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Imperfect vaccine-induced immunity and whooping cough transmission to infants

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Abstract

Whooping cough, caused by *B. pertussis* and *B. parapertussis*, has increased in incidence throughout much of the developed world since the 1980s despite high vaccine coverage, causing an increased risk of infection in infants who have substantial disease-induced mortality. Duration of immunity and epidemically significant routes of transmission across age groups remain unclear and deserve further investigation to inform vaccination strategies to better control pertussis burden. The authors analyze age- and species-specific whooping cough tests and vaccine histories in Massachusetts from 1990–2008. On average, the disease-free duration is 10.5 years. However, it has been decreasing over time, possibly due to a rising force of infection through increased circulation. Despite the importance of teenage cases during epidemics, wavelet analyses suggest that they are not the most important source of transmission to infants. In addition, the data indicate that the *B. pertussis* vaccine is not protective against disease induced by *B. parapertussis*.

Keywords

Bordetella; Immunity; Transmission

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1. Introduction

Whooping cough remains an important public health problem worldwide and a major cause of infant mortality. Despite routine and mass vaccination campaigns for over 50 years incidence in many developed countries has been increasing since the 1980's [1], with a marked rise in cases in teenagers and adults [2,3]. Infections in adults and/or teenagers have been shown to be responsible for transmission to non-fully immunized infants [4,5,6], who have close to a 1% case-fatality rate [7]. The rise in cases in older, vaccinated individuals raises the concern that infants receive decreasing protection by vaccine-induced herd immunity. We explore the population-level effects of imperfect or temporary vaccine-induced immunity against both dominant etiological agents, *Bordetella pertussis* and *B. parapertussis*, and the impact of the resultant cases in teenagers and adults on transmission to infants through analysis of temporal and age-related patterns of *B. pertussis* and *B. parapertussis* infections in Massachusetts from 1990 through 2008.

The Massachusetts Department of Public Health (MDPH) provides most childhood vaccinations free of charge, and has very high immunization rates. It provides pertussis diagnostic services statewide and operates a robust pertussis surveillance program, which, since 1999, includes contact tracing to identify the source for cases in infants less than one year old. The MDPH recommends administering five doses at ages two, four, six and 15–18 months, and the last one between ages four and six years. In October 1995, the immunization guidelines changed from recommending the whole cell to the acellular pertussis vaccine for all five doses [2]. However, the transition between the vaccines was prolonged, precluding analysis of vaccine efficacy based solely on time period, and necessitating the use of individuals' vaccine histories, as we use here. Teenage and adult boosters (TDaP) are recommended as well and have been available since 2005.

The duration of immunity against *B. pertussis* provided by the pertussis vaccines has been estimated to be a maximum of 15 years [8]. This implies that in a highly vaccinated population, without any boosters, there are wide age-classes in which *B. pertussis* can circulate, and from which it can escape to cause infections in infants. Two hypotheses have been put forward regarding the impact of teenage- and adult-cases on infections in infants. Either epidemics among teenagers lead to infections in infants [9], or subclinically-infected adults are responsible for infection of prevaccine-age infants [10]. Subclinical infections are often not diagnosed until long after the infection took place because the symptoms were not severe enough to bring a patient to the doctor's office right away. Additionally, the contact tracing program in Massachusetts identified some cases that were too mild to be identified except through contact tracing from an infant infection. It is suspected that these individuals were actually the cause of the infant case, despite the fact that their date of diagnosis was later.

Whooping cough can be caused by other etiological agents as well and the vaccine does not fully prevent infection and disease from all of them. In particular, *B. parapertussis* can cause similar symptoms and has been reported to be the dominant species at times in several European countries [11]. We investigate the impact of imperfect vaccine-induced immunity on whooping cough epidemiology by examining (1) the duration of immunity provided by the vaccine, (2) the likely role of infections in teenagers and adults on transmission to infants through investigating the relative timing of cases in the different groups and (3) the effectiveness of *B. pertussis* vaccines, both acellular and whole cell, against disease caused by *B. parapertussis*.

Age distributions, time series analysis and correlation tests were used to compare *B. pertussis* and *B. parapertussis* prevalence and dynamics and confirmed that the *B. pertussis*

vaccine is not strongly protective against *B. parapertussis*. We further showed that (1) the time between vaccination and infection has been decreasing, (2) teenagers are disproportionately affected during outbreaks, and (3) teenage outbreaks are consistently out of phase with prevaccine-age infants, whereas adult cases are largely in phase with infant outbreaks suggesting that the chain of transmission in teenagers is somewhat separate from the very young.

2. MATERIALS AND METHODS

2.1. Study design

The Massachusetts State Laboratory Institute (SLI) is the standard provider of *Bordetella* cultures in Massachusetts, in addition to performing serology and PCR tests. A serum test for IgG to pertussis toxin was performed if the patient was ≥ 11 years old and had a cough for more than 14 days. Because *B. parapertussis* does not produce pertussis toxin, the serology test was not sensitive to infection with *B. parapertussis*. In all other cases (< 11 years old or ≤ 14 days of cough) a nasopharyngeal swab was cultured [12]. Two different types of records of laboratory-confirmed pertussis were analyzed, a 19-year data set (Jan 1990 – Dec 2008) generated through clinicians' reports, since pertussis is a reportable disease in Massachusetts; and a 16-year data set (Jan 1992 – Dec 2007) of all results, both positive and negative, from nasopharyngeal swabs.

For the entire span of these data, Massachusetts has recommended five doses of vaccine. Until 1995, all five doses were whole cell vaccine, produced by the Massachusetts Department of Public Health Biologic Laboratories. They stopped manufacturing this in 1995, the same year they switched to distributing Tripedia, a DTaP vaccine manufactured by Aventis Pasteur containing 23.4*μg* of inactivated pertussis toxin (PT) and 23.4*μg* of filamentous hemagglutinin (FHA). In 2004, the MDPH also began distributing Pediarix produced by GlaxoSmithKline, another acellular pertussis vaccine, which contains 25*μg* PT, 25*μg* FHA and 8*μg* pertactin (PRN). In 2005, two booster vaccines were licensed for us in teenagers and adults in Massachusetts. The MDPH distriubted Boostrix (by GlaxoSmithKline, containing 8*μg* PT, 8*μg* FHA and 2.5*μg* PRN) to 11–18 year olds. Additionally Adacel (by Sanofi Pasteur) was licensed, containing 2.5*μg* PT, 5*μg* FHA, 3*μg* PRN and 5*μg* Fimbriae Types 2 and 3 (FIM).

For analyses of *B. pertussis* transmission between age groups and time interval between vaccination and infection (disease-free duration), the 19-year data set was used. It included all reported *Bordetella* cases in Massachusetts, both those tested at SLI and those reported through epilink to the Massachusetts Department of Public Health. Each case had over 60 categories of information about each patients' symptoms, vaccine history, and demographics. This 19-year data set identified 16,620 *B. pertussis* cases, of which 14,654 had information on age at diagnosis, and 5,020 had vaccine history information, and 82 *B. parapertussis* cases, of which 18 had vaccine history information. We used (1) the full data set for temporal analysis of *B. pertussis* by age group; (2) the subset with vaccine histories for estimating disease-free durations and comparing patterns among whole cell and acellular vaccines; and (3) the *B. parapertussis* data with vaccine histories to estimate disease-free duration for this non-target etiological agent. The data were collected between 1990 and 2008 and are now maintained in the Massachusetts Virtual Epidemiological Network (MAVEN).

For all other comparisons between *B. pertussis* and *B. parapertussis* we used the 16-year data set, which includes 44363 records from the nasopharyngeal swabs submitted to SLI between 1992 and 2007. This data set included information on the patient's age, date of testing and the result of the test. The possible results were negative, inconclusive and

positive for *B. pertussis* or *B. parapertussis*. No dual infections were noted in the data set, though it is possible that some of the specimens that tested positive for *B. pertussis* may also have contained *B. parapertussis* but were not investigated further once *B. pertussis* was identified. This 16-year data set included 2,628 *B. pertussis* cases and 273 cases of *B. parapertussis*. See [13] for details on media used and tests performed. Although the data set is strongly age-biased with respect to incidence (due to the fact that cultures were performed on all patients under 11 years of age, but only a subset of the older ones) this bias should not affect the estimates of the comparison of age-specific proportions of positive tests between the two species.

2.2. Statistical analyses

Analysis of the 19-year data-set—We analyzed the disease-free durations after the full 5 doses of vaccine to compare the protection between the whole cell and acellular vaccines and to indirectly estimate the trend in the force of infection over time. We compared the disease-free duration after immunization with five doses of the whole cell and acellular vaccines in the cohort of individuals first vaccinated between January 1994 and December 1996. The acellular vaccine became prevalent in 1995 and the whole cell vaccine was phased out by 1997, so this was the only time period during which the numbers of whole cell and acellular vaccines given were similar and thus temporal trends in the data would not bias the comparison. An individual was classified as being whole cell or acellularly vaccinated based on the type of the first dose.

To assess the temporal trend in the lag between last vaccination and subsequent infection (hereinafter referred to as 'disease-free duration'), we selected the data subset that only included the 2,446 cases whose last vaccination was administered between Jan 1, 1990 and Dec 31, 1995. The disease-free duration includes both the duration of immunity and the time to reinfection once immunity has been lost; the latter component is inversely proportional to the force-of-infection, as it is affected by overall circulation of the pathogens. Before fitting a linear regression to the data, we removed all waning times greater than 13 years to create comparable right-censoring of all cohorts, since the data do not include records of infections more than 13 years later for individuals last vaccinated in 1995.

We also investigated which age groups were primarily responsible for the epidemic outbreaks of *B. pertussis*. To identify 'outbreaks' we first smoothed the time-series data using a flexible cubic spline function [14]. The beginnings of epidemics were somewhat arbitrarily defined as weeks in which the slope of the spline was in the upper 5th percentile of the slopes along the whole time series. Epidemics were defined to have ended when the next minimum in the smoothed data was reached. A Pearson's χ^2 test for indepndence was used to compare the proportion of cases in each age group in epidemic peaks vs. outside. The null hypothesis is that the variables (age group and epidemic status) are independent, and therefore the joint distribution (observed) is the product of the marginal distributions (expected, see Table 1).

Finally, we examined the temporal relationship between cases in different age groups. We identified the points in the seasonal cycle at which different age groups peaked and determined which age groups were in phase with each other, thereby allowing for transmission among them. To do this we calculated the complex-valued Morlet wavelet for the time series of each age group (0–0.5, 0.5–1, 1–4, 5–9, 10–19, 20+ years, [15]). The annual scale of the wavelet decomposition was used to compute the phase angles (the angle between the x-axis and the vector designated by the complex value of the Morlet wavelet for annual periodicity). Phase angles are circular statistics restricted to $\pm\pi$ radians. We converted the phase differences to weeks prior to graphing.

Analysis of the 16-year data set of cultured nasopharyngeal swabs—To examine temporal dynamics of *B. parapertussis* we assessed its periodicity from the time series of monthly incidence. We used a fast Fourier transform with the linear mean trend removed [16]. The frequency of the maximum spectral density was used to calculate the dominant period (1/frequency). A randomization test with 1,000 samples was carried out to determine which frequencies were significant.

We next calculated the proportions of culture tests performed that were positive for *B. pertussis* and *B. parapertussis*. We looked at the age structure of *B. parapertussis* cases and compared it to that of *B. pertussis* using a Pearson's product moment correlation coefficient. To ensure that the different patterns seen in the age-distributions for the two species were statistically significant, we tested for over-dispersion in the age distribution data [17]. We found that all dispersion parameters were under 1.01, indicating that binomial error bars appropriately capture the uncertainty.

All analyses were carried out in R v. 2.6.1 [18].

3. RESULTS

3.1. Time between vaccination and infection (disease-free duration)

The whole cell and acellular vaccines provided very similar disease-free durations for cohorts first vaccinated between 1994 and 1996, with similar shapes, and the mean and median times from last vaccination to infection between 6.5 and 7 years for both (t-test for comparison of means: p-value = 0.61. Figure 1a). However, among all other cohorts whose first dose of vaccine was whole cell, the mean time to infection was ~ 10.5 years (Supplemental figure 5).

The discrepancy between the two estimates of disease-free duration after whole-cell vaccination (10.5 vs. 6.6 years, 2-sided t-test with unequal variance, $P < 0.001$) is consistent with the fact that the time between vaccination and infection has decreased over time (Figure 1b, slope estimate = −0.37, 95% CI = [−0.40, −0.33]) at an average rate of 4.4 months duration per year. This result assumes that the reporting rate for each age group was constant over time, which may not have been the case. However, the biologically and statistically significant trend in disease-free duration, together with the increase in early teenage cases (see Supplemental figure 5), suggests that the disease-free duration did indeed decrease over time. This trend may be a result of a rising force of infection in recent years, which increases the rate at which people will be exposed after their vaccine-induced immunity had waned.

3.2. Seasonal timing in teens, adults, and infants

We next looked at whether some age groups contributed to epidemic peaks more than others. We found that the age distribution during epidemics significantly differed from the overall age distribution. In particular teenagers (ages 10–19 years) were over-represented in the epidemics, with the proportion of teenage cases during epidemics approximately twice as high as that of infants and a third again as much as that of adults (Table 1).

The analysis of age-specific seasonality (Figure 2a and Supplemental figure 6) showed that cases in infants were not associated with the winter peak in teenage cases. Instead, for both *B. pertussis* and *B. parapertussis* (*B. parapertussis* data not shown), infants and young children had their peak number of cases in the summer (July-September), preceding the teenage rise in cases that began in September and peaked in November, suggesting that these may represent somewhat independent chains of transmission.

Finally, we used spectral and wavelet analyses to identify in which phase of the annual epidemic cycle each age group was, which groups were in phase with each other, and how these patterns changed over time. Consistent with observations for pertussis dynamics around the globe [19], incidence in Massachusetts exhibited significant annual and 4-year cycles. Pre-vaccine age infants were never in phase with teenagers but often in phase with adults as well as children of all other ages (Figure 2b, 10–19 year olds' range does not overlap horizontal line, whereas all other age groups do). There was a total span of almost three months between prevaccine-age infants' and teenagers' annual cycles, suggesting few sustained chains of transmission between these age groups. The adult peak in incidence varied in timing, sometimes being in phase with teens and at other times with younger children. On average, the adult peak occurred about three weeks before the peak in infants. This is most likely explained by a delay in adult diagnosis due to a combination of mild symptoms and case identification from contact tracing.

3.3. Comparison between B. pertussis and B. parapertussis

B. parapertussis comprised approximately 10% of whooping cough cases identified by cultured nasopharyngeal swabs in Massachusetts, and exhibited annual and mildly biennial cycles (Figure 3 and Supplementary figure 7). It primarily caused whooping cough in 5–10 year olds, who are expected to have strong vaccine-induced immunity against *B. pertussis*. The mean time between immunization with either whole cell or acellular vaccine and infection with *B. parapertussis* was 5.4 (3.9) years. The age distributions for *B. pertussis* and *B. parapertussis* in individuals expected to have strong vaccine-induced immunity (ages 3–15 years) in Massachusetts mirrored each other (Figure 4 between the two vertical lines). The age distribution of proportion of tests positive for each infection in every year-long age class was highly and significantly negatively correlated ($r = -0.75$, $P = 0.003$). The distributions of cases in each age class were also negatively correlated ($r = -0.55$, $P = 0.051$). There was low reported incidence of both infections in adults (Figure 4).

4. DISCUSSION

We contribute new insights into the duration and epidemiological importance of waning immunity to the pertussis vaccines, and quantify the disease-free duration from both *B. pertussis* and *B. parapertussis*. The estimates of mean duration of vaccine-induced immunity against *B. pertussis* are consistent with previous estimates that range from five to 15 years [20,21]. Additionally, we show that the time between vaccination and infection has steadily decreased over the past decade. However, the durations of immunity provided by the two vaccines are very similar [8], and therefore the change from whole cell to acellular vaccine is not likely the cause of the decrease in disease-free duration. We hypothesize that an elevated force of infection in recent years led to the reduction in time to infection after vaccination because of more frequent exposure.

We also showed that reinfection of older individuals is important in contemporary disease dynamics. Consistent with previous data, teenagers comprised the majority of all cases even in this highly vaccinated population. Epidemic peaks had a unique age distribution with a disproportionate number of cases in teenagers (aged 11–19 years), identifying teens as the primary cause of large, symptomatic outbreaks. However, despite their primacy in outbreaks and the evidence from contact studies that they do sometimes transmit to infants [4], the clinical cases observed in teenagers did not appear to be the main source for the large numbers of cases in prevaccination-age infants. Infants and teenagers had different seasonal peaks and were out of phase with each other, suggesting that they may have belonged to somewhat separate chains of transmission. A recent study of age-specific *B. pertussis* seasonality in the Netherlands reported similar results [22], suggesting that separation of infant and teenage peaks may be a geographically widespread phenomenon. This lends

credence to the theory that cases in infants are more likely due to contact with sub-clinically infected adults than symptomatically infected teenagers [23].

It has long been known that immunity to pertussis, even to natural infection, wanes [24,25], which raises the following question: Why then were very few cases seen in teenagers and adults, both during the prevaccination era and for the first forty years post vaccination? One potential explanation is that in the prevaccine era, when pertussis circulation was high and symptomatic infections more common than they are now, most people got a natural immune boost by coming in contact with infection before their immunity had completely waned [8]. However, by the 1970s, most people obtained immunity through vaccination rather than transmissible natural infection. With so little circulating pathogen people's immunity was rarely boosted, thereby creating a large pool of people susceptible to pertussis, and allowing epidemic outbreaks in the current era despite high vaccine coverage. Another potential explanation is that vaccine-driven pathogen evolution selected for a strain that can infect more quickly or symptomatically after vaccination [26].

B. parapertussis was always a minor cause of whooping cough cases in Massachusetts. However, the two etiological agents had surprisingly different age-attack rates. *B. parapertussis* incidence was highest in the age group with the strongest vaccine-induced immunity (ages 3–15 years) suggesting that vaccine-induced immunity against *B. parapertussis* is either not as strong or wanes more quickly than immunity to *B. pertussis*. Prevaccination population-level studies [27], and studies in model organisms [28,29,30,31,32,33,34] have provided mixed evidence for effects of exposure to *B. pertussis* antigens (either by natural infection or vaccination with whole cell or acellular vaccines) and subsequent infection with *B. parapertussis*. Unlike data from the pre-vaccination setting, which exhibited antisynchronous cycles [27] (and thus temporal niche separation), *B. pertussis* and *B. parapertussis* in contemporary Massachusetts showed niche separation based on host age. The mean age of *B. pertussis* infection in Massachusetts rose from 5.5 years of age in the prevaccine-era [35] to 21.6 years in the current era. This general pattern has been documented extensively in other locations as well [36,37]. *B. parapertussis* peak incidence, in contrast, has remained in the younger age classes that appear to have strong vaccine-induced protection against *B. pertussis*. There is evidence from both prospective epidemiological surveillance [33] and recent experiments in model organisms [38,30] that immunization with the acellular vaccine may actually increase the host's susceptibility to infection by *B. parapertussis*. The difference in age-attack rates between the two species may therefore be a vaccine-mediated effect in which the acellular vaccine decreases susceptibility to *B. pertussis* while at the same time increasing susceptibility to *B. parapertussis*.

The results of this study offer insight into future directions for vaccine policy. Infants are the only age-group in whom there is a significant whooping cough-induced mortality rate. However, it is not possible to provide complete vaccine-induced immunity at birth. Therefore, we add support to the current recommendation that vaccine policy should focus on providing boosters to the reservoir age group. This study suggests that it is not primarily the clinical cases in teenagers that form a reservoir for *B. pertussis*, but rather subclinical infections, presumably in adults. Our findings support that the current recommendation to cocoon neonates by vaccinating parents and other frequent contacts is the most important way to reduce pertussis-induced morbidity and mortality in infants. However, this will not likely prevent epidemic outbreaks. To achieve this goal teenagers, in whom vaccine-induced immunity has waned and who form the bulk of *B. pertussis* epidemics, need to receive boosters. Without creating vaccine-enhanced herd immunity in this highly gregarious age group, we should expect to continue to see pertussis epidemics even in regions with high vaccine coverage. Finally, with the increase in use of the acellular vaccine, it is important to

have *B. parapertussis* surveillance in place and generate new research on the effects of various pertussis vaccines against *B. parapertussis*.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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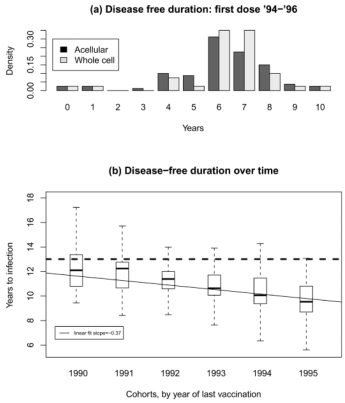

Figure 1. Duration of immunity by cohort

(a) The distributions of time between last vaccination and infection for those who received their first dose between 1994 and 1996. The height of the black bars represents the proportion of infections that occurred a given number of years (x-axis) after receiving a fifth dose of acellular vaccine. The grey bars are the same except for individual's vaccinated with whole cell vaccine. The distributions are not significantly different. (b) Each boxplot represents one cohort, where a cohort is defined by the calendar year of last vaccination (x-axis). For example, everyone who received their last vaccination between Jan 1 and Dec 31 1990 are in the first cohort. The boxplots represent the spread of the disease-free durations from each cohort. Each boxplot shows the median, interquartile range (IQR), and range of each year. Outliers were defined as points outside of 1.5 times the IQR and were omitted from the plot. The best fit line is from a linear regression of waning times against date of last vaccination (as a continuous variable), but with all durations over 13 years (data above dashed line) removed since we only have data on the first 13 years after vaccination for people who were last vaccinated in 1995. The probability of the data, if the true slope were 0, is < 0.001.

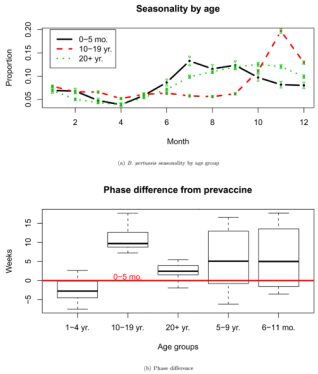

Figure 2. Time lags among age groups

(a) **To examine age-specific seasonality** the *B. pertussis* data are aggregated by calendar month to show the seasonal patterns of the three age groups on which we focus: prevaccine-age infants (solid), teens (dashed), and adults (dotted). 95% confidence intervals for proportions are shown. Other age groups are shown in supplemental figure 6. (b) **Phase difference between each age group and prevaccine-age infants**. A boxplot is shown to summarize the phase-angle difference between prevaccine-age infants (0–5 months) and each other age group over the course of the data set. The 0-line is drawn to highlight the pre-vaccine age group. Positive values for a given age group suggest that 0–5 month olds preceded that age group. Groups that cross the 0-line are frequently in phase with the 0–5 month olds.

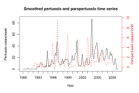

Figure 3. Cases of B. pertussis and B. parapertussis in Massachusetts

Number of *B. pertussis* cases by week (black curve) and *B. parapertussis* cases by month (dashed red line).

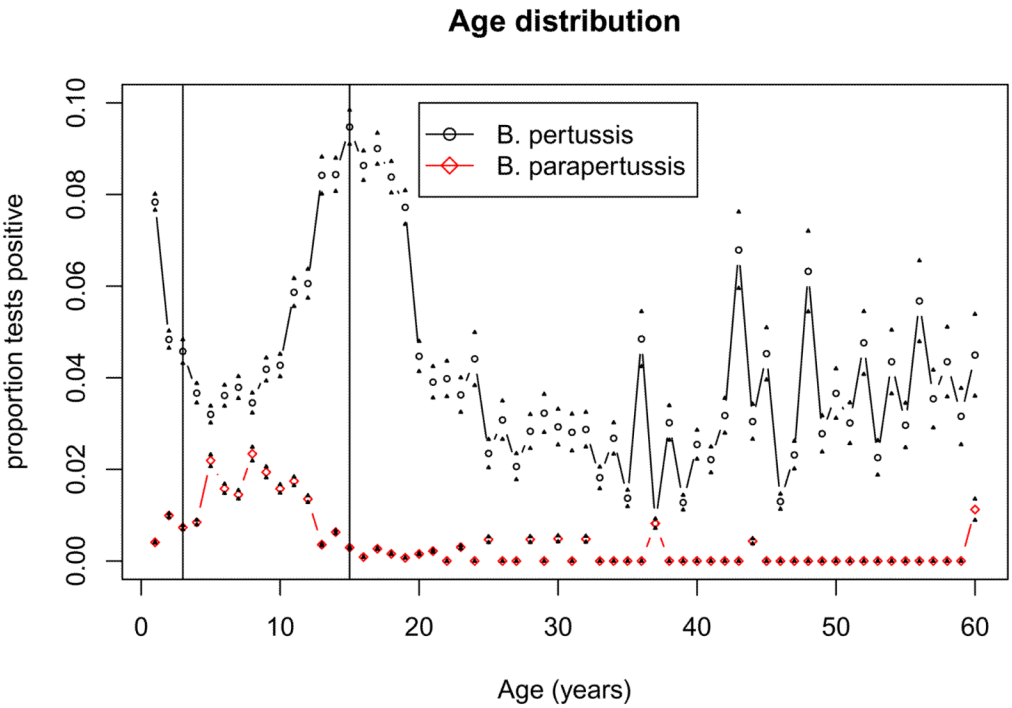

Figure 4. Age distributions for B. pertussis and B. parapertussis in Massachusetts

The proportion of tests that were positive is shown for *B. pertussis* (top line) and *B. parapertussis* (bottom line). Binomial error bars are shown, representing 95% confidence intervals.

Table 1

Age Distribution During Epidemics in Massachusetts, 1990–2008[1]

Age distribution during epidemic outbreaks compared to the overall age distribution of cases. The top row shows the age distribution of the cases identified as being part of epidemic outbreaks, as defined in the methods section. The second row shows the age distribution of all other *B. pertussis* cases between 1990 and 2008 in Massachusetts. These two distributions are significantly different according to a χ^2 test (d.f. = 5, P < 0.001). The bottom row shows the proportion of epidemic cases in each age group.

		0–5 mo.	6–11 mo.	1–4 yr.	5–9 yr.	10–19 yr.	20+ yr.
Cases	Epidemics	111	26	66	46	2595	1078
	Non-epidemics	574	115	287	373	5820	3563
Proportion epidemic cases		0.16	0.18	0.19	0.11	0.31	0.23

[1] χ^2_5: $P < 0.001$