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# Competition, coinfection and strain replacement in models of *Bordetella pertussis*

Emily J. Nicoli [a], Diepreye Ayabina [b], Caroline L. Trotter [c], Katherine M.E. Turner [a], Caroline Colijn [b,*]

[a] School of Social and Community Medicine, University of Bristol, Canynge Hall, 39 Whatley Road, Bristol, BS8 2PS, UK
[b] Department of Mathematics, Imperial College London, South Kensington Campus, London SW7 2AZ, UK
[c] Department of Veterinary Medicine, University of Cambridge, UK

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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.


## 1. Introduction

Whooping cough, or pertussis, is an important respiratory infection. Approximately 16 million cases and 195,000 deaths among children occur annually worldwide (W.H. Organization, 2013). 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 (Deora et al., 2001; Kowalzik et al., 2007; Long et al., 1990). 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 (Cherry, 2012; Kerr and Matthews, 2000). There is also evidence that the age profile of the cases has changed (Celentano et al., 2005; Skowronski et al., 2002), 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 (Gustafsson et al., 1996; Olin et al., 1997; Witt et al., 2013), 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 (Mooi et al., 2001, 1998). However, there are also other sources of genetic variation (Godfroid et al., 2005; Heikkinen et al., 2007).

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 (Granstrom and Askelof, 1982; Eldering and Kendrick, 1938). As differential diagnosis has no effect on clinical treatment, clinicians rarely specifically test for *B. parapertussis*,

* Corresponding author.
*E-mail address:* c.colijn@imperial.ac.uk (C. Colijn).

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and the reported percentage of pertussis cases caused by *B. parapertussis* varies, with studies in Europe suggesting it ranges from 2% to 36% (Bergfors et al., 1999; He et al., 1998; Liese et al., 2003; Mastrantonio et al., 1998) and a large study in the US reporting 14% of pertussis cases identified as *B. parapertussis* (Cherry and Seaton, 2012). 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 (Wolfe et al., 2007; David et al., 2004; Heininger et al., 1998). Watanabe and Nagai (2001) 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 (Long et al., 2010) within hosts. In 2008, Restif et al. (2008) 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 (Long et al., 2010) 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 (Lipsitch et al., 2009; Colijn et al., 2010). 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 (Lipsitch et al., 2009); 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. (2008) 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 parameterized 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

### *Modelling strategy*

We developed a compartmental SIR-type model, allowing for coinfection and immunity. Both our model and the model by Restif et al. (2008) incorporate coinfection, and we note that if coinfection 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. (2009), 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 (Colijn et al., 2010; Lipsitch et al., 2009). 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 (Fig. 1(a)).

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 Lipsitch et al., 2009) and gives the structure shown in Fig. 1(b).

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 (Fig. 2). When $s = 1$ there is