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COMMENTARY

Commentary: resolving pertussis resurgence and vaccine immunity using mathematical transmission models

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ABSTRACT

The epidemiology of pertussis—a vaccine-preventable respiratory infection typically caused by the bacterium Bordetella pertussis—remains puzzling. Indeed, the disease seems nowhere close to eradication and has even re-emerged in certain countries—such as the US—that have maintained high vaccination coverage. Because the dynamics of pertussis are shaped by past vaccination and natural infection rates, with the relevant timescale spanning decades, the interpretation of such unexpected trends is not straightforward. In this commentary, we propose that mathematical transmission models play an essential role in helping to interpret the data and in closing knowledge gaps in pertussis epidemiology. We submit that recent advances in statistical inference methods now allow us to estimate key parameters, such as the nature and duration of vaccinal immunity, which have to date been difficult to quantify. We illustrate these points with the results of a recent study based on data from Massachusetts (Domenech de Cellès, Magpantay, King, and Rohani, Sci. Transl. Med. 2018;10: eaaj1748. doi:10.1126/scitranslmed.aaj1748), in which we used such methods to elucidate the mechanisms underlying the ongoing resurgence of pertussis. In addition, we list a number of safety checks that can be used to critically assess mathematical models. Finally, we discuss the remaining uncertainties surrounding pertussis vaccines, in particular the acellular vaccines used for teenage booster immunizations.

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The recent epidemiology of pertussis – an acute respiratory infection characterized by a prolonged cough[1] – cautions us against complacency about seemingly familiar infectious diseases. Historically, whooping cough was a prominent cause of mortality and morbidity in young children,[2] but the development of whole-cell pertussis vaccines in the 1930s marked a breakthrough that paved the way for routine pediatric immunization.[3] In the US, the roll-out of whole-cell vaccines led in a few decades to a substantial, typically >10-fold, decline in reported cases.[4] Since the mid-1970s, however, the disease has re-emerged, despite sustained high vaccine coverage.[4] The implementation of additional control measures, such as booster vaccination in adolescents,[5] appears to have had a modest impact on this growing burden.[6] These control difficulties emphasize the need to better understand the drivers of pertussis resurgence

The many complexities of pertussis epidemiology were noted by early investigators.[2] Age-specific incidence data in Massachusetts provide a case in point. As shown in Figure 1 (a), the time series are noisy and apparently irregular, with several notable, but unevenly spaced, peaks. A robust feature, however, is the marked increase in cases in adolescents and adults, a shift typical of the recent epidemiology of pertussis in the US and other locations.[6,13] From a public health perspective, interpreting such data is not straightforward. Focusing on a narrow time period, for example that embracing the large 2003 outbreak in adolescents (95% of whom had received 5 vaccine doses), one might conclude that vaccines are ineffective and confer only short-term protection. Looking at the entire time period, however, we see that other epidemics occurred in 1996 and 2000. The occurrence of multi-annual epidemic cycles is in fact a distinct feature of pertussis epidemiology that has persisted in the vaccine era.[14] The interval between peaks is well predicted by the time needed for the growing susceptible pool to reach a threshold.[15,16] This example demonstrates the need to interpret recent pertussis data in an appropriately broad historical context, with the help of epidemiological theory to establish baselines and suggest the relevant timescales. Essentially, the dynamics of pertussis infections depend on the degree of susceptibility of the population, a complex quantity shaped both by the birth rate and by the level of immunity, which is a legacy of long-term vaccination and previous natural infection. Heterogeneities in rates of contact between individuals of different ages also play a key role in these dynamics,[17] since two equally susceptible age groups are expected to suffer different infection risks

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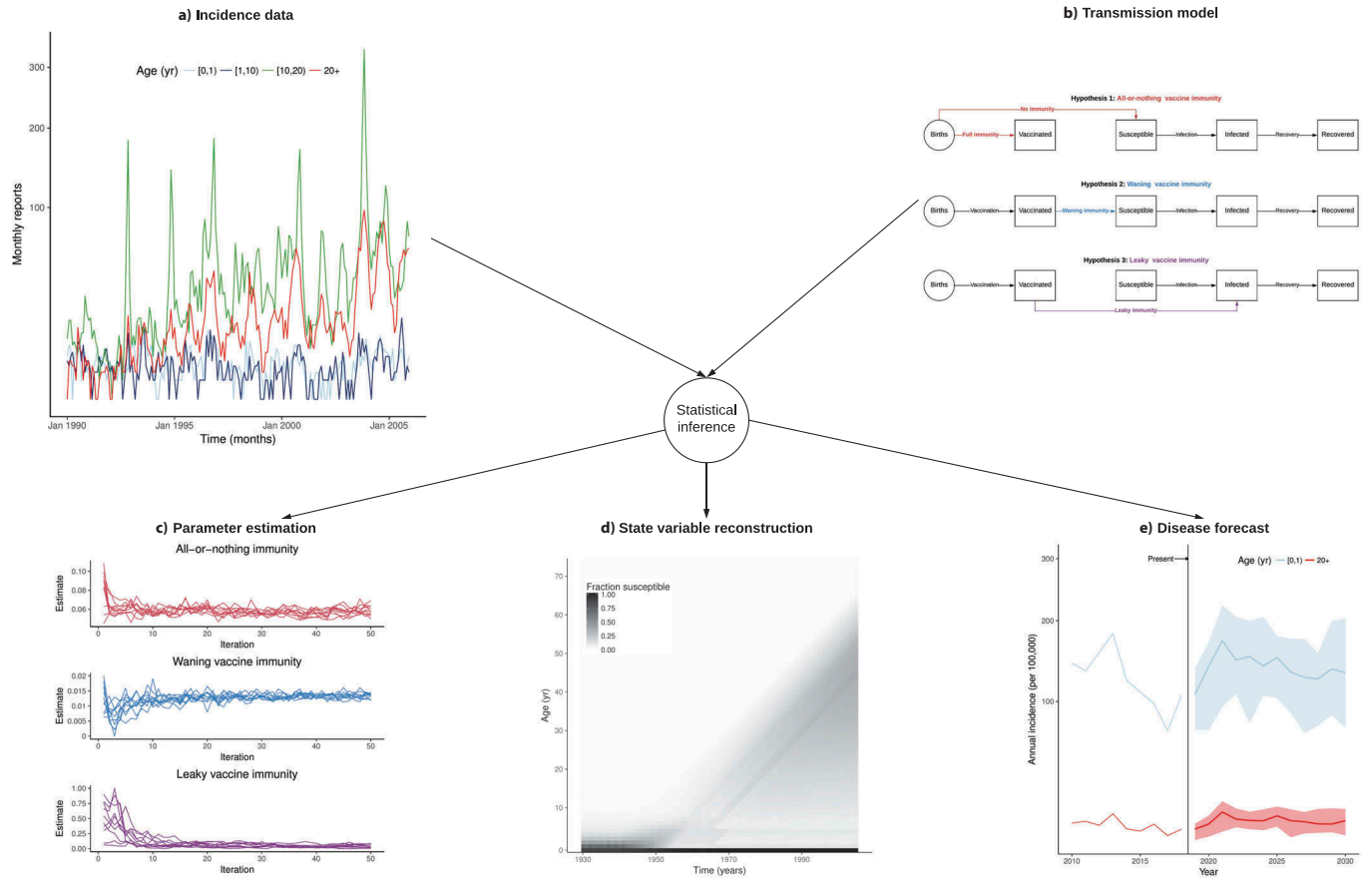

Figure 1. Confronting transmission models with incidence data to elucidate the epidemiology of pertussis.

(a) Age-specific monthly case reports of pertussis in Massachusetts during 1990–2005 (data from Ref. 7). (b) Schematic of three mathematical transmission models with three different assumptions on the nature of vaccine-derived immunity (all-or-nothing, waning, or leaky[7-9]). (c) Convergence plot of vaccine parameters (as defined in panel B) to their maximum likelihood estimates. (d) Model-based hindcasts of the fraction of individuals susceptible to pertussis infection, according to time (*x*-axis) and to age (*y*-axis). (e) Model-based forecasts of pertussis annual incidence in infants [0,1) yr and adults $\geq$ 20 yr. The figure illustrates how, via statistical inference methods,[10-12] pertussis incidence data (panel A) can be confronted with transmission models to test different scientific hypotheses about the nature of vaccine immunity (panel B). Each fitted model leads to different parameter estimates and receives a different degree of support from the data (panel C). The best-fitting model (here the model with waning vaccine immunity) can then be used to infer quantities that are not directly observable (like the degree of susceptibility in the population, panel D) and to forecast the burden of disease (panel E). Panel D illustrates the end-of-honeymoon effect.[7] In the prevaccine era, cases are concentrated in young children who, upon recovery, develop long- lived immunity against reinfection, resulting in strong herd immunity in older individuals. The inception of mass vaccination leads to an overall reduction in transmission in those vaccinated and in the population at large. Hence, children who were not vaccinated (or in whom vaccinal protection did not initially take) are increasingly likely to reach adulthood having avoided natural infection. Concomitantly, older cohorts, with their long-lived immunity derived from natural infection during the prevaccine era, gradually die out. The result is the gradual buildup of susceptibles, which leads to a gradual resurgence.

if their exposures to infection in other groups differ. In sum, interpreting pertussis data requires a thorough bookkeeping of the kinetics of infection and susceptible recruitment over the timescale of decades.

Mathematical transmission models provide a formal and robust framework for this bookkeeping exercise and for contextualizing epidemiological data.[15,18] Their key strength is in translating between processes that occur at different scales, from the disease's natural history at the scale of the individual infection to population-scale epidemic dynamics. Mathematical models represent the epidemiological system under study by a simplified mathematical object, typically a set of equations that govern the dynamics of so-called *state variables*. These variables typically include numbers of individuals with similar infection or immune status. Other important ingredients of such models are *parameters*, i.e., fixed quantities that control the pace at which individuals transition between different states. Because different parameter values can lead to markedly different model behaviors and predictions, appropriate model parametrization is essential. Model parameters can be fixed according to external evidence, but sometimes their values are not known, or are known only imprecisely. Because of the lack of definite correlates of protection, for example, key parameters like the duration of infection- or vaccine-derived immunity are challenging to estimate for pertussis. In such cases, models can be confronted to time series of epidemiological records, allowing the latter to voice an opinion as to the most likely parameter values. In recent years, a range of robust statistical inference methods have been developed for this purpose.[10] Such methods allow one not only to estimate unknown parameters, but also to weigh the evidence for different biologically-motivated hypotheses, as expressed in the form of competing models.[19]

In recent work,[7] we applied these techniques to dissect the epidemiology of pertussis in Massachusetts, where, as in other US states, a resurgence of pertussis has been observed since the mid-1970s (Figure 1(a) and Refs. 4, 20). To close current knowledge gaps in pertussis epidemiology,[21,22] we formulated age-stratified transmission models that expressed a range of hypotheses about the nature and the degree of vaccinal immunity[8] and about the transmissibility and the observability of post-vaccine infections.[23,24] A novel feature of our models was the inclusion of age-specific reporting rates to correct for observation biases caused by the use of highly sensitive serology to detect cases in adolescents and adults.[25] Using the aforementioned statistical methods, we confronted these models with age-specific incidence data to elucidate the drivers of pertussis resurgence. We found unambiguous evidence that pertussis vaccines confer imperfect, but quite slowly waning, immunity, a result that also held for DTaP vaccines, in opposition to widespread belief.[26,27] How, then, to interpret the resurgence of pertussis, despite high vaccine coverage? We demonstrated that it resulted from a so-called "end-of-honeymoon" effect,[28] that is, a predictable consequence of incomplete historical coverage with an imperfect but highly effective vaccine (see legend of Figure 1). This result was based on the model-based reconstruction of the age-specific susceptibility profile over time (Figure 1(d)). This further illustrates the usefulness of transmission models to infer quantities, such as susceptibility to pertussis infection, that cannot be directly observed.

Although potentially powerful tools for unraveling pertussis epidemiology, mathematical models should be critically reviewed at each of the three steps of model development: model implementation, model estimation, and model validation. Regarding model implementation, the choice of a deterministic or stochastic model has important consequences for parameter estimation and model interpretation. Although deterministic models are commonly used because they are easy to implement and to fit to data,[29] mounting evidence indicates that fully stochastic models explain the dynamics of pertussis much better and in potentially very different ways.[7,9,30] Regarding model estimation, appropriate statistical inference methods are needed and now easily applicable via well-tested software packages.[10] In this respect, one should keep in mind the "curse of dimensionality", whereby the volume of parameter space grows exponentially with the number of parameters to be estimated. This implies that even a large pre-specified random sample of parameter sets may be inadequate for proper exploration of the parameter space, a problem aggravated when – as is invariably the case in practice – parameters are correlated.[31,32] During the model estimation step, it is also typical to carry out sensitivity analyses to assess the robustness of parameter estimates to realistic aspects of model misspecification. Regarding model validation, agreement between model and data requires careful assessment. Standard checks include the visual inspection of typical model simulations and the quantification of model-data agreement based on goodness-of-fit metrics (e.g., R^2 and its generalizations) or on more specific signatures (quantified using summary statistics) that capture important features of the data. When the data are sufficiently numerous, model predictions tested on data not used for parameter estimation (out-of-fit predictions) are indispensable as independent checks on the model's predictive power and for diagnosis of over-fitting. Although not foolproof,[33] a careful examination of the elements of the above list can help establish confidence in scientific conclusions based on mathematical models.

Although our study provided a coherent and possibly unifying explanation for pertussis resurgence in the US, many questions remain. In particular, a more precise estimation of the duration of immunity conferred by DTaP is needed – though, as explained above, our results rule out very rapid waning. A similar estimate for Tdap will also prove valuable in quantifying the impact of the booster dose in teenagers, which was possibly masked by cohort effects due to the aging of the first DTaP-vaccinated birth cohorts.[6] We propose that applying the methods discussed here to more recent data should allow to pinpoint these quantities and help design future control strategies.

Disclosure of potential conflicts of interest

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