Modeling Fitness of Immune Evading Pertussis Mutants

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INTRODUCTION

Pertussis (whooping cough) is caused mainly by the bacterium *Bordetella pertussis*. Many countries use acellular pertussis vaccines containing the antigen pertactin (PRN), which plays an important role in pathogenesis. In recent years, we've observed an increasing number of *B. pertussis* strains able to infect vaccinated people that are PRN-deficient. We use SIRV models to look at the fitness cost of the bacterium losing PRN and the advantage of being able to infect already vaccinated people.

METHODS

Mutation Model for (n = 3) strains

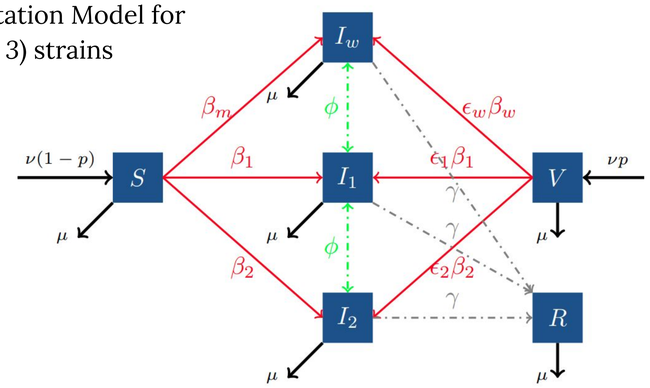


Figure 1: Extended SIRV model for a three-strain model, using the equations and parameters below. I_w is the wild type strain and I_i are the mutant strains.

$$\frac{dS}{dt} = \nu(1-p) - \mu S - \sum \beta_i S I_i$$
$$\frac{dI_w}{dt} = \beta_w S I_w (S + \epsilon_0 V) - I_w(\gamma + \mu) - \phi I_w + \phi I_1$$
$$\frac{dI_1}{dt} = \beta_1 I_1 (S + \epsilon_1 V) - I_1(\gamma + \mu) - 2\phi I_1 + \phi I_w + \phi I_2$$
$$\frac{dI_2}{dt} = \beta_2 I_2 (S + \epsilon_2 V) - I_2(\gamma + \mu) - \phi I_2 + \phi I_1$$
$$\frac{dR}{dt} = \gamma I_w - \mu R + \sum \gamma I_i$$
$$\frac{dV}{dt} = \nu p - \mu V - \sum \epsilon \beta_i V I_i$$

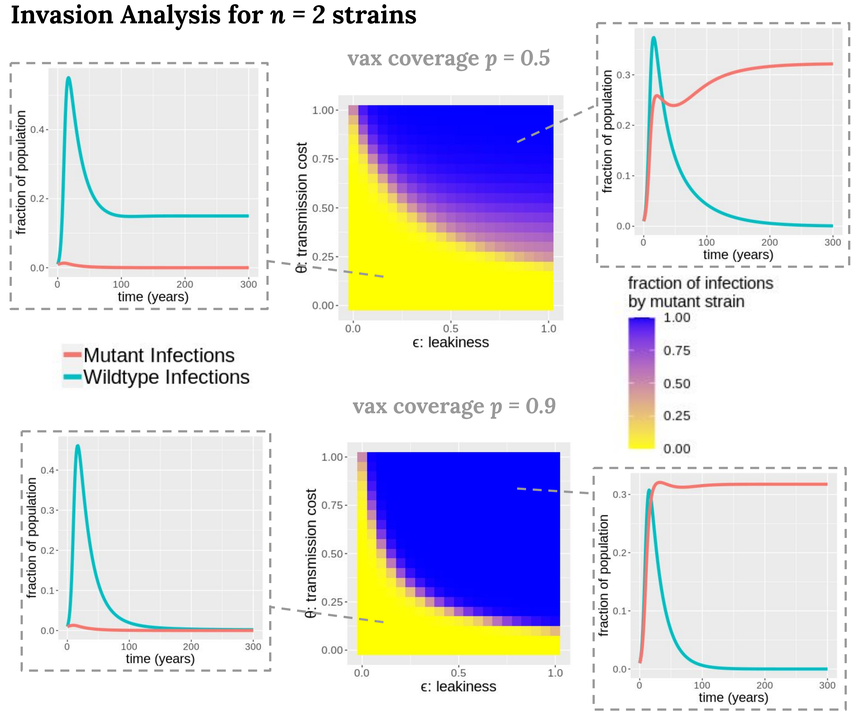
Figure 2 (left): Differential equations for a three-strain model.

Table 1 (below): Parameters, definition and values used in the model.

parameter	definition	value
R_0	basic reproduction number	10
μ	death rate	0.02
ν	birth rate	0.02
p	vaccination coverage	variable
γ	recovery rate	1/30
ϕ	mutation rate	0.001
ρ	fitness cost of immune evasion	variable
β	infectiousness	$\beta(i) = \begin{cases} R_0(\gamma+\mu), & \text{if } i = 0 \\ \beta_w \frac{\frac{n}{10}}{\rho\sqrt{i+\frac{n}{10}}}, & \text{if } i \neq 0 \end{cases}$
ϵ	leakiness: the ability to infect already vaccinated people	$\epsilon(i) = \begin{cases} 0, & \text{if } i = 0 \\ \frac{1}{1+e^{-(\beta_m \frac{i}{2} - 4)}}, & \text{if } i \neq 0 \end{cases}$

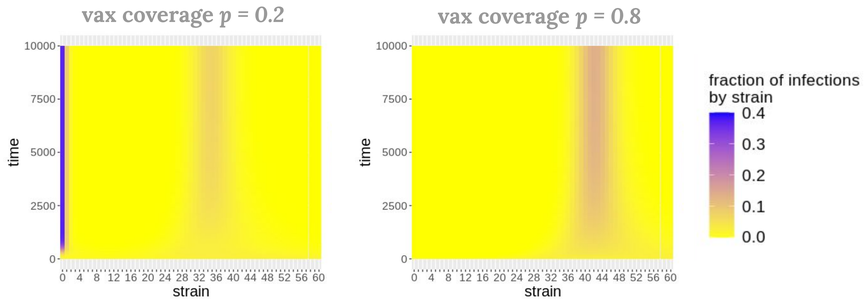
RESULTS

Invasion Analysis for n = 2 strains



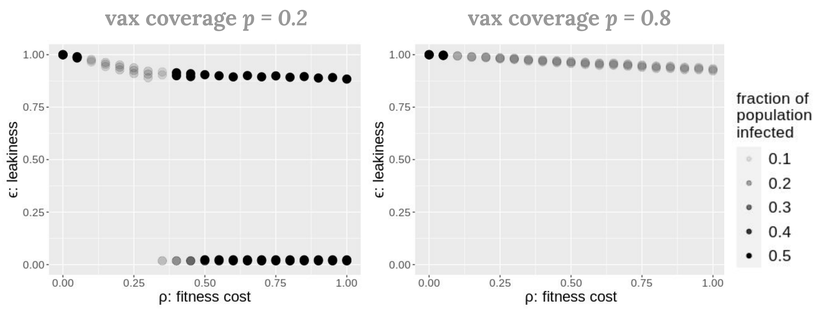
For intermediate vaccine coverage, the mutant can invade the population only if its leakiness and transmission are sufficiently high. For high vaccine coverage, the mutant can invade even if it has a lower leakiness or transmission, because the threshold for invasion is lowered. If the mutant can't meet that threshold, it fades out.

Stability Analysis for n = 60 strains



For fitness cost ρ = 0.5, we plotted the progression of the simulation with 60 strains, each of which have a different infectiousness, β, and leakiness, ϵ (Table 1). As the strains mutate, their leakiness increases and infectiousness decreases. At low vaccine coverage, there is bi-stability between the wild type (*strain* 0) and a cluster of mutants around strain 35. At high vaccine coverage, the wild type fades out and mutants with higher leakiness but lower infectiousness dominate.

Fitness Analysis



We plot the fitness cost, ρ, and leakiness, ϵ, of the top three mutants the simulation stabilized at, with opacity representing how much of the population the mutant infected. At lower vaccination coverage, mutants with high leakiness invade the system when fitness cost is low. When fitness cost for immune evasion is higher, there's bistability between the wild type (ϵ = 0) and mutants with high leakiness. At higher vaccination coverage, the wild type fades out completely, and mutants with high leakiness (ϵ) invade and dominate the system.

DISCUSSION

Our models explored how deletions in the pertactin gene can make a strain both leakier and less infectious. This cost-benefit payoff also changes depending on vaccination coverage of a population. At lower vaccination coverage, the wild type strain is able to exist in tandem with a strain with high leakiness and less infectiousness. At higher coverage, it is more advantageous for strains with high leakiness in the system.

In the future, we would like to model the effect of mutations on vaccine escape and virulence. Although *B. pertussis* deaths mostly occur in infants in severe cases, in the future, novel mutations affecting virulence might affect infection and transmission.

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