Combating pertussis resurgence: One booster vaccination schedule does not fit all

Maria A. Riolo and Pejman Rohani

Departments of *Mathematics and †Ecology & Evolutionary Biology, and ‡Center for the Study of Complex Systems, University of Michigan, Ann Arbor, MI 48109; and §Fogarty International Center, National Institutes of Health, Bethesda, MD 20892

Edited by Burton H. Singer, University of Florida, Gainesville, FL, and approved December 8, 2014 (received for review August 12, 2014)

Pertussis has reemerged as a major public health concern in many countries where it was once considered well controlled. Although the mechanisms responsible for continued pertussis circulation and resurgence remain elusive and contentious, many countries have nevertheless recommended booster vaccinations, the timing and number of which vary widely. Here, using a stochastic, age-stratified transmission model, we searched for cost-effective booster vaccination strategies using a genetic algorithm. We did so assuming four hypothesized mechanisms underpinning contemporary pertussis epidemiology: (I) insufficient coverage, (II) frequent primary vaccine failure, (III) waning of vaccine-derived protection, and (IV) vaccine “leakages.” For scenarios I–IV, successful booster strategies were identified and varied considerably by mechanism. Especially notable is the inability of booster schedules to alleviate resurgence when vaccines are leaky. Critically, our findings argue that the ultimate effectiveness of vaccine booster schedules will likely depend on correctly pinpointing the causes of resurgence, with misdiagnosis of the problem epidemiologically ineffective and economically costly.

Despite the discussion surrounding the efficacy and epidemiological effectiveness of pertussis vaccines, several countries experiencing increased pertussis incidence have supplemented their existing routine infant immunization schedule with additional booster doses (24). Importantly, the timing and number of recommended booster doses vary considerably among countries. To examine the conundrum of how best to mitigate pertussis, we used a validated age-stratified transmission model integrated within a genetic algorithm (GA) framework. Our aim is to identify, assuming different causes of pertussis circulation, booster schedules that afford the greatest reduction in disease burden for the least economic cost.

Situational Analysis

Given the absence of consensus regarding the causes of ongoing pertussis transmission and resurgence, and potential heterogeneity underlying recent rises in incidence across different populations, we focused our attention on identifying successful booster schedules, assuming a subset of resurgence mechanisms described above. Because previous work on pertussis in the United States has indicated that resurgence substantially predated both the introduction of modern molecular diagnostics and the switch from whole-cell to acellular vaccines (5), we excluded these factors but discuss their potential impacts later. Instead, we focused on other candidate explanations, two that lead to persistent pertussis circulation and two that generate a clear rebound in incidence following a honeymoon period.

Scenario I: Insufficient Vaccine Coverage. Perhaps the simplest reason behind the persistence of an infectious disease despite infant vaccination is inadequate uptake. This scenario would describe settings where logistic and economic factors may present significant barriers to large-scale immunization (25). According to the WHO, as of October 2013, in 10% of countries for which vaccination data are available, 80%, at most, of infants

Significance

Pertussis has reemerged as a major public health concern in many countries where vaccine uptake remains high and pertussis has been considered well controlled until recently. In our paper, we address the important scientific and practical problem of developing optimal booster vaccination schedules by using a genetic algorithm. Our results argue that booster vaccination schedules developed based on misdiagnosis of the problem are likely to be epidemiologically ineffective and economically costly.

Author contributions: M.A.R. and P.R. designed research; M.A.R. performed research; M.A.R. contributed new reagents/analytic tools; M.A.R. analyzed data; M.A.R. wrote the paper; and P.R. contributed to the writing of the paper. The authors declare no conflict of interest.

This article is a PNAS Direct Submission.

1To whom correspondence should be addressed. Email: mariolo@umich.edu.

This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1415573112/-/DCSupplemental.
receive the recommended three doses of pertussis vaccine (26). Inadequate coverage may also result from the reluctance of a sizable fraction of the population to comply with recommended routine vaccination (27, 28), as evidenced by the strong spatial correlation between pertussis outbreaks and the concentration of unvaccinated or undervaccinated children in some US populations (28, 29). In our simulations for this scenario, we assumed an efficacious vaccine with 70% uptake (Fig. 1C).

**Scenario II: Low Efficacy.** Primary vaccine failure, where a vaccine sometimes fails to elicit protection when administered, is another mechanism by which a disease might persist despite infant vaccination efforts. For example, the outbreaks of pertussis in Canada beginning in the late 1980s have largely been attributed to the poor efficacy of the Connaught Laboratories adsorbed vaccine that was used between 1985 and 1998 (30, 31). To explore this possibility, our simulations assumed 100% eventual vaccine uptake, with a 30% probability of failure in “take” (Fig. 1D).

**Scenario III: Waning Vaccine Immunity.** Even if vaccination is widespread and initially efficacious, infant immunization programs alone may fail to achieve elimination if vaccine-derived immunity is temporary. Some waning of vaccine-derived immunity to pertussis is supported by data at both the population and individual scales, but whereas population-level patterns of incidence generally suggest long-lasting immunity for whole-cell and acellular vaccines (17, 21, 22, 32), individual-level data on reinfections are better explained by a much shorter duration of protection (18). In this scenario, we assumed 100% uptake with a fully efficacious vaccine, with a mean duration of vaccine-derived immunity of 15 y (Fig. 1E). We also explored the impact of different durations of immunity, as discussed below.

**Scenario IV: Leaky Immunity.** Finally, we examined vaccine “leakiness,” whereby, with some probability, a previously vaccinated individual may become infected upon exposure (33, 34). One potential mechanism for imperfect vaccine protection is strain polymorphism, such that the cocirculation of multiple strains of *B. pertussis* for which the vaccine induces limited cross-protection may permit a transmissible, symptomatic infection after contact with an infectious individual (35, 36). Thus, leaky vaccine-derived immunity is a further mechanism with the potential to facilitate the persistence of pertussis despite infant vaccination. Here, a vaccinated individual has a 14.5% probability of infection upon exposure (Fig. 1F).

In reality, it likely that more than one of these mechanisms may be at play simultaneously in a given population. However, to disentangle the control impacts of each factor systematically, we make the pragmatic assumption that in each scenario, only the focal mechanism is responsible for ongoing chains of pertussis transmission. Given this simplifying assumption, it would be straightforward to evaluate the merits of introducing a single booster at a predefined age (22, 37–39). However, identifying successful, cost-effective, comprehensive booster schedules remains a nontrivial task because it requires the identification of appropriate timing, frequency, and uptake of boosting, stratified by age. Hence, this high dimensionality of the space of possible schedules, combined with the dynamical complexity of pertussis epidemiology (subject as it is to nonlinearity, stochasticity, and seasonal forcing), makes many traditional optimization tools ill-suited for the problem.

Here, we instead adopt a GA (40) to evolve cost-effective booster schedules by mimicking the operation of natural selection on a “population” of diverse schedules for booster vaccination (Methods and SI Appendix, section S2). Each strategy in the population is represented by a genotype that encodes its prescribed age-specific schedule of boosters (SI Appendix, Fig. S1A). Strategies receive reproductive opportunities based on their fitness (SI Appendix, Fig. S1B), which is calculated as a mixture of the disease burden and economic cost, both quantified in disability-adjusted life years (DALYs) lost (41). To evaluate the fitness of a strategy, we simulate transmission dynamics following the introduction of the booster schedule using our epidemiological model (Methods and SI Appendix, section S3). Strategies reproduce sexually, which allows for the generation of novel strategies via recombination (SI Appendix, Fig. S1C), and the resulting offspring have a chance to be further altered by point mutations (SI Appendix, Fig. S1D).

Because the past history of pertussis incidence and infant vaccination are known to have long-lasting effects on ongoing transmission dynamics (12), we simulated prebooster conditions with an identical history of vaccination and chose parameters of coverage, efficacy, duration, and leakiness to generate similar overall disease burden (measured in DALYs lost) in the two decades preceding the rollout of the candidate booster campaign.

![Fig. 1](https://example.com/figure1.jpg)

**Fig. 1.** Simulations generating the prebooster era. Initial conditions for GA runs. Prebooster incidence (solid red line) and infant vaccine uptake (dashed blue line) with 70% coverage (A), 70% efficacy (B), a 15-y mean duration of immunity (C), and leaky immunity preventing infection in 85.5% of risky contacts (D). In each case, we simulated 100 y pre-vaccine (plotted starting at year 50). In year 100, vaccination began at 60% of its eventual coverage level and increased linearly over 20 y. The various values for uptake, efficacy, waning, and leakiness were chosen to generate roughly similar DALYs lost before the introduction of boosters.
Families of successful booster strategies. Best of many PNAS PLUS distance between genomes) strategies. The strat-
numbers found by our GA had, on average, very little vacci-
nor low vaccine efficacy (scenario II), the successful booster
primarily due to low coverage in the routine schedule (scenario I).
To find clusters in this network with high modularity (i.e., many
connections within a cluster and few between clusters), we applied
a multiway spectral community detection algorithm (42),
which looks for a division based on the leading eigenvectors of the
modularity matrix of the network. This method allows us to vi-
ualize the distribution of alleles within each cluster of schedules
in a more intuitive way, such as looking at the interquartile range
of booster coverage in each age group, without losing as much
information about the correlation between traits as we would by
looking at the same summary statistics over the whole population.

Fittest Strategy Families

In all four scenarios, the GA rapidly converged on a population of
booster schedules with lower combined vaccination and dis-
case costs than the initial, randomly generated population of
strategies (SI Appendix, Fig. S2). When the pertussis burden was
primarily due to low coverage in the routine schedule (scenario I)
or low vaccine efficacy (scenario II), the successful booster
schedules found by our GA had, on average, very little vacci-
nation in older age groups, focusing most of their effort on tar-
geting young children (Fig. 2 A and B); this strategy achieved
greater disease reduction at lower vaccination effort than the
initial random population of strategies (SI Appendix, Fig. S3A).
Specifically, for scenario I, we found five distinct clusters of
strategies, each corresponding to the introduction of a single
booster dose at the age of 1, 2, 3, 4, or 5 y (Fig. 2A). Our results
for a low-efficacy vaccine were very similar (Fig. 2B and SI Appen-
dix, Fig. S3B), with the exception that a greater vaccination
effort was necessary to achieve the same effective coverage from
the booster vaccine. In both cases, the most effective strategies
came in the form of a single preschool booster, the precise timing
of which had little effect on fitness as long as it came before
children entered primary school, with the attendant high contact
rates and strong age-assortative mixing (SI Appendix, Fig. S4 A
and B). The results for scenarios I and II are explained by
examining the right eigenvector of the next-generation matrix
(see Fig. 5B), which quantifies the age-specific contribution to
transmission. It indicates a steep increase in transmission after
the transition from the toddler to primary school ages.

Booster schedules for waning vaccine-derived immunity (scenario
III) differ greatly from those booster schedules evolved to deal with
low coverage or efficacy (Fig. 2C). In this case, assuming a 15-y av-
average duration of immunity in vaccinees, the most successful sched-
ules call for a series of three boosters in the 6- to 19-y-old age groups
approximately every 5 y, followed by additional boosters between 25
and 45 y of age. To dissect the evolution of strategies aimed at
combating waning vaccine immunity, we explored the population
immunity profile by age as the mean duration of immunity varied
(Fig. 3). Successful strategies aim to maintain herd immunity by
ensuring the proportion of the population protected typically remains
above ~80%. Exceptions to this pattern occur when waning leads to
an increased susceptible population in age groups with low trans-
mission potential (Fig. 3), such as toddlers or the elderly (see Fig. 5).

Finally, leaky immunity (scenario IV) presents a significantly
different picture (Fig. 2D). The GA found no booster schedules
that effectively reduce disease burden (SI Appendix, Fig. S3J). The
nearest-neighbor network of the most successful strategies reveals
no discernible community structure, and the best strategies eschew
booster vaccination altogether (Fig. 2D). Again, the explanation
lies in the patterns of susceptibility in the population. With infant

![Fig. 2. Families of successful booster strategies. Best booster schedules found for 70% infant coverage (A), 70% efficacy (B), a 15-y mean duration of immunity (C), and leaky immunity preventing 85.5% of infections (D) are shown. The best 500 booster schedules found in the last algorithm generation of each scenario are arranged into a network, where each schedule is connected to the nearest 25 (under L₁ distance between genomes) strategies. The strategies are clustered using a spectral partitioning algorithm (cluster indicated in the figure by color). The large plot shows the interquartile radius within each cluster of coverage at each age group (colors in plot correspond to colors in network). (Inset) Plot shows the fitness costs (in DALY’s lost) of strategies in each family, ordered from most fit (red, Left) to the least fit (purple, Right).]
vaccination already granting leaky protection to everyone, any remaining transmission already occurs among vaccinated individuals and cannot be disrupted by additional boosters with the same leaky vaccine (SI Appendix, Fig. S4D). We also examined the possibility that booster doses serve to reduce leakiness. Here, the best strategies resemble those strategies for a low level of primary vaccine failure, targeting the youngest age groups (SI Appendix, Fig. S5).

To quantify the penalties incurred by misdiagnosing the underlying reason for resurgence, we systematically implemented the best strategy for each scenario against all scenarios (Fig. 4A). As mentioned above, if pertussis resurgence is caused by pathogen evolution or strain polymorphism that renders the vaccine leaky (scenario IV), no booster strategy with a vaccine of the same composition can alleviate the problem. For scenario III, it is evident that correct identification of the cause of pertussis burden (waning vaccine immunity) and its associated parameter (duration of immunity) is paramount because ill-suited boosting strategies lead to high disease incidence (Fig. 4B). Our analyses indicate that even when the best booster schedule is adopted, the greatest overall costs arise when vaccine-derived immunity is transient, in large part, due to the expense associated with administering frequent boosters (Fig. 4C). Perhaps not surprisingly, there is only a small epidemiological cost to pay when mistaking insufficient uptake (scenario I) for primary vaccine failure (scenario II) and vice versa, given the broad similarity of their best boosters. In all cases, we found the overwhelming penalty is the failure of the incorrect strategy in suppressing disease (Fig. 4B) rather than economic costs via inefficient vaccine use (Fig. 4C). Similarly, we also examined the consequences of incorrectly estimating the duration of vaccine-derived immunity (SI Appendix, Fig. S6). Not surprisingly, there is a substantial epidemiological cost that is paid for overestimating the duration of immunity, with boosters administered too infrequently to break chains of transmission (SI Appendix, Fig. S6B). In contrast, there is a lesser economic burden incurred when immunity is underestimated (SI Appendix, Fig. S6C). Superficially, this result might appear to argue in favor of an overeager boosting strategy when vaccine-derived immunity is known to be temporary; however, this conclusion would need to be tempered by considering the concomitant evolutionary consequences of such a strategy (43, 44).

Discussion

Complex applied problems are ubiquitous in epidemiology, and making predictions or policy recommendations frequently involves grappling with high-dimensional and hard-to-predict systems. In recent years, public health policy makers have made use of models to conduct a cost-benefit analysis of interventions for a number of high-profile infectious diseases, including rubella (45), the human papilloma virus (46), and influenza (47). Here, focusing on a comprehensive age-stratified schedule of pertussis vaccine boosters, we have adopted GAs as a useful tool for exploring complex optimization.

Our model is relatively simple and leaves out many putative mechanisms that may affect pertussis transmission and control, including the spatial or social aggregation of unvaccinated individuals (28), asymptomatic infections (48), and household structure (48). Other potential factors that could drive changes in the effectiveness of a booster vaccination strategy over the course of its use, such as vaccine-driven pathogen evolution, changing attitudes to vaccination, and changing public awareness of pertussis, are also excluded from our model. Perhaps equally importantly, our model does not attempt to mimic the real vaccination history and demographics of any particular location, instead exploring the relatively simple and defensible case of a linear increase in routine vaccine uptake after its introduction, followed by sustained high levels of infant vaccination. We stress that the precise structure of successful schedules we have obtained may be sensitive to the network of assumed contacts, which was derived from diary-based surveys of European populations (49).

Although the booster schedules discovered by the GA evolved in the absence of much of the complexity and uncertainty of the real world and are not intended to predict the quantitative impact of any particular vaccine schedule in any particular population, we submit that our results nonetheless have substantial implications for vaccine policy. Importantly, we have found that optimal booster schedules for controlling pertussis differ markedly depending on the mechanism responsible for the failure of routine immunization.

The four scenarios we considered are by no means an exhaustive exploration of the possible mechanisms by which an infant vaccine might fail to curtail the transmission of an infection. For example, we did not consider any scenarios incorporating diagnostic or surveillance changes that might generate the appearance of resurgence. The reason for this omission is that, in our GA, selection acts on the actual number and age distribution of infections, with a disproportionate contribution to DALYs lost by infant cases. Hence, the strategies that evolve in any scenario would not be affected by changes in reporting, including improved surveillance leading to an apparent resurgence.

**Fig. 3.** Booster strategies to combat waning immunity. The most fit booster schedules under 5-y, 15-y, 25-y, 35-y, and 45-y mean durations of immunity, respectively, are plotted in the five panels. In each case, the 500 best strategies found during the past 25 generations of the GA are used. (In the case of 5-y immunity and 15-y immunity, the GA ran for 100 and 50 generations, respectively. All other cases ran for 25 generations.) The percentage of individuals protected by vaccination (in the absence of pertussis) is plotted for each age, with the interquartile range among the 500 strategies shaded in. The color of the shading indicates the median vaccine coverage among the strategies for that age, with blue indicating high levels of vaccination.
Similarly, we did not investigate the possibility that vaccination may protect against disease but not transmission (19). In such a scenario, regardless of the strategy adopted, the ongoing dynamics of pertussis transmission would remain identical to the dynamics of pertussis transmission of the prevaccine era, with the incidence of disease in each age group simply reduced by the fraction of individuals who are protected by vaccination. Thus, in the case where this nonsterilizing immunity is lifelong, we expect the optimal strategy would be to administer a single dose of vaccine as early as possible so as to protect as much of the population as possible from disease. However, if this protection from disease wanes over time, we would expect a strategy with boosters continuing throughout life, timed to balance the cost of vaccination with the probability that immunity has waned since the last dose.

Another potential mechanism behind resurgence is natural immune boosting, which has previously been shown to have complex, often counterintuitive, interactions with infant vaccination (50, 51). We did not include this possibility on the basis of the epidemiological data. Some studies have found no empirical evidence in support of the immune boosting hypothesis (17, 21), whereas others have found that its epidemiological impact is small, even if statistically significant (52).

Our results reinforce the importance of ongoing efforts to understand vaccine-derived pertussis immunity better because it is central to developing cost-effective control strategies. If the cause of the resurgence is vaccine leakiness, then no worthwhile booster strategies are able to combat this problem (53), pointing toward the need for new vaccines (54). Our findings also emphasize the need for trouble-shooting pertussis resurgence: misdiagnosis of the problem will lead to implementing economically costly control measures with little or no epidemiological gains.

Methods

Transmission Dynamics. We use a standard compartmental transmission model (55, 56) of pertussis that incorporates empirical age-specific rates of contact from the POLYMOD study (49). This model was previously parameterized using data from the vaccine-free period in Sweden and was validated by predicting age-specific pertussis incidence following the transition to infant immunization (22). Individuals are born susceptible, with routine infant vaccination occurring at 5 mo of age in order to mimic the protective effects afforded following the receipt of two doses of pertussis vaccine. Susceptible individuals become exposed through contact with infectious individuals and, after a latent period, become infectious. After recovering, individuals are immune to further infection. We assume infection-derived immunity to be lifelong, based on previous epidemiological studies of pertussis in Sweden (22), England and Wales (21), and Thailand (17), which found that repeat infections contributed very little to transmission (57). The number of individuals of each age in each state (susceptible, exposed, infectious, recovered, and vaccinated) is updated stochastically (56). The model equations and associated parameter values are presented in detail in SI Appendix, section S3.

To set the context for our results, in Fig. 5A, we present the next generation matrix, which connects the number of cases of each age group in the prevaccine or a specific vaccination scenario to the number of cases of each age group in the next generation. This next-generation matrix, which contains the “blueprint” for the course of disease in each age group simply reduced by the fraction of individuals who are immune to further infection. We assume infection-derived immunity to be lifelong, based on previous epidemiological studies of pertussis in Sweden (22), England and Wales (21), and Thailand (17), which found that repeat infections contributed very little to transmission (57). The number of individuals of each age in each state (susceptible, exposed, infectious, recovered, and vaccinated) is updated stochastically (56). The model equations and associated parameter values are presented in detail in SI Appendix, section S3.

To set the context for our results, in Fig. 5A, we present the next generation matrix, which connects the number of cases of each age group in the prevaccine or a specific vaccination scenario to the number of cases of each age group in the next generation. This next-generation matrix, which contains the “blueprint” for the course of disease in each age group simply reduced by the fraction of individuals who are immune to further infection. We assume infection-derived immunity to be lifelong, based on previous epidemiological studies of pertussis in Sweden (22), England and Wales (21), and Thailand (17), which found that repeat infections contributed very little to transmission (57). The number of individuals of each age in each state (susceptible, exposed, infectious, recovered, and vaccinated) is updated stochastically (56). The model equations and associated parameter values are presented in detail in SI Appendix, section S3.
Note that although more fit strategies are likely to appear more often as parents than less fit strategies, a strategy's reproductive opportunities are only determined by its rank. Tournament selection has the benefit of reduced sensitivity to the particular fitness function used compared with a selection method relying on the actual fitness values of strategies.

Once $N$ parents have been selected, these parents are divided into pairs and each (not necessarily unique) couple produces a pair of offspring. The parent chromosomes undergo cross-over at a randomly chosen point (SI Appendix, Fig. 51C). In each child chromosome, point mutations occur (SI Appendix, Fig. 51D) at a fixed rate, set to 0.05 per site in our experiments, which yields an average of 1.25 mutations per chromosome. This process leaves us with a new generation of booster strategies, ready to be evaluated through simulation. It is worthwhile to note that the choice of how to encode strategies can have important effects on the ease with which this reproductive process generates and preserves improved strategies, affecting both linkage and epistasis between genes as well as the topographical features of the fitness space itself (59, 60).

ACKNOWLEDGMENTS. We thank Aaron King, Micaela Martinez-Bakker, Matthieu Domenech de Celis, and Felicia Magpantay for stimulating discussion. We also thank Alison Galvani, Meagan Fitzpatrick, and an anonymous reviewer for their insightful comments on this manuscript. This work was supported by the Research and Policy in Infectious Disease Dynamics Program of the Science and Technology Directorate, Department of Homeland Security, the Fogarty International Center, NIH; by a research grant from the NIH (Grant R01AI101155); and by the Models of Infectious Disease Agent Study, National Institute of General Medical Sciences (Grant U54-GM111274).

17. Van Loo P, Moya A, Veling E, et al. (2014) Improved strategies, affecting both linkage and epistasis between genes as well as the topographical features of the fitness space itself (59, 60).