

Deciphering the impacts of vaccination and immunity on pertussis epidemiology in Thailand

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Pertussis is a highly infectious respiratory disease that is currently responsible for nearly 300,000 annual deaths worldwide, primarily in infants in developing countries. Despite sustained high vaccine uptake, a resurgence in pertussis incidence has been reported in a number of countries. This resurgence has led to critical questions regarding the transmission impacts of vaccination and pertussis immunology. We analyzed pertussis incidence in Thailand—both age-stratified and longitudinal aggregate reports—over the past 30 y. To dissect the contributions of waning pertussis immunity and repeat infections to pertussis epidemiology in Thailand following a pronounced increase in vaccine uptake, we used likelihood-based statistical inference methods to evaluate the support for multiple competing transmission models. We found that, in contrast to other settings, there is no evidence for pertussis resurgence in Thailand, with each model examined pointing to a substantial rise in herd immunity over the past 30 y. Using a variety of empirical metrics, we verified our findings by documenting signatures of changing herd immunity over the study period. Importantly, this work leads to the conclusion that repeat infections have played little role in shaping pertussis epidemiology in Thailand. Our results are surprisingly emphatic in support of measurable impact of herd immunity given the uncertainty associated with pertussis epidemiology.

Pertussis, or whooping cough, was historically considered a serious disease of childhood. Because of the high burden of morbidity and mortality associated with pertussis (1), routine vaccination programs were implemented in many developed countries during the 1940s and 1950s that led, in some instances, to a 99% reduction in reported incidence (2, 3). The success of these vaccination programs in reducing pertussis notifications led to optimism over its potential eradication, a sentiment that has since been replaced by widespread concern following high-profile outbreaks in populations with long-standing immunization, with the United States and Australia arguably experiencing the largest impacts of these resurgences (4–7).

Recent attempts to explain contemporary pertussis epidemiology have largely attributed the resurgence to the immunological consequences of vaccination and natural infection. In turn, uncertainty surrounding the role of a number of potentially key players has been highlighted, including the duration of naturally acquired and vaccine-induced immunity (8–11), limited natural immune boosting following the introduction of vaccine programs (10, 12), loss of vaccine efficacy resulting from antigenic divergence (13, 14), and, crucially, whether vaccines prevent pertussis transmission or simply reduce the incidence of disease (15–17). To assess the population-level consequences of immunity, we confront high-resolution incidence reports in Thailand with modern techniques for statistical inference to provide a mechanistic interpretation of the transmission impact of vaccination on pertussis immunity in Thailand. Using a series of competing transmission models, we demonstrate that declines in pertussis incidence coinciding with increases in vaccine uptake between 1984 and 1989 arose following reduction in pertussis circulation. Indeed, the maximum-likelihood estimate associated with each model points to a small or negligible

transmission contribution of repeat infections, with vaccination effectively generating herd immunity.

To verify our conclusions, we use several empirical metrics to demonstrate that there is a true increase in herd immunity. We document dramatic changes in patterns of pertussis epidemiology, and quantify shifts in population measures of herd immunity. We report that over the time span of this study, there was a drastic decline in reported pertussis cases from Thailand, an effect that is especially pronounced among infants. Coincident with reduced incidence, we also found a rise in the critical community size. Overall, these observations are consistent with reduced pertussis circulation in Thailand.

Our findings shed light on key hotly debated aspects of pertussis epidemiology. First, these results indicate that current pediatric immunization programs in Thailand have successfully reduced pertussis transmission. Second, there is no empirical evidence for a resurgence in Thailand, with circulation of *Bordetella pertussis* effectively controlled by current vaccines. Finally, repeat infections appear to play an insignificant role in pertussis epidemiology in Thailand.

Results

Pertussis Data in Thailand. Fig. 1 provides a summary of the data from Thailand by displaying pertussis incidence, per capita birth rate, and vaccine uptake estimates in Thailand from 1981 to 2000 (see *Materials and Methods* for data sources). We split the incidence data into three distinct eras, according to vaccine uptake. During the first era (1981–1983), immunization levels were in the range 26–46%. The second era (1984–1989) was a transitional period with a rapid rise in uptake from ~40% in 1984 to 90% in 1989. Finally, during the years from 1990 to 2000 (third era), uptake levels exceeded 90%. Pertussis outbreaks in Thailand were strongly annual during the first and second eras (1981–1990; Fig. 1). By the third vaccine era, epidemics were no longer significantly annual, incidence was low (<0.12 per 100,000), and has remained substantially below 1 per 100,000 since 2001, as shown by the most recently available incidence estimates from 2009 and 2010 (18, 19).

As shown in Fig. 1, over the time span of these data, Thailand underwent a demographic transition to lower per capita birth rates (20) in addition to substantial increases in vaccine uptake. Epidemiological theory has demonstrated that each of these covariates can lead to decreased incidence by reducing the rate at which the pool of susceptibles is replenished (21–23). Indeed, a negative relationship exists between pertussis incidence in Thailand and vaccine uptake (correlation coefficient $r = -0.897$,

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Table 1. Fitting results for each model

Model	Description	MLE	AIC	Δ AIC
I	SIR	-1,059.8	2,151.6	0
II	SIRS	-1,597.2	3,228.4	1,076.8
III	SIRS _{2/2}	-1,480.3	2,998.6	847
IV	SIRS _{2/2} ⁰	-1,060.3	2,168.6	17

MLE of models II and III correspond to durations of 69 and 70 y, respectively, whereas the duration of immunity is not identifiable in model IV. The difference in Δ AIC score between models I and IV results from accounting for the additional parameters required to estimate in model IV (e.g., κ , ϵ).

aggregate incidence. We explored mean annual incidence in all provinces to document shifts in cases through time. A reduction in reported cases may indicate reduced transmission or a reduction in symptomatic cases only. We investigated whether the observed reductions exceed those expected from reduction in symptomatic cases among vaccines alone. (ii) Fadeout frequency. Extinction likelihood, or the number of months without reported cases for a given population size, is predicted to increase with vaccine uptake if there is reduced transmission (21, 26, 27). To examine this, we calculated the mean number of fadeouts per year and plotted this quantity against the population size of each province (Fig. 4). Identifying a disease fadeout, or extinction, depends on the characteristic time scale of a disease, or the mean latent plus mean infectious period. In pertussis, with a mean latent period of ~ 8 d and an infectious period of ~ 14 – 21 d, a fadeout may be defined as 1 mo with no reported cases. We scrutinized the critical community size (CCS; the population size above which extinctions are very infrequent) (26, 28) to assess the relative change in extinction profile with vaccine uptake. A substantial rise in the CCS with vaccine uptake would reflect increasing frequency of extinctions in large provinces, consistent with increased herd immunity. (iii) Age-specific incidence. Incidence within specific birth cohorts can be very informative about infection hazard. We tracked incidence in infants (<1 y), where a significant decline has been argued to be a strong indicator of reduced transmission; infants are too young to be fully immunized, and infants <6 mo of age suffer the largest burden of pertussis (5, 29). Therefore, infants are thought akin to a “canary in the coal mine” (30).

Our examination of extinction profiles in each era is presented in Fig. 4. In the first era, the frequency of fadeouts declined rapidly with population size, leading to endemicity when the number of inhabitants in a province exceeded $\sim 700,000$. During the transitional phase, extinctions were more frequent with the estimated CCS in excess of 10^6 . In the high vaccine-uptake era, extinctions occurred often, irrespective of population size. These patterns are consistent with increasing herd immunity corresponding to continued rises in immunization levels (31). To test the robustness of our conclusions, we provide an identical analysis in *SI Materials and Methods* that defines a fadeout as 2 mo with no case notifications, and we again find that the CCS increases with vaccine uptake.

We have investigated the spatial consistency of declining incidence at a finer geographical resolution and found that in almost all provinces, incidence was highest in the first vaccine era and declined throughout the second era, remaining at low levels since the 1990s. This finding was demonstrated by mapping the mean annual incidence in all provinces during each vaccine era (Fig. 5).

Also consistent with the generation of strong herd immunity, we found that as vaccine uptake increased, there was a substantial reduction in incidence in infants in nearly every province (Fig. 5). Between the first and third vaccine eras, incidence dropped on average by nearly 85% in infants. This decline in incidence for the recent birth cohorts indicates substantially reduced transmission to infants. Further, we explored the change in incidence for five age classes (<1 y, 1–4 y, 5–9 y, 10–14 y, and >15 y old) corresponding to a shift from low ($<46\%$, 1981–1983) to high ($>95\%$, 1996–2000) vaccine uptake. This finding again highlights the shift to lower incidence in infants as well as older age groups (Fig. 6).

Discussion

Pertussis remains a public health priority in part because of the associated high mortality in developing countries, but also due to the reported rise in incidence in several countries that have long-standing pediatric vaccination programs (4, 6, 32–34). Developing appropriate public health policies, especially vaccination campaigns, is critical in minimizing the mortality and morbidity associated with pertussis. Using incidence data from Thailand, we sought to investigate vital issues in pertussis epidemiology—namely, the transmission impact of immunity following vaccination.

We confronted pertussis incidence data in Thailand with statistical inference using a series of biologically plausible transmission models to assess the success of the National Expanded Program on Immunization (EPI) of Thailand in reducing incidence. The dynamics in Thailand are characterized by declining incidence corresponding to three vaccine eras with consecutive increases in vaccine uptake, and because there is not a significant spatial variance between provinces with reducing incidence, we used the aggregate data for finding the population-level consequences of immunity on pertussis dynamics in Thailand. Loss of immunity is commonly thought to be important in pertussis epidemiology, and it has been hypothesized to be a driving mechanism for the reported resurgence of pertussis in many developed countries (8, 9, 11). Under the assumption that primary and repeat infections contribute equally to transmission, the results of our hypothesis testing and maximum-likelihood approaches for model selection clearly reflect a long mean duration of immunity, consistent with a long-term longitudinal individual-level study in Senegal (35), and previous quantitative studies of pertussis incidence data (10, 25). It is important to emphasize that a central assumption in our model is that the duration of immunity is exponentially distributed. Consequently, though the mean duration

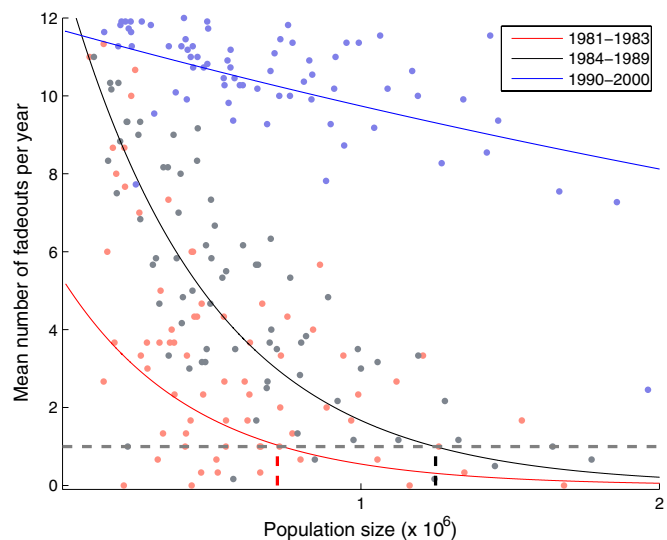


Fig. 4. Mean number of fadeouts for each of Thailand’s provinces in all vaccine eras. Exponential curves [i.e., $y \sim A \exp(-bN)$ where N is the population size and A and b are the estimated parameters] are fit to each vaccine era using standard regression techniques to determine an estimate of the CCS; similar protocols have been used elsewhere (23). Bangkok is excluded from the fit as it is an outlier due to its high population size relative to other provinces ($\sim 5 \times 10^6$). The horizontal dashed gray line represents a mean of one fadeout per year, and the intersection of the vertical dashed red and black lines with the gray line represents the estimated CCS in the first and second vaccine eras, respectively. Below the CCS, frequent disease extinctions are expected to occur. Though some of the shift may be attributed to an increase in the age of infection, leading to more asymptomatic cases, the magnitude of the shifts strongly points to reduced transmission following vaccination (*SI Materials and Methods*).

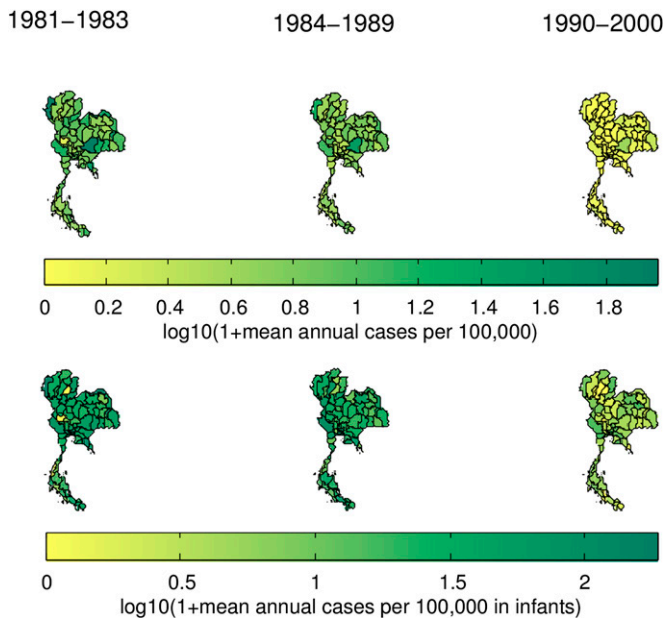


Fig. 5. Log transformation of the average annual incidence (*Upper*) and in infants only (*Lower*) for each vaccine era for all of Thailand's provinces.

of immunity is long, the large variance in the exponential distribution will lead to rapid loss of immunity in some individuals, which may provide an explanation for documented short protective periods in some clinical studies (9). Wearing and Rohani (10) have shown that alternative distributions of duration of immunity (such as the gamma distribution) were less parsimonious with pertussis data from England and Wales, arguing that loss of immunity may be an intrinsically variable process (10).

The aforementioned analysis indicated that the duration of protective immunity, once averaged across a large population, is much longer than patient-level estimates, which may represent a biased sample of the population (those whose protective immunity lasted only a short period). Alternatively, however, immunity may be in fact relatively short-lived, but individuals experiencing repeat pertussis infections may not be contributing significantly to transmission (36, 37), effectively generating *SIR*-type dynamics. This possibility has been previously highlighted in studies of pertussis in England and Wales (10), Sweden (38), and a broader comparative exploration of incidence in 64 countries worldwide (25). Further, natural immune boosting has been recently suggested to play a significant role in shaping pertussis epidemiology. We therefore confronted the data with a model that allowed for individuals undergoing primary and repeat infections to transmit at different rates, and individuals with a primed immune system were subject to immune boosting upon exposure to the pathogen. In contrast to the previous models, the duration of immunity is not well identified but instead, the contribution of transmission from repeat infections to individuals with naive immune system is limited, accounting for only 4–6% of all primary infections. However, for all models tested, the best-performing model, as indicated by the ΔAIC score, was the *SIR* model.

Since the oft-cited work of Fine and Clarkson (15), there has been uncertainty over whether pertussis vaccine successfully reduces transmission or simply reduces symptomatic disease. Our estimation work clearly points to the former, and we confirm our conclusions through use of several empirical metrics on pertussis incidence in Thailand. We first demonstrated that incidence declined in almost every province during each vaccine era, suggestive of increasing herd immunity. Second, we found the mean number of disease fadeouts for each province and compared these profiles for each vaccine era. Our findings indicated a much higher frequency of fadeouts when vaccine uptake is high, again

providing support for increased herd immunity. Finally, we observed that incidence declined in infants in nearly every province in successive vaccine eras. Infants are likely not yet fully protected from vaccination, and this significant decline of incidence in young age groups is a strong indication of herd immunity.

We note that reporting fidelity is a common concern of studies based primarily on case notification data. Though we identify a low reporting rate for pertussis in Thailand, reflecting incomplete notification data, we argue that our parameter estimation and resulting conclusions based on a constant reporting rate are justified. The justification is twofold: the case notification data exhibit clear annual epidemics when vaccine uptake is low, and in the absence of systematic reporting, these signals would likely be absent from the data. Further, in *SI Materials and Methods* we demonstrate that accounting for systematic changes in reporting over time does not affect the predicted model dynamics.

We sought to address several important issues in pertussis epidemiology using a unique high-resolution dataset of incidence in Thailand. Our findings were striking, demonstrating the success of pediatric immunization in Thailand in reducing pertussis transmission and pointing to vaccine-induced herd immunity with an insignificant dynamical impact of repeat infections. Finally, we note that some of our findings are at odds with other studies (12, 39). However, given differences in methodology—specifically, very different metrics used in model validation—and the disparate data sources, the heterogeneity in conclusions is not surprising. Here, we used likelihood-based methods of statistical inference to parameterize and assess the performance of several plausible competing models of pertussis transmission dynamics to develop unified conclusions about pertussis dynamics in Thailand. Moving toward a more unified global picture will require similar systematic analyses of competing transmission models fitted to the diverse datasets of pertussis incidence.

Materials and Methods

Data. The EPI of Thailand was initiated in 1977 to implement infant vaccination programs. The diphtheria/tetanus/pertussis (DTP) whole-cell vaccine was administered as two doses until 1982, when a third dose was added to the schedule (40). In 1987 and 1992, the fourth and fifth doses, respectively, were introduced, yielding a complete schedule comprised of DTWP at 2, 4, 6, and 18 mo and 4–6 y of age. The whole-cell vaccine (DTWP) was solely administered until 1998, since when vaccines in the public sector have remained whole cell, and vaccines in the private sector have been replaced by acellular vaccines (DTaP). Annual national vaccine uptake data from 1981–1996 and 1999 were obtained from the Vaccine Coverage Survey of

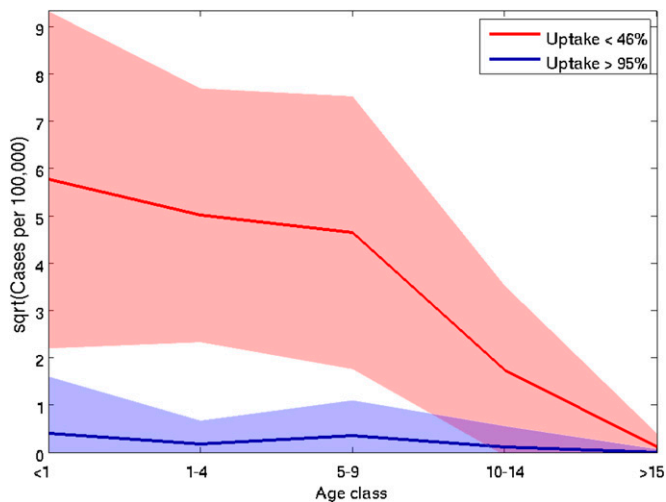


Fig. 6. Mean age structure of case notifications in Thailand with vaccine uptake of <46% (1981–1983, red) and high vaccine uptake of >95% (1996–2000, blue). Shading indicates the SEM, noting that the high variation results from province-level differences in the magnitude of incidence.

Thailand, where uptake was measured as the percent of children aged 12–23 mo that had received two doses in 1981, and three doses for the remaining years of the pertussis vaccine at the time of the survey. For missing years (1997–1998, 2000), the vaccine uptake was assigned the value of the most recently recorded year, and we assumed the administration of vaccines was uniform throughout the year (see Fig. 1 for an illustration of annual uptake through time; further details are provided in *SI Materials and Methods*).

Monthly case notification data from 72 provinces of Thailand between 1981 and 2000 were obtained from the Ministry of Public Health (41). These cases are identified by clinicians using the World Health Organization case definition and reported to the Ministry of Public Health in a passive surveillance system (41). These same cases were available aggregated annually into the following age groups (in years): under 1, 1–4, 5–9, 10–14, 15–24, 25–34, 35–44, 45–54, 55–64, and older than 65 from 1981 to 1984. Beginning in 1985, these data are further subdivided into 1-y age groups up to the age of 7. In our analyses, we assumed the ages of cases were uniformly distributed among ages within each age category. Annual case notification data for 2001–2010 were also obtained from the World Health Organization (19). Annual births from 1981 to 1998 were obtained from ref. 42 and assumed to remain constant from 1998 to 2000. Births were also assumed to occur uniformly throughout the year. Population data for 1980, 1990, and 2000 were obtained from the censuses performed by the National Statistical Office of Thailand (18, 43, 44). Log-linear fits between census years were used to estimate population size for the duration of the time series.

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