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Dynamics of Pertussis Transmission in the United States

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Past patterns of infectious disease transmission set the stage on which modern epidemiologic dynamics are played out. Here, we present a comprehensive account of pertussis (whooping cough) transmission in the United States during the early vaccine era. We analyzed recently digitized weekly incidence records from *Morbidity and Mortality Weekly Reports* from 1938 to 1955, when the whole-cell pertussis vaccine was rolled out, and related them to contemporary patterns of transmission and resurgence documented in monthly incidence data from the National Notifiable Diseases Surveillance System. We found that, during the early vaccine era, pertussis epidemics in US states could be categorized as 1) annual, 2) initially annual and later multiennial, or 3) multiennial. States with predominantly annual cycles tended to have higher per capita birth rates, more household crowding, more children per family, and lower rates of school attendance than the states with multiennial cycles. Additionally, states that exhibited annual epidemics during 1938–1955 have had the highest recent (2001–2010) incidence, while those states that transitioned from annual cycles to multiennial cycles have had relatively low recent incidence. Our study provides an extensive picture of pertussis epidemiology in the United States dating back to the onset of vaccination, a back-story that could aid epidemiologists in understanding contemporary transmission patterns.

early vaccine era; interepidemic periods; pertussis; susceptible recruitment; vaccines; whooping cough

Abbreviations: ANOVA, analysis of variance; CI, confidence interval; NNDSS, National Notifiable Diseases Surveillance System.

Pertussis, commonly known as whooping cough, is a contagious disease caused by the bacterium *Bordetella pertussis*. Historically, pertussis was responsible for substantial morbidity and mortality in children. In the prevaccine era in the United States, it is estimated that pertussis accounted for 200,000 cases and 4,000 deaths annually (1). The widespread rollout of infant vaccination in the 1940s and 1950s (2) dramatically reduced pertussis incidence in much of the developed world (3). However, over the past decade or so, a clear rise in pertussis incidence has been observed in some countries with consistently high vaccine coverage (4–8). The absence of a clear explanation for these events highlights gaps in our understanding of pertussis epidemiology, particularly the nature of the immunity rendered by infection and vaccination (9–13).

While some authors have touted improvements in surveillance and diagnostic methods (14) as an important factor in rising incidence, much of the recent resurgence literature has focused on explanations rooted in biology, attempting to identify changes in the epidemiologic landscape that have led to increasing pertussis transmission. Candidate explanations include loss of vaccine-derived immunity (15), evolutionary changes in bacterial virulence (7) and antigenic escape (16), and the lower protection afforded by acellular vaccines (17). Intriguingly, it was recently suggested that in populations with a long-standing history of incomplete vaccination with an imperfect vaccine, pertussis resurgence may be inevitable even in the absence of changes in underlying transmission biology (18). These authors demonstrated that a rebound in transmission, especially among older age groups, can arise as a natural consequence of demographic changes and changes in the immune profile of the population.

In this paper, our intention is to examine the epidemiologic dynamics of pertussis during the transition to mass infant immunization, partly with a view toward exploring the link between past patterns of transmission (and immunity) and contemporary pertussis epidemiology in the United States. Specifically, we

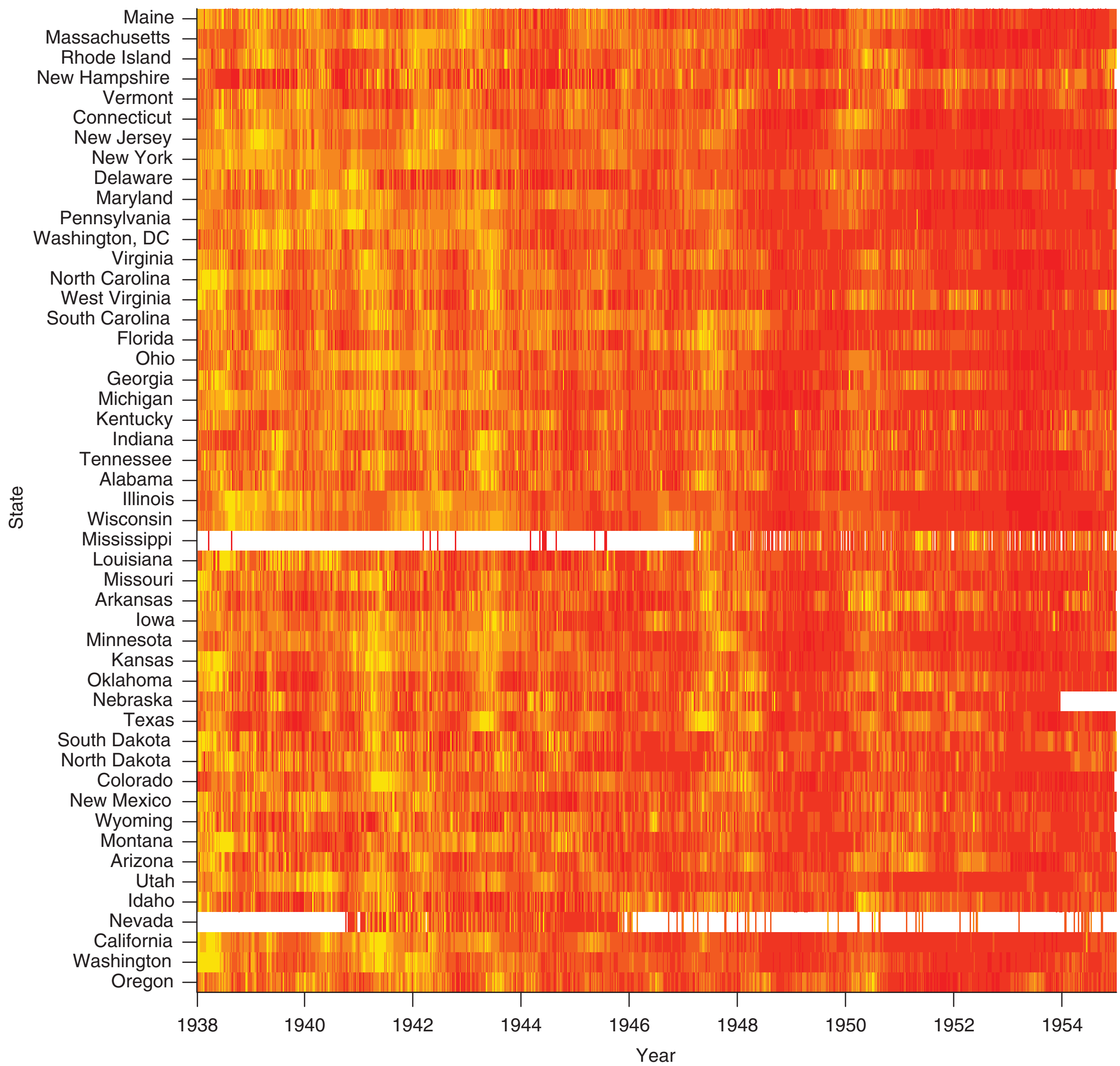

Figure 1. Pertussis incidence in the United States from 1938 to 1955. The figure shows normalized square-rooted incidence rates for each continental state and Washington, DC, ordered by longitude. Yellow indicates high levels of incidence, and red indicates low levels of incidence. Missing data were interpolated for all states except Mississippi and Nevada.

present results from analyses of newly digitized records on pertussis incidence (19) in the 48 contiguous states and Washington, DC, from 1938 to 1955 (Figure 1). One of the key challenges to understanding how the profile of pertussis immunity in the United States has changed over the past few decades is the absence of quantitative information regarding vaccine uptake, with the earliest national estimates dating back only to 1962 (20). As shown in Table 1, while the combined diphtheria-tetanus-pertussis whole-cell vaccine became widely available in the United States in 1948 (21), other pertussis vaccines were already accessible and in sporadic use as early as the 1930s (22–24). Indeed, some states, such as Michigan, were known to have already started routine infant vaccination ahead of the national immunization program (2). Thus, we sought an explanation for contrasting dynamics in different states by examining potential predictors of vaccine uptake, demographic information, and insights from epidemiologic theory. Finally, we investigated the extent to which historical transmission dynamics in each state were predictive of modern observed resurgence patterns.

METHODS

Pertussis incidence data

Weekly pertussis notifications from the 49 continental states (including Washington, DC) were obtained from the Project Tycho (University of Pittsburgh; http://www.tycho.pitt.edu/) level I database (19). We used data from the early vaccine

Table 1. Timeline of Key Events in Pertussis Control Efforts During the Early Vaccine Era

Year	Event
1906	*Bordetella pertussis* isolated by Jules Bordet and Octave Gengou (49)
1914	First pertussis vaccine licensed in the United States (21)
1936	Kendrick and Eldering (50) publish results from a promising 1934–1935 vaccine trial carried out in Michigan; Bell (22–24) conducts trials on alum-precipitated vaccine in Maryland
1938	Biologic Products Division of the Michigan Department of Health begins mass-producing pertussis vaccine (51); Bell conducts trials of alum-precipitated vaccine in Virginia (22–24)
1940	Pertussis vaccines are widely distributed across the United States (51)
1944	American Medical Association recommends the pertussis vaccine (51)
1948	Pertussis vaccine combined with diphtheria and tetanus toxoids (DTP) made widely available in the United States (21)

Abbreviation: DTP, diphtheria-tetanus-pertussis.

era, starting from 1938 and extending to 1955 when available. Missing data near the end of this period resulted in shorter time series for some states (see Web Table 1, available at http://aje.oxfordjournals.org/). Mississippi, Nevada, North Dakota, South Dakota, and Wyoming were omitted from our analyses due to overrepresentation of missing data in these states, as explained in Web Appendices 1–3. We also obtained monthly pertussis incidence data spanning the years 1951–2010 from the National Notifiable Diseases Surveillance System (NNDSS).

Periodicity analysis and classification into groups

We characterized the interepidemic period in each state from 1938 to 1955. The dominant period at each time step was determined using the `biwavelet` package (25), which computes the bias-corrected wavelet power spectrum (26). Additional description of the wavelet analysis method is provided in Web Appendix 2. We noted the state-specific interepidemic period corresponding to the dominant signal in the wavelet decomposition and examined its evolution over time. We detected 4 distinct patterns, which formed the basis for the grouping of states. The estimated timing of any transitions is given in Web Table 2.

All time-series preprocessing involved 1) square-root transformation of incidence data to stabilize the variance and 2) imputation of missing data using linear interpolation. Linear trends were removed, and each time series was normalized to have a mean value of 0 and a variance of 1. To reduce edge effects, we padded the time series with zeros prior to wavelet decomposition, and the signals from the first and last 3 years of the time period were discarded.

Contrasting demographic and epidemiologic features across groups

To provide a mechanistic underpinning for the observed variation in state-specific periodicity, we compiled a set of potentially

Table 2. State Characteristics From the Early Vaccine Era (1938–1955) and the Subsequent Time Period (1951–2010) Used in an Analysis of Periodicity in Pertussis Patterns

Characteristic	Definition	Data Source
Population size	Mean population size (in millions) from 1938 to 1955	Census Bureau (52)
Birth rate[a]	Mean monthly birth rate per 1,000 population from 1938 to 1955	Centers for Disease Control and Prevention (53), Martinez-Bakker et al. (46)
Variation in population size	Change in population size from 1938 to 1955 relative to mean population size	Calculated from population size data
Variation in birth rate[a]	Change in monthly birth rate from 1938 to 1955 relative to mean birth rate	Calculated from birth rate data
Proportion urban[a]	Fraction of population living in an urban area in 1940	University of Virginia Historical Census Browser (54)
School attendance[a]	Fraction of children aged 5–13 years attending school in 1940	University of Virginia Historical Census Browser (54)
Household crowding	Percentage of households with >1 person per room in 1940	Census Bureau (55)
Health spending[a]	Mean per capita state annual health and hospital expenditure from 1940 to 1950 in thousands of dollars	Census Bureau (56)
Fraction of families with no children	Fraction of families with no children under 10 years of age in 1940	Census Bureau (57)
Fraction of families with >1 child	Fraction of families with >1 child under 10 years of age in 1940	Census Bureau (57)
Latitude	Latitude of the state centroid according to population density in 1940	Census Bureau (58)
Historical incidence	Mean weekly pertussis incidence per 100,000 population from 1938 to 1955	Project Tycho (University of Pittsburgh) (19)
Phase	Residual phase of the annual period derived using wavelet decomposition of 1938–1955 data	Calculated from incidence data (19)
Resurgence slope	Slope of the resurgence calculated using segmented regression of NNDSS monthly data from 1951 to 2000	Calculated as in Rohani and Drake (36)
Breakpoint	Start of the resurgence calculated as the breakpoint in segmented regression of NNDSS monthly data from 1951 to 2000	Calculated as in Rohani and Drake (36)
Recent incidence	Mean monthly pertussis incidence per 100,000 population from 2001 to 2010, estimated from NNDSS data	NNDSS (36)

Abbreviation: NNDSS, National Notifiable Diseases Surveillance System.
[a] Data on this characteristic were unavailable for Washington, DC.

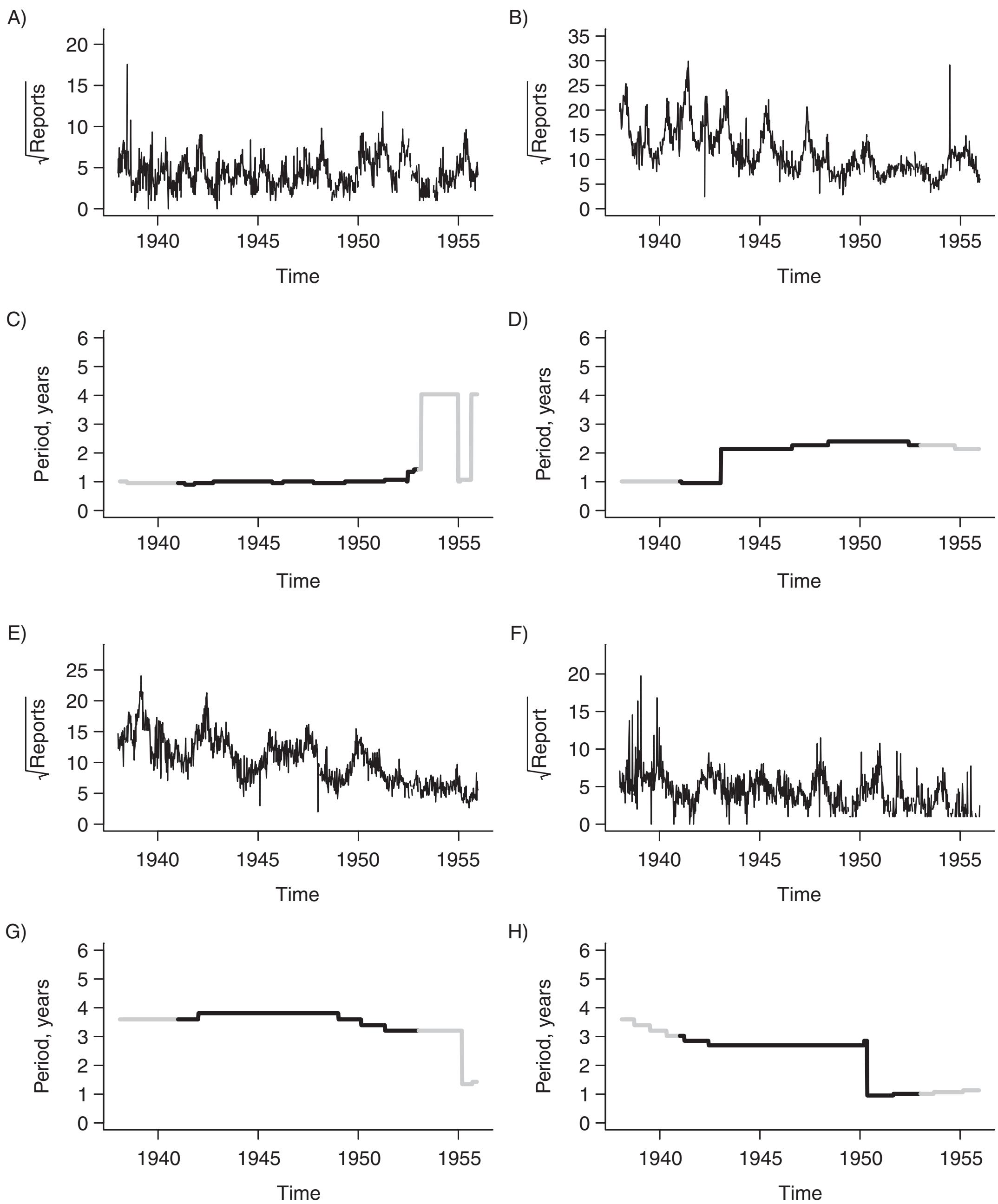

Figure 2. Weekly pertussis incidence data (1938–1955) for 4 states: A) Arizona (group 1), B) California (group 2), E) New Jersey (group 3), and F) Vermont (group 4). The associated dominant periods are plotted below the corresponding incidence data for C) Arizona, D) California, G) New Jersey, and H) Vermont. The dominant periods represent the periods with the largest power in the wavelet spectrum. Black and gray lines distinguish the significance (or otherwise) of the detected interepidemic periods (see Methods).

explanatory characteristics in each state, described in Table 2. Group 4 was not included in this comparison since it contained only 2 states. Many attributes were unavailable for Washington, DC, during the early vaccine era, so it was omitted from the analyses for these characteristics (indicated in Table 2).

We chose possible predictors of periodicity based on epidemiologic theory regarding childhood infectious diseases that are subject to seasonally varying transmission (27–32), such as pertussis. It has been shown that the periodicity of epidemics is determined by a combination of factors, including the baseline transmission rate, the magnitude of the seasonal variation in transmission, and the birth rate, which modulates the rate of susceptible-pool replenishment (4, 31, 33). High transmission and birth rates are predicted to

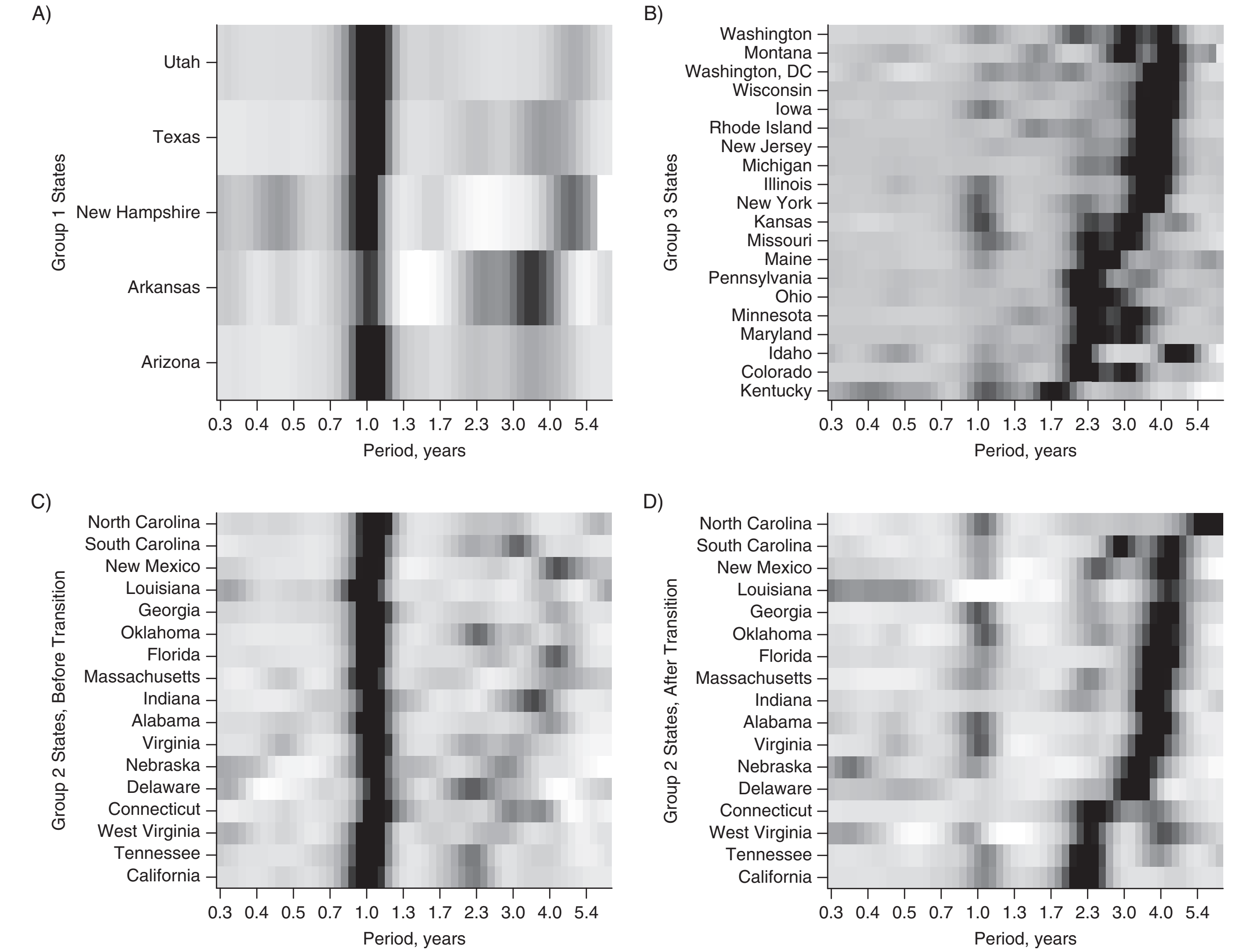

Figure 3. Normalized global power spectrum derived from the wavelet decomposition of 1938–1955 pertussis time series. Darker shades represent higher powers in the wavelet spectrum. The dominant period is the 1-year period for group 1 states (A) and a multiyear period for group 3 states (B). For the group 2 states, the 1-year period is originally dominant (C) but is replaced by a multiyear period after some transition time (D). The estimated timing of the transition in group 2 is given in Web Table 2.

lead to annual epidemics, while lower rates lead to multiennial cycles (33, 34). Seasonality generates annual cycles when its magnitude is small, with these cycles giving way to multiennial oscillations with increasing large-amplitude seasonality (27, 34).

Consequently, we selected household crowding and the fraction of people living in urban environments as potential determinants of transmission. In the absence of information on vaccine uptake during this era, the per capita birth rate remained our only indicator of the rate of recruitment of susceptible persons (susceptibles). The number of children per family was assumed to serve as an indicator of both susceptible recruitment and transmission within households. In states where multiennial epidemics, rather than annual outbreaks, were observed, we expected the fraction of families with no children to be higher and conversely the fraction with more than 1 child to be lower. Additionally, school attendance was considered as a potential indicator of both transmission between children and the amplitude of seasonality.

Historical per capita health spending was selected as a possible correlate for vaccine uptake during the early vaccine era. The other demographic characteristics that we considered were the mean population size, variation in population size, and variation in the birth rate. We also considered the latitude of the population centroid of each state and epidemiologic quantities such as the mean incidence and timing of seasonal peaks, quantified by the residual phase. The residual phase was calculated by extracting the phase from the wavelet decomposition and then subtracting the mean phase over all of the time series (35). This reflects the relative timing of the peak in each state as compared with the average timing of the peaks across the country.

In order to examine whether historical patterns may have influenced recent pertussis epidemiology, we compiled summary

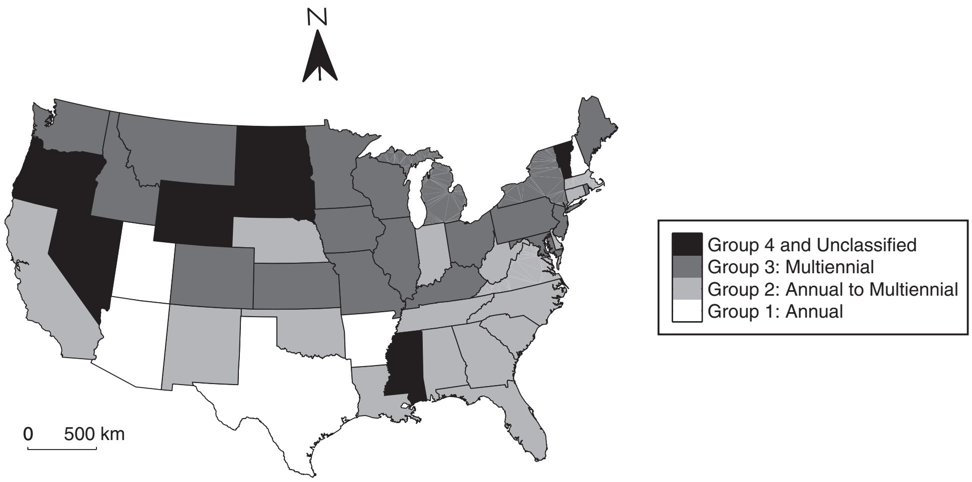

Figure 4. Classification of US states according to periodicity of pertussis outbreaks from 1938 to 1955. Oregon and Vermont are the only states in group 4 where the period displayed a transition from multiyear outbreaks to annual outbreaks—the reverse of the group 2 transition. Mississippi, Nevada, North Dakota, South Dakota, and Wyoming were not classified (refer to Web Appendix 3 for details).

features of pertussis incidence using the 1951–2010 NNDSS records. To characterize pertussis resurgence, we carried out segmented or piecewise linear regression analysis, wherein the independent variable (time) was partitioned into intervals joined at an unknown but estimated breakpoint, with independent slopes fitted to each interval (further details are available in Web Appendix 4 and Web Figure 1). Therefore, for each state, pertussis incidence could be separated into 2 intervals separated by a state-specific turning point, or breakpoint. This breakpoint was used as an indicator of the onset of resurgence in a given state and the associated slope of the subsequent linear regression as an indicator of its speed. We also calculated mean monthly incidence of pertussis per 100,000 people for each state from 2001 to 2010.

Analysis of variance (ANOVA) and the Kruskal-Wallis test were used to compare the values of the characteristics across groups. The differences in the underlying assumptions and implications of these 2 tests are discussed further in Web Appendix 5. To compare the residual phases of the annual outbreak periods, we used the circular versions of these tests. The mean values for each characteristic in each group are presented in Web Tables 3 and 4.

RESULTS

Interepidemic periods

Four distinct patterns of periodicity were detected in the 1938–1955 data (Figure 2), with states classified as follows. Group 1 consisted of 5 states in which epidemics were annual throughout the period (see Figure 2A and 2C for an example of incidence data and the associated dominant period of a group 1 state). Group 2 was comprised of 17 states in which a clear transition from annual epidemics to multiennial epidemics was observed (Figure 2B and 2D). Twenty states with consistent multiennial epidemics were categorized in group 3 (Figure 2E and 2G), while group 4 was populated by Oregon and Vermont, in which multiyear outbreaks gave way to annual epidemics (Figure 2F and 2H).

In Figure 3, we dissect the diversity of observed patterns in periodicity across states. Epidemics in states belonging to group 1 (Figure 3A) or group 2 before the transition (Figure 3C) were characterized by a significant dominant annual component alone. After the transition, however, group 2 states exhibited a range of periodicities from approximately 2 years to 6 years (Figure 3D). Similarly, interepidemic periods in states that were characterized by multiennial outbreaks throughout this interval (group 3) were found to vary from approximately 2 years to 5 years (Figure 3B). We mapped the classification of each state in Figure 4. This figure is visually suggestive of a latitudinal gradient in pertussis epidemiology, a suggestion that was confirmed by our statistical analyses (Figure 5). For comparison, we also present the periodicity of incidence data from 1951 to 1970 in Web Appendix 6 (refer to Web Figure 2). During this era, throughout the United States, pertussis epidemics were characterized by a strong 4-year signal, in addition to an annual component in group 1 and many group 2 states.

Comparison among groups

Results of the comparison of state-specific characteristics (outlined in Table 2) across groups are summarized in Figure 5. We found the following characteristics to be different between groups according to both ANOVA and the Kruskal-Wallis test: per capita birth rate, household crowding, the fraction of families with no children, the fraction of families with more than 1 child, latitude of the state population centroid, and recent pertussis incidence (from 2001–2010). In particular, group 1 states had higher per capita birth rates, more household crowding, and higher fractions of families with more than 1 child than states in group 3. The reverse relationship held for the fraction of families with no children. We found that group 3 states were mainly concentrated in the northern part of the country. Our results also indicated contemporary pertussis incidence to be highest among group 1 states and lowest in group 2 states.

ANOVA and the Kruskal-Wallis test generated dissimilar P values concerning group differences in mean population size, population size variation, school attendance, and the slope of resurgence. In these instances, the disagreement resulted from the presence of outliers (shown in Figure 5), which is inconsistent with the assumptions of ANOVA. Thus, conclusions based on the Kruskal-Wallis test are appropriate. For instance, consider school attendance. The outlier in group 3 is due to the very low (53%) school attendance in Kentucky. Removing this point from the analysis yields P values of 0.001 and 0.003 for ANOVA and the Kruskal-Wallis test, respectively, suggesting that school attendance is different between groups, with the values for group 3 being higher than those in group 1. Regarding population size and variation in population size, the Kruskal-Wallis test does not indicate any significant difference among groups.

Similarly, our statistical tests lead to contradictory conclusions concerning differences in 1938–1955 mean incidence among groups. Here, because none of the assumptions of either test are clearly violated, we cannot confidently conclude that differences in mean incidence exist among groups.

There were no differences among groups in population size, per capita birth rate, variation in population size, variation in birth rates, proportion of the population living in urban regions, per capita health spending, timing of the annual peaks in pertussis incidence, or the timing of the breakpoint.

Although group 4 was not included in the analysis, we note that the historical mean weekly incidence and recent monthly incidence of the group 4 states were 4.2 per 100,000 population and 0.9 per 100,000 population, respectively, both of which are higher than the group mean values of groups 1–3. Vermont contributed the higher values in both cases.

DISCUSSION

The resurgence of pertussis in some countries with high vaccine coverage has identified gaps in our understanding of the pathogen (5). In the United States, pertussis has rebounded in almost every state, yet the timing of its resurgence has been highly variable, spread out over 3 decades (36)—an observation that has yet to be explained. Part of the answer may lie in the differential historical epidemiology of the bacterium across states. Studies of a variety of infectious diseases have indicated that past patterns of transmission can have long-term consequences for disease dynamics due to their effects on the susceptibility profile of the population (18, 37–41). For this reason, we scrutinized records on pertussis incidence during the transition to routine infant immunization in the United States.

We began by examining the interepidemic periods of pertussis in the continental United States from 1938 to 1955. Using wavelet decomposition, we identified 4 distinct patterns of periodicity (Figure 4), according to which dynamics in each state were classified. We found that most commonly (20 group 3 states), pertussis epidemics during this era occurred 2–5 years apart. In a further 17 states (group 2), initially annual outbreaks gave way, by the late 1940s, to multiennial cycles, with a period ranging from 2 years to 6 years. Finally, 5 group 1 states exhibited annual epidemics throughout the time period.

We sought to explain these contrasting patterns among states assuming that they arose from differences in demographic and epidemiologic factors (Figure 5). For instance, epidemiologic theory predicts that annual epidemics can result from low transmission seasonality, high rates of baseline transmission, and rapid recruitment of susceptibles. Thus, we correctly predicted that school attendance and the proportion of families with no children would be lower in group 1 states than in group 3 states and that crowding, per capita birth rates, and the proportion of families with more than 1 child would be higher in group 1 than in group 3, with group 2 having intermediate values. Additionally, because per capita health spending correlates with estimates of pertussis vaccine uptake in the contemporary setting (see Web Appendix 7 and Web Figure 3), we predicted that group 3 states would be associated with higher historical estimates of health spending than states in group 1. While indeed the mean level of health spending in group 3 states was higher, the difference was not statistically significant (in Web Appendix 8, we use cross-validation to demonstrate the robustness of this conclusion to the removal of outliers). The remaining demographic covariates we examined were not significantly different across groups.

Our prediction on the association between periodicity and school attendance assumed the latter to be a surrogate for transmission seasonality (42, 43). However, in previous studies of seasonality in pertussis incidence (e.g., 1996–2006 in the Netherlands (44) and 1977–1982 in England and Wales (45)), investigators concluded that seasonality of pertussis incidence is not driven by the school calendar. Although these findings were based on data from other countries collected in different time periods, they indicate that alternative mechanisms may underpin our observed association between school attendance and periodicity. Specifically, because school attendance was inversely correlated with household crowding (regression slope 95% confidence interval (CI): −0.58, −0.29; adjusted $R^2 = 0.047$), our detection of a correlation may indeed be mostly due to the association with household crowding.

Somewhat surprisingly, the proportion of the population living in an urban area—which intuitively may be assumed to be a driver of transmission—was not significantly different across groups in either test. Subsequent analyses revealed a negative correlation between urban population and crowding within households (regression slope 95% CI: −1.57, −0.86; adjusted $R^2 = 0.53$). Hence, although a larger urban concentration could have provided greater opportunities for contacts and transmission between households, we found its main transmission impact to be neutral, perhaps as a result of improved living conditions in historical urban settings.

As an additional test of our conclusions regarding the influence of demographic factors in shaping pertussis epidemiology in the 1938–1955 data, we fitted a multinomial logistic model. As detailed in Web Appendix 9 (Web Table 5 and Web Figure 4), we classified states into group 1, 2, or 3 based on those demographic parameters that determine the susceptible recruitment rate, including the per capita birth rate and the fraction of families with no children. Reassuringly, the

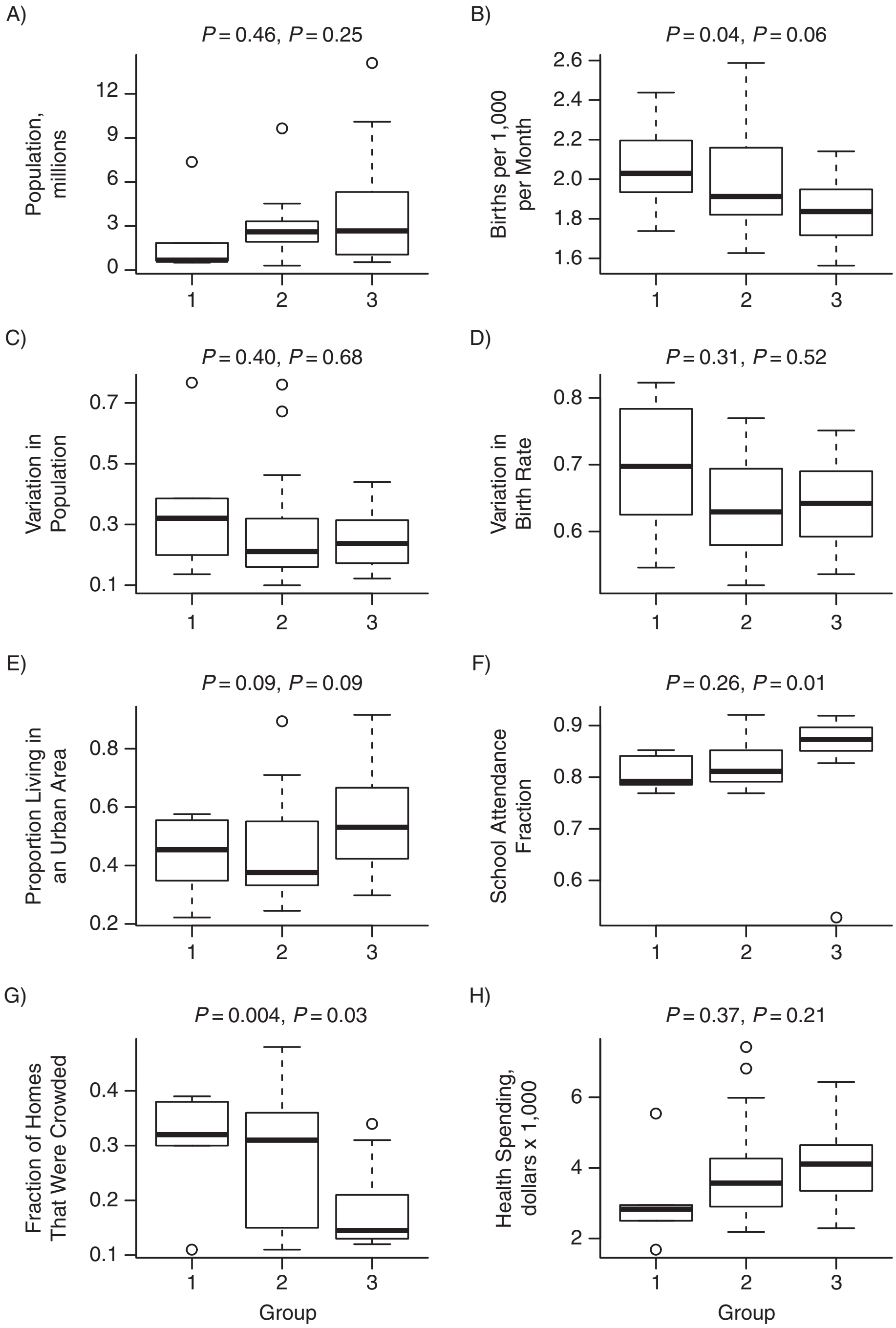

Figure 5 continues

signs of the model coefficients were consistent with the relationships described in Figure 5.

The next set of state characteristics we explored was that associated with the geography of states and the historical epidemiology of pertussis. Of these, latitude, historical weekly incidence, and the seasonal peak were significantly different across groups. We emphasize that historical pertussis incidence was higher in group 1 states than in group 3 states. Assuming comparable reporting fidelity across groups, this finding suggests higher rates of transmission in group 1, as also indicated by our analyses of demographic factors.

The association with latitude is intriguing. However, because of the negative correlations between latitude and household crowding (regression slope 95% CI: −36.6, −17.2; adjusted $R^2 = 0.42$) and per capita birth rate (regression slope 95% CI: −13.2, −1.3; adjusted $R^2 = 0.11$), we suspect

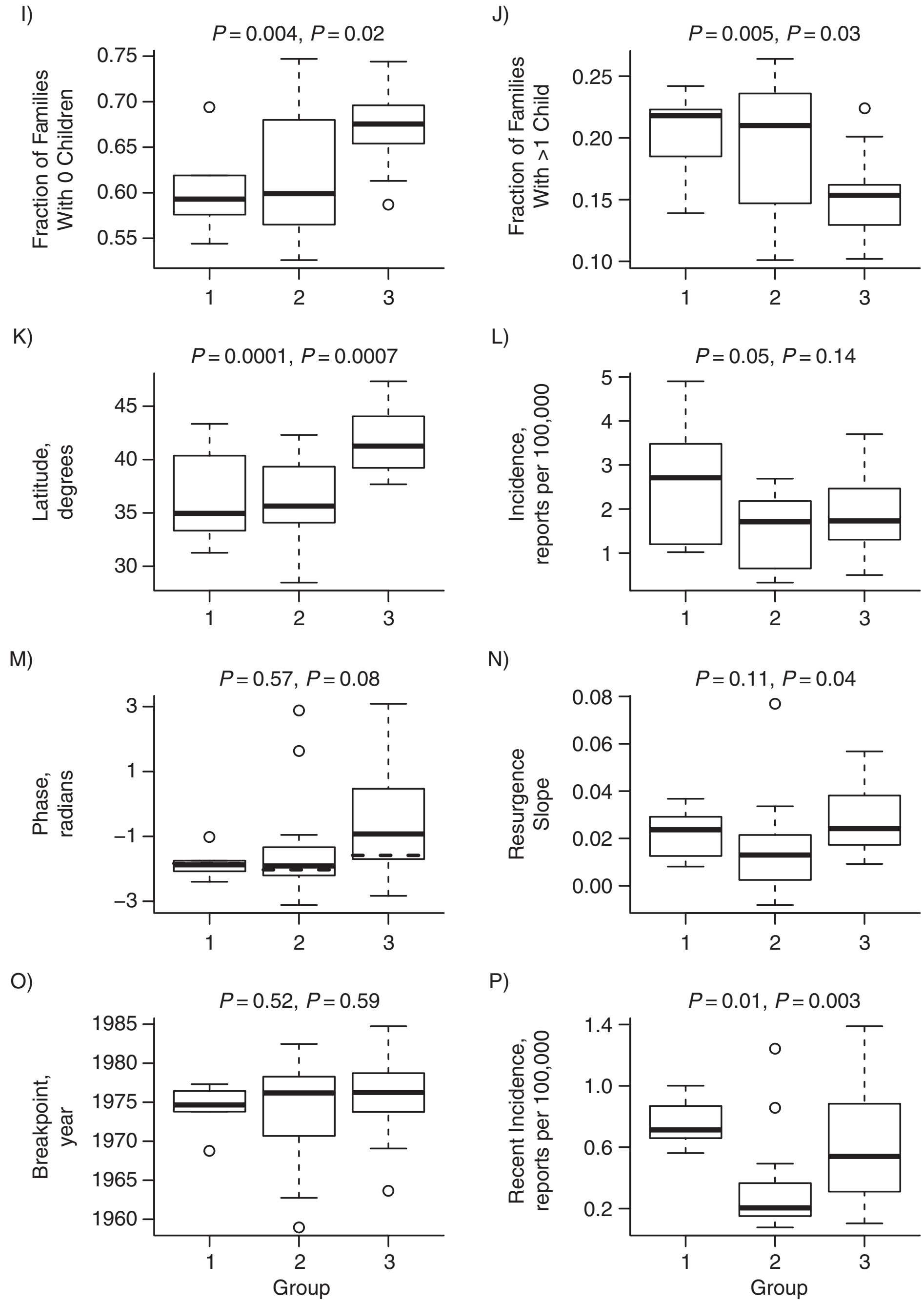

Figure 5. Comparison of the distribution of values for the characteristics listed in Table 2, according to state pattern of pertussis periodicity (groups 1–3) during the early vaccine era (1938–1955). In each panel, the first *P* value presented is from analysis of variance and the second is from the Kruskal-Wallis test. The whiskers represent the most extreme data points—no greater than 1.5 times the interquartile range. Variation in population (panel C) was calculated as change in population size from 1938 to 1955 relative to the mean population size. Variation in birth rate (panel D) was calculated as change in the monthly birth rate from 1938 to 1955 relative to the mean birth rate. For residual phase of the annual period (panel M), it was inappropriate to compare arithmetic mean values because phases varied from $-\pi$ to π; hence, we calculated circular means instead. (This involves conversion of the phase from an angle to a point on the unit circle, from which the arithmetic mean is computed.) The circular means for phase are shown with heavy dashed lines.

that the difference in mean latitude between groups may be due to these demographic differences among northern and southern states. Thus, we submit that differences in periodicity with respect to latitude may be more parsimoniously attributed to latitudinal demographic variation (46) than to climatic drivers, such as day length or average temperature (47).

Further analyses of geographical variation in US pertussis dynamics can be found in Web Appendices 10 and 11 (Web Figures 5–7).

We also attempted to relate the historical epidemiology of pertussis to recent pertussis dynamics. We compared summary measures of resurgence across groups by performing segmented linear regression on the NNDSS data from 1951 to 2000. This pinpointed the start date (the breakpoint) and the speed (the subsequent slope) of the resurgence. We also compared the 2001–2010 mean monthly incidence rates across groups. Interestingly, the slope of the resurgence and recent incidence were lowest for group 2 states. To better understand this finding, we explored the association between contemporary vaccine coverage (1995–2012) and historical grouping. As shown in Web Table 4, recent vaccine uptake is highest in group 2 states and lowest in group 1. If this hierarchy in coverage across groups was also in effect during the early vaccine era, and perhaps more pronounced, then it would likely explain the relationship between the historical grouping of states and recent resurgence and incidence. Lastly, there was no significant difference in breakpoints across groups.

To our knowledge, this is the first study of pertussis epidemiology in the United States during the early vaccine era. Despite the absence of information on vaccine uptake, we were able to paint a comprehensive picture of the epidemiology of pertussis during this period. Our analyses revealed how the dynamics of pertussis incidence are associated with state-specific demographic characteristics. In particular, in contrast to those states with multiennial epidemics, states in which pertussis incidence was rigidly annual tended to have higher per capita birth rates, greater household crowding, more children per family, and lower school attendance. These factors would lead to rapid recruitment of susceptibles, high transmission rates within households, and possibly a lower impact of school terms on transmission seasonality. Epidemiologic theory has shown these conditions to favor annual epidemics (33, 34, 48).

These findings add to the back-story of contemporary pertussis in the United States, providing clues as to the historical processes that have shaped its modern epidemiology. Finally, our analyses revealed substantial geographical variation in the patterns of pertussis incidence, highlighting the potential pitfalls of drawing conclusions based solely on analyses of national-level incidence data.

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