stochastic extinction would be possible (though if there were also mutation and stochastic generation of diversity, non-vaccine strains could arise again). However, Nicoli's work [37] incorporating age structure into similar models for meningococcus found that the competition effects – coexistence and replacement – were not changed when age and population mixing were modified and we believe that our results on competition, replacement and the specificity of immunity are robust. They are also in accordance with the detailed individual-based model of pneumococcal diversity of Cobey and Lipsitch [10].

The model we have developed is generic and could be applied to model independence and competition in other organisms. For example, it might be assumed, based on the effect of vaccination programmes, that there are high levels of competition between strains of *Streptococcus pneumoniae* [25]; an intermediate value of s would capture some non-specific immunity while preserving some serotype-specific immunity (as in Cobey and Lipsitch [10]). For entirely independent strains, as studies suggest may be the case for *Haemophilus influenzae* [26], s could be set close to 1. Furthermore, immune specificity is not the only way to alter the extent of competition in this model or others. While different choices for the parameters q (the relative infectiousness of dually infected individuals compared to singly infected ones) and c (which alters the re-infection dynamics for dually infected individuals) could make the model non-neutral they could also reflect differing scenarios for how dual infection plays out. We therefore suggest that this model and those like it are a helpful framework for understanding how re-infection, dual infection and pathogen variation at the simplest level of two strains affect the strain frequencies over time. And while the mechanism and extent of competition between *B. pertussis* and *B. parapertussis* (or other non-vaccine strains) is unknown, clarifying the consequences of strain interactions at the level of immunity, and other mechanisms that may result in strain replacement, is very important in understanding how this pathogen is responding to vaccination.

Acknowledgements

This study was supported by the Engineering and Physical Sciences Research Council (CC: EPSRC EP/K026003/1) and the National Institute for Health Research (KT: NIHR PDF 2009-02-55)

5 Figures



(a) Neutral null coinfection model without specific immunity.

(b) Coinfection model with specific immunity that doesn't meet the neutral null criteria.

Figure 1 – Coinfection models with neutrality, but no specific immunity and with specific immunity, but no neutrality. See Table 1 for parameter definitions

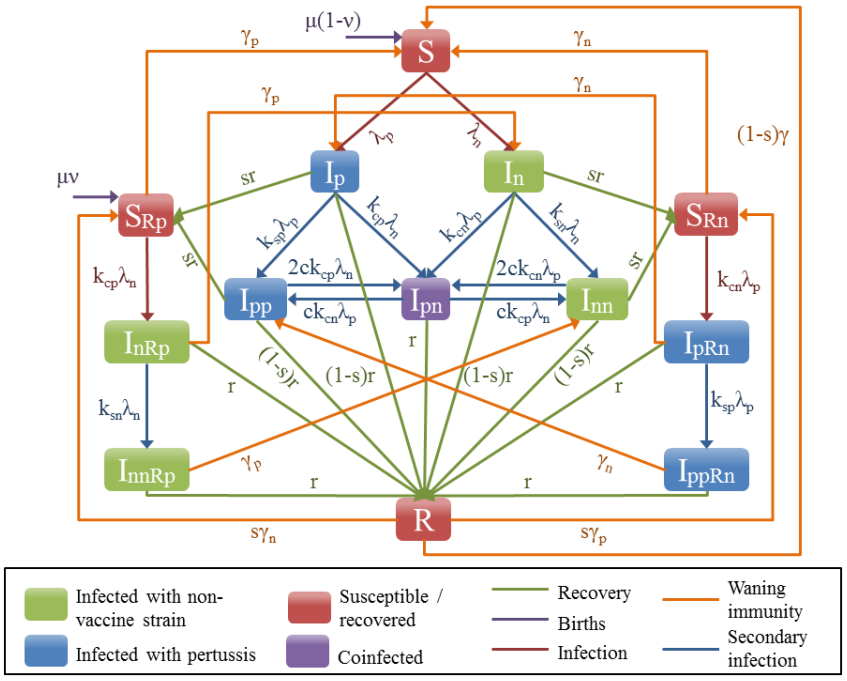
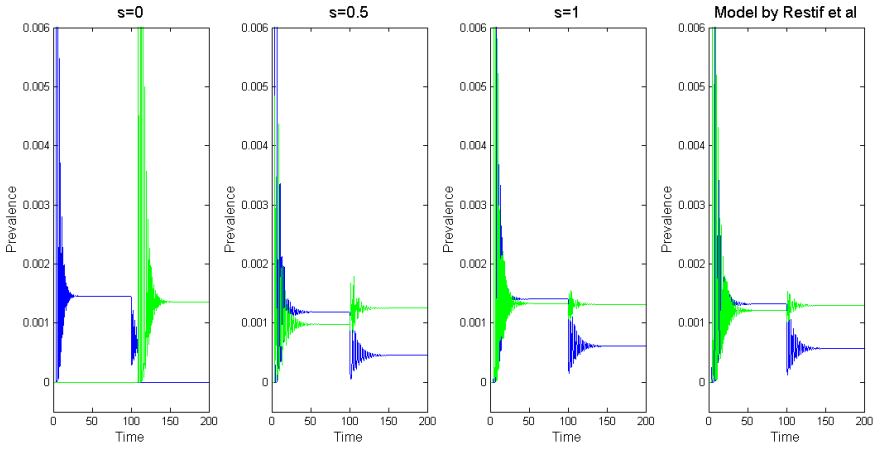
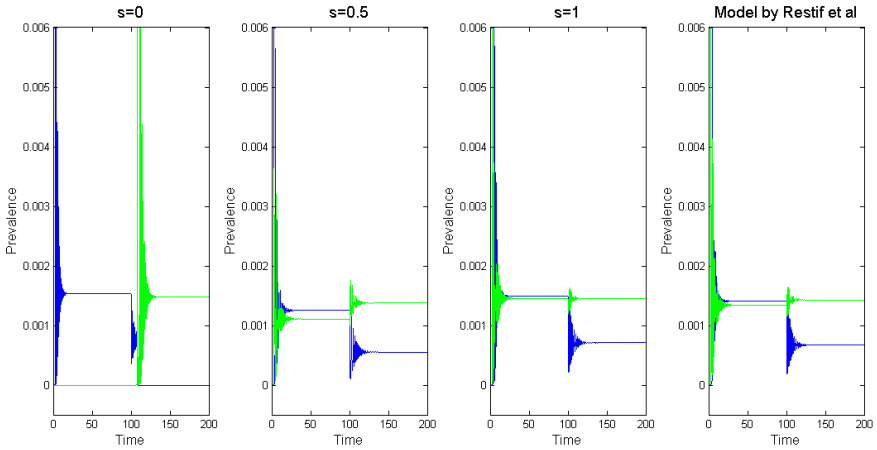


Figure 2 – Coinfection model for B. pertussis and B. parapertussis with variable specific immunity. See Table 1 for parameter definitions. In particular, throughout this work, symmetric interactions are assumed such that $k_{sn} = k_{sp} = k_s$, $k_{cn} = k_{cp} = k_c$.

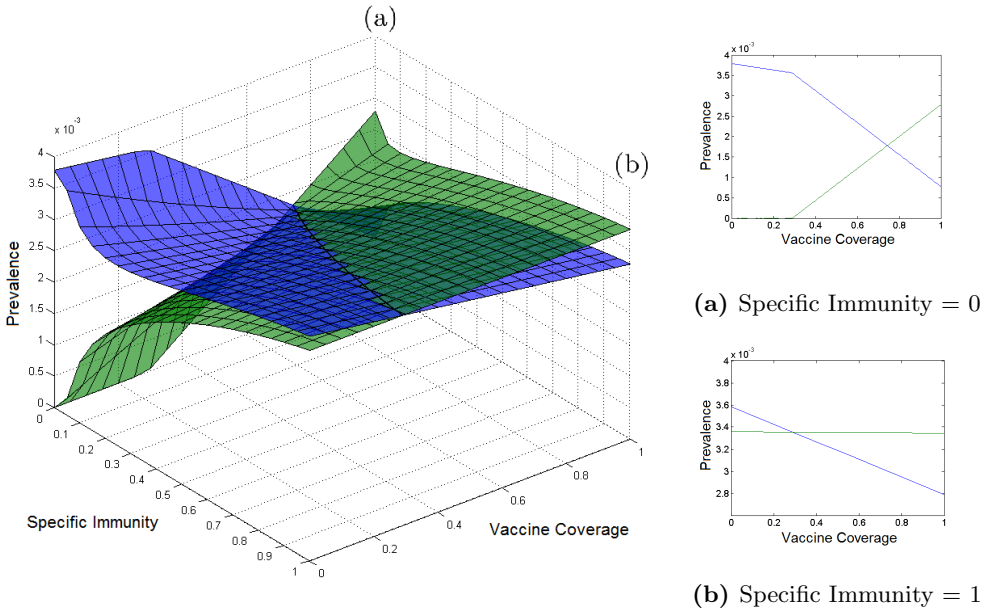


(a) $R_{0p} = 9$, $R_{0n} = 7$



(b) $R_{0p} = 15$, $R_{0n} = 12$

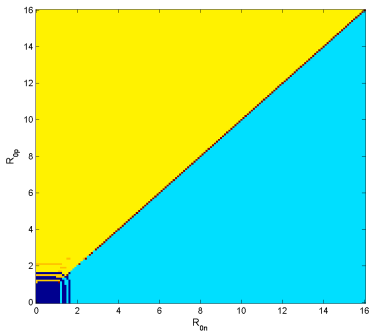
Figure 3 – Trajectory plots of prevalence and incidence for different values of specific immunity, s. Blue line = pertussis; green line = parapertussis. Introduction of vaccination at $t = 100$, vaccine coverage $\nu = 0.95$. Parameters and initial conditions: $R_{0p} = 15$, $R_{0n} = 10$, $r = 1/20$ days, $k_{cn} = k_{sn} = k_{sp} = k_{cp} = 0.7$, $c = 0.5$, $q = 0.5$, $\gamma = 1/70$ years, $\mu = 1/70$ years. At $t = 0$, $I_p = I_n = 0.003$, $S = 0.994$ and $I_{nn} = I_{pp} = I_{pn} = S_{Rp} = S_{Rn} = I_{pRn} = I_{ppRn} = I_{nRn} = I_{nnRn} = 0$. A small amount of non-vaccine strain was introduced when $s = 0$ mimicking importation by mutation or immigration, at the time of the introduction of vaccine ($I_n(t_{vac}) = 0.0001$). High-frequency oscillations occur as a transient effect in the model, resulting from instantaneous introduction of high levels of vaccine coverage, or (at the start of the simulation) the fact that the model has fast time scales in its relaxation to equilibrium. These high-frequency oscillations would not be expected to be observed because such sharp transitions (0 to 95% vaccination coverage essentially instantaneously, together with instantaneous homogeneous mixing in the population) are not realistic.



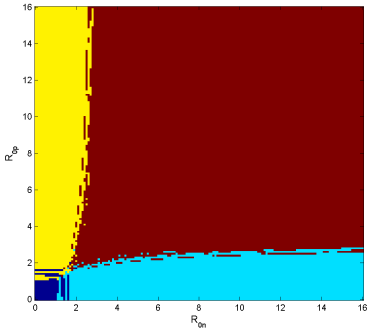
(a) Specific Immunity = 0

(b) Specific Immunity = 1

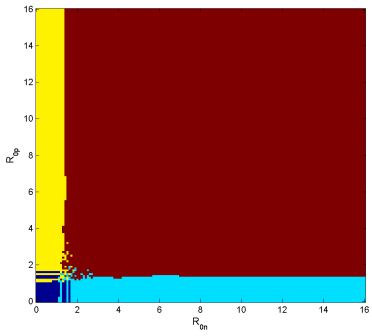
Figure 4 – Prevalence for different levels of vaccine coverage and specific immunity. Blue surface = pertussis; green surface = parapertussis. [$R_{0p} = 7$ [40], $R_{0n} = 5.6$, $r = 1/20$ days, $k_{cn} = k_{sn} = k_{sp} = k_{cp} = 0.7$, $c = 0.5$, $q = 0.5$, $\gamma = 1/20$ years, $\mu = 1/70$ years. These parameter values were chosen to reflect similar parameters to those used by Restif et al. At $t = 0$, $I_p = I_n = 0.003$, $S = 0.994$ and $I_{nn} = I_{pp} = I_{pn} = S_{Rp} = S_{Rn} = I_{pRn} = I_{ppRn} = I_{nRn} = I_{nnRn} = 0$.



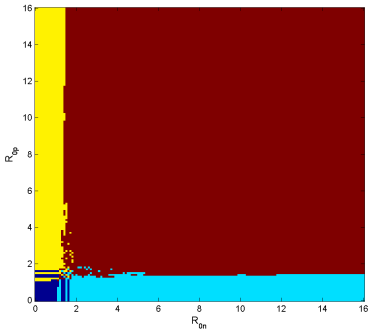
(a) $s = 0$: Neutral null, no specific immunity



(b) $s = 0.5$

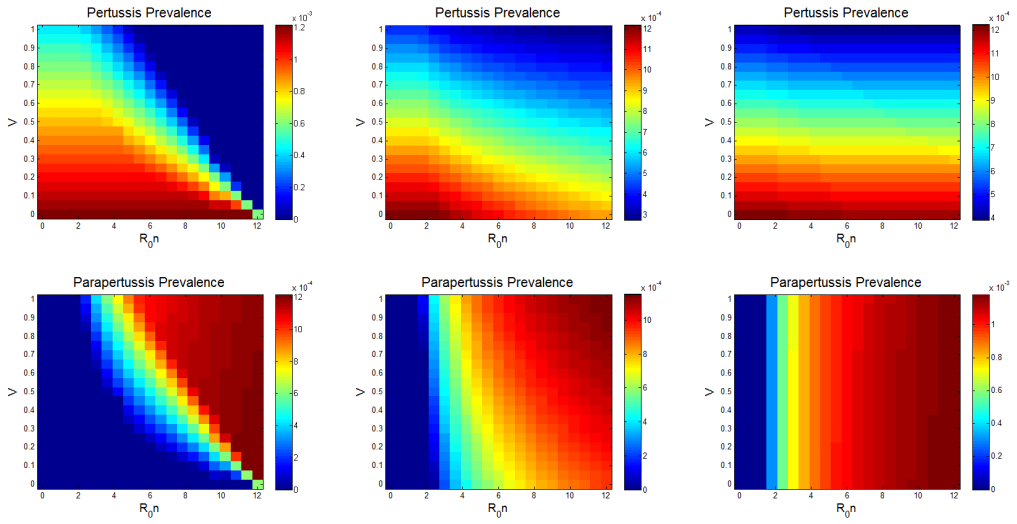


(c) $s = 1$: Specific immunity, not neutral



(d) Model by Restif *et al.*

Figure 5 – Bifurcation diagrams for different values of specific immunity, s. Navy = no disease; yellow = pertussis only; blue = parapertussis only; red = coexistence. $r = 1/20$ days,$k_{cn} = k_{sn} = k_{sp} = k_{cp} = 0.7$, $\nu = 0$, $c = 0.5$, $q = 0.5$, $\gamma = 1/10 years$, $\mu = 1/70$ years. At $t = 0$, $I_p = I_n = 0.003$, $S = 0.994$ and $I_{nn} = I_{pp} = I_{pn} = S_{Rp} = S_{Rn} = I_{pRn} = I_{ppRn} = I_{nRn} = I_{nnRn} = 0$.



(a) $s = 0$: Neutral **(b)** $s = 0.5$ **(c)** $s = 1$: Specific immunity

Figure 6 – Bifurcation diagrams of prevalence for varying levels of vaccine coverage and parapertussis transmission. (a) $s = 0$: there is a trade-off such that where pertussis prevalence is low, parapertussis prevalence is high and vice versa. Both the R_0 values and the vaccination rate affect both strains' prevalence. (b) $s = 0.5$ Intermediate specificity of immunity reduces the trade-off. (c) $s = 1$ (specific immunity): here, the R_0 value of the non-vaccine (parapertussi) strain does not affect pertussis prevalence, and the vaccination rate does not affect the parapertussis prevalence. Other parameters are: $R_{0p} = 12$, $r = 1/20$ days, $k = 0.7$, $c = 0.5$, $q = 0.5$, $\gamma = 1/10$ years, $\mu = 1/70$ years. At $t = 0$, $I_p = I_n = 0.003$, $S = 0.994$ and $I_{nn} = I_{pp} = I_{pn} = S_{Rp} = S_{Rn} = I_{pRn} = I_{ppRn} = I_{nRn} = I_{nnRn} = 0$.

6 Tables

Table 1 – Definitions of all states and parameters

Symbol	Definition
States	
S	Susceptible to both pathogen strains
I_p	Infected with pertussis
I_n	Infected with non-preventable strain (*Bordetella parapertussis*)
I_{pn}	Coinfected with both strains
I_{pp}	Dually infected with pertussis
I_{nn}	Dually infected with non-preventable strain
S_{Rp}	Susceptible to non-preventable, immune to pertussis
I_{nRp}	Infected with non-preventable, immune to pertussis
I_{nnRp}	Dually infected with non-preventable, immune to pertussis
S_{Rn}	Susceptible to pertussis, immune to non-preventable
I_{pRn}	Infected with pertussis, immune to non-preventable
I_{ppRn}	Dually infected with pertussis, immune to non-preventable
R	Immune to both strains
Variables	
p	As underscore: vaccine preventable pertussis
n	As underscore: non-vaccine preventable pertussis
λ	Force of infection
β	Transmission rate ($\beta = R_0(\mu + r)$)
R_0	Reproductive number ($R_{0p} = 15,9; R_{0n} = 12,7$)
μ	Birth/Death rate ($\mu = \frac{1}{70years}$)
ν	Vaccination coverage against pertussis ($\nu = 0.95$)
γ	Rate of lose of immunity ($\gamma = \frac{1}{20years}$)
k_s	Self-protection($k_{sn} = k_{sp} = k_s = 0.7$)
k_c	Cross-protection ($k_{cn} = k_{cp} = k_c = 0.7$)
r	Recovery rate ($r = \frac{1}{20days}$)
c	Probability of replacement with other strain upon successful reinfection ($c = 0.5$)
q	Relative infectiousness of the dual to single infection ($q = 0.5$)
s	Allowing for specific ($s = 1$) & non-specific immunity ($s = 0$)

[1] R. Aguas, G. Goncalves, and G. M Gomes. *Pertussis*: increasing disease as a consequence of reducing transmission. *Infectious Diseases*, 26(2 Suppl):112–117, 2006.

[2] R. M. Anderson, R. M. May, and B. Anderson. *Infectious diseases of humans: dynamics and control*, volume 28. Wiley Online Library, 1992.

[3] J. W. Bass and R. R. Wittler. Return of epidemic *pertussis* in the united states. *Pediatric Infectious Disease Journal*, 13(5):343 – 345, 1994.

[4] E. Bergfors, B. Trollfors, J. Taranger, T. Lagergård, V. Sundh, and G. Zackrisson. Parapertussis and pertussis: differences and similarities in incidence, clinical course, and antibody responses. *International journal of infectious diseases*, 3(3):140–146, 1999.

[5] S. Black. Epidemiology of *pertussis*. *Pediatric Infectious Disease Journal*, 16(4 Suppl):S85–9, 1997.

[6] L. Celentano, M. Massari, D. Paramatti, S. Salmaso, A. Tozzi, et al. Resurgence of pertussis in Europe. *The Pediatric infectious disease journal*, 24(9):761, 2005.

[7] J. D. Cherry. Epidemiological, clinical, and laboratory aspects of *Pertussis* in adults. *Clinical Infectious Diseases*, 28(2 Suppl):S112–17, 1999.

[8] J. D. Cherry. Epidemic pertussis in 2012 - the resurgence of a vaccine-preventable disease. *New England Journal of Medicine*, 367(9):785–787, 2012.

[9] J. D. Cherry and B. L. Seaton. Patterns of *Bordetella parapertussis* respiratory illnesses: 2008–2010. *Clinical infectious diseases*, 54(4):534–537, 2012.

[10] S. Cobey and M. Lipsitch. Niche and neutral effects of acquired immunity permit coexistence of pneumococcal serotypes. *Science*, 335(6074):1376–1380, 2012.

[11] C. Colijn, T. Cohen, C. Fraser, W. Hanage, E. Goldstein, N. Givon-Lavi, R. Dagan, and M. Lipsitch. What is the mechanism for persistent coexistence of drug-susceptible and drug-resistant strains of *Streptococcus pneumoniae*? *Journal of The Royal Society Interface*, 7(47):905–919, 2010.

[12] S. David, R. van Furth, and F. R. Mooi. Efficacies of whole cell and acellular pertussis vaccines against bordetella parapertussis in a mouse model. *Vaccine*, 22(15-16):1892–1898, 7 May 2004.

[13] R. Deora, H. J. Bootsma, J. F. Miller, and P. A. Cotter. Diversity in the *Bordetella* virulence regulon: transcriptional control of a Bvg-intermediate phase gene. *Molecular microbiology*, 40(3):669–683, 2001.

[14] G. Eldering and P. Kendrick. *Bacillus parapertussis*: a species resembling both *Bacillus pertussis* and *Bacillus bronchisepticus* but identical with neither. *Emerging infectious diseases*, 35(6):561 – 572, 1938.

[15] B. Ermentrout. Simulating, analyzing, and animating dynamical systems: A guide to XPPAUT for researchers and students. *Society of Industrial and Applied Mathematics*, 2002.

[16] S. Flasche, W. J. Edmunds, E. Miller, D. Goldblatt, C. Robertson, and Y. H. Choi. The impact of specific and non specific immunity on the ecology of *Streptococcus pneumoniae* and the implications for vaccination. *Proc R Soc*, 280(2 Suppl):1771, 2013.

[17] F. Godfroid, P. Denoël, and J. Poolman. Are vaccination programs and isolate polymorphism linked to pertussis re-emergence? *Expert review of vaccines*, 4(5):757–778, 2005.

[18] M. Granstrom and P. Askelof. *Parapertussis*: an abortive *pertussis* infection ? *Emerging infectious diseases*, 320(3 Suppl):1249– 1250, 1982.

[19] L. Gustafsson, H. O. Hallander, P. Olin, E. Reizenstein, and J. Storsaeter. A controlled trial of a two-component acellular, a five-component acellular, and a whole-cell pertussis vaccine. *New England Journal of Medicine*, 334(6):349–356, 1996.

[20] Q. He, M. Viljanen, H. Arvilommi, B. Aittanen, and J. Mertsola. Whooping cough caused by *Bordetella pertussis* and *Bordetella parapertussis* in an immunized population. *JAMA: the journal of the American Medical Association*, 280(7):635–637, 1998.

[21] E. Heikkinen, T. Kallonen, L. Saarinen, R. Sara, A. King, F. Mooi, J. Soini, J. Mertsola, and Q. He. Comparative genomics of *Bordetella pertussis* reveals progressive gene loss in Finnish strains. *PLoS One*, 2(9):e904, 2007.

[22] U. Heininger, J. D. Cherry, K. Stehr, S. Schmitt-Grohé, M. Uberall, S. Laussucq, T. Eckhardt, M. Meyer, and J. Gornbein. Comparative efficacy of the Lederle/Takeda acellular pertussis component DTP (DTaP) vaccine and lederle whole-cell component DTP vaccine in german children after household exposure. pertussis vaccine study group. *Pediatrics*, 102(3 Pt 1):546–553, Sept. 1998.

[23] J. Kerr and R. Matthews. *Bordetella pertussis* infection: pathogenesis, diagnosis, management, and the role of protective immunity. *European journal of clinical microbiology & infectious diseases*, 19(2):77–88, 2000.

[24] F. Kowalzik, A. P. Barbosa, V. R. Fernandes, P. R. Carvalho, M. L. Avila-Aguero, D. Y. Goh, A. Goh, M. J. G. de Miguel, F. Moraga, J. Roca, et al. Prospective multinational study of pertussis infection in hospitalized infants and their household contacts. *The Pediatric infectious disease journal*, 26(3):238–242, 2007.

[25] M. H. Kyaw, R. Lynfield, W. Schaffner, A. S. Craig, J. Hadler, A. Reingold, A. R. Thomas, L. H. Harrison, N. M. Bennett, M. M. Farley, R. R. Facklam, J. H. Jorgensen, J. Besser, E. R. Zell, A. Schuchat, and C. G. Whitney. Effect of introduction of the pneumococcal conjugate vaccine on drug-resistant *Streptococcus pneumoniae*. *New England Journal of Medicine*, 354(14):1455–1463, 2006.

[26] S. Ladhani, M. E. Ramsay, M. Chandra, and M. P. Slack. No evidence for *Haemophilus influenzae* serotype replacement in Europe after introduction of the Hib conjugate vaccine. *The Lancet Infectious Diseases*, 8(5):275 – 276, 2008.

[27] J. Liese, C. Renner, S. Stojanov, B. Belohradsky, et al. Clinical and epidemiological picture of *B pertussis* and *B parapertussis* infections after introduction of acellular pertussis vaccines. *Archives of disease in childhood*, 88(8):684–687, 2003.

[28] M. Lipsitch, C. Colijn, T. Cohen, W. Hanage, and C. Fraser. No coexistence for free: neutral null models for multistrain pathogens. *Epidemics*, 1(1):2, 2009.

[29] C. Locht. Bordetella*: Molecular Microbiology)*. Horizon Scientific Press, Norfolk, UK, 2007.

[30] G. H. Long, A. T. Karanikas, E. T. Harvill, A. F. Read, and P. J. Hudson. Acellular pertussis vaccination facilitates bordetella parapertussis infection in a rodent model of bordetellosis. *Proc. Biol. Sci.*, 277(1690):2017–2025, 7 July 2010.

[31] S. S. Long, C. J. Welkon, and J. L. Clark. Widespread silent transmission of pertussis in families: antibody correlates of infection and symptomatology. *Journal of Infectious Diseases*, 161(3):480–486, 1990.

[32] M. Martcheva, B. M. Bolker, and R. D. Holt. Vaccine-induced pathogen strain replacement: what are the mechanisms? *Journal of The Royal Society Interface*, 5(18):3–13, 2008.

[33] P. Mastrantonio, P. Stefanelli, M. Giuliano, Y. H. Rojas, M. C. degli Atti, A. Anemona, and A. Tozzi. *Bordetella parapertussis* infection in children: epidemiology, clinical symptoms, and molecular characteristics of isolates. *Journal of clinical microbiology*, 36(4):999–1002, 1998.

[34] MATLAB. *version 8 (R2012b)*. The MathWorks Inc., Natick, Massachusetts, 2012.

[35] F. Mooi, I. Van Loo, and A. King. Adaptation of *Bordetella pertussis* to vaccination: a cause for its reemergence? *Emerging infectious diseases*, 7(3 Suppl):526, 2001.

[36] F. Mooi, H. Van Oirschot, K. Heuvelman, H. van der Heide, W. Gaastra, and R. Willems. Polymorphism in the *Bordetella pertussis* virulence factors P. 69/pertactin and pertussis toxin in the Netherlands: Temporal trends and evidence for vaccine-driven evolution. *Infection and immunity*, 66(2):670–675, 1998.

[37] J. E. Nicoli. *Mathematical modelling of coinfection with important respiratory pathogens*. PhD thesis, University of Bristol, September 2013.

[38] P. Olin, F. Rasmussen, L. Gustafsson, H. O. Hallander, and H. Heijbel. Randomised controlled trial of two-component, three-component, and five-component acellular pertussis vaccines compared with whole-cell pertussis vaccine. *The Lancet*, 350(9091):1569–1577, 1997.

[39] W. H. Organization. Pertussis. `http://www.who.int/immunization/topics/pertussis/en/index.html`, Retrieved May 2013.

[40] O. Restif, D. Wolfe, E. Goebel, O. Bjornstad, E. Harvill, et al. Of mice and men: asymmetric interactions between Bordetella pathogen species. *Parasitology*, 135(13):1517, 2008.

[41] D. Skowronski, G. De Serres, D. MacDonald, W. Wu, C. Shaw, J. Macnabb, S. Champagne, D. Patrick, and S. Halperin. The changing age and seasonal profile of pertussis in Canada. *Journal of Infectious Diseases*, 185(10):1448–1453, 2002.

[42] M. Watanabe and N. Masnaki. Reciprocal protective immunity against *Bordetella pertussis* and *Bordetella parapertussis* in a murine model of respiratory infection. *Infection and Immunity*, 69(11):6981 – 6986, 2001.

[43] M. A. Witt, L. Arias, P. H. Katz, E. T. Truong, and D. J. Witt. Reduced risk of pertussis among persons ever vaccinated with whole cell pertussis vaccine compared to recipients of acellular pertussis vaccines in a large US cohort. *Clinical Infectious Diseases*, 2013.

[44] D. Wolfe, E. Goebel, O. Bjornstad, O. Restif, and E. Harvill. The o antigen enables *Bordetella parapertussis* to avoid *Bordetella pertussis*-induced immunity. *Infection and immunity*, 75(10):4972–4979, 2007.