The decline and resurgence of pertussis in the US

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ABSTRACT

Although the resurgence of pertussis in nations with long-standing vaccination programs has raised serious concerns about the effectiveness of current immunization policy, the epidemiology of resurgence remains poorly understood. We analyzed pertussis notifications in US states obtained from the National Notifiable Disease Surveillance System from 1951 to 2010 to explore the timing, spatial pattern and consistency of resurgence across the country. Here we show that resurgence occurred at different times in different states, spread out over a transition period of roughly three decades. Further, despite this spatial variation, broad patterns in pertussis epidemiology can be described by two dominant phases: (1) a period of decline ending in the mid-1970s, followed by (2) nationwide resurgence. Together, these patterns explain 89.7% of the variation in US case notifications between 1951 and 2005. This resurgence was interrupted, however, by a synchronized downturn in 2005 that continues to the present in many large states. The causes of these two transitions in pertussis epidemiology remain hotly debated, though our findings suggest that evolution of the Bordetella pertussis bacterium, loss of immunity and persistent transmission among adults, and demographic drivers are more probable explanations than changes in reporting or the introduction of acellular vaccines.

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Introduction

Pertussis, or whooping cough, is a highly contagious respiratory disease caused by the bacterium Bordetella pertussis. Despite concerted and long-standing pediatric immunization programs dating to the 1950s, pertussis control in many developed nations remains a significant public health challenge. Perhaps the most high profile instance of pertussis resurgence has been observed in the US, where a clear increase in incidence has been observed over the past 30 years (Fig. 1A; Cherry, 2003; Hewlett and Edwards, 2005). Inevitably, this increase in incidence has led to alarm over its possible causes and skepticism about the effectiveness of pertussis control (Celentano et al., 2005; Forsyth, 2007; Forsyth et al., 2007; Halperin, 2007). Candidate explanations for these observed patterns may be grouped into two categories (Bamberger and Srugo, 2008; Wood and McIntyre, 2008). On the one hand, increasing incidence may reflect a rise in pertussis transmission, with potential underlying causes rooted in biology, including loss of infection and vaccine-derived immunity (Cherry, 2005; Wendelboe et al., 2005), vaccine efficacy (Cherry and Olin, 1999; Crowcroft and Pebody, 2006) and pathogen evolution (Bouchez et al., 2009; Mooi et al., 2001). Alternatively, it has been suggested that there is no re-emergence per se, but that increased awareness of pertussis by physicians, especially in adolescents and adults, coupled with improved laboratory methods for its detection, have resulted in reduced under-reporting and a more accurate picture of B. pertussis circulation in the population (Cherry, 2003, 2005).

Clearly, if pertussis incidence is increasing and is driven by a biological mechanism, the implications for vaccine development and pertussis control strategies will be significant. It is imperative, therefore, to explore which of these explanations is correct. This paper reports results of a quantitative analysis of pertussis incidence in the US over the past sixty years. We have three principal aims: (I) to document the systematic pattern of national increase in pertussis reporting over the past thirty years (the resurgence), (II) to capture the diverse and contrasting state-specific trends in the epidemiology of pertussis, and (III) to report a largely unnoticed recent decline in notifications.

Methods

Incidence data

We obtained from the National Notifiable Disease Surveillance System (NNDSS) publicly available fully anonymized monthly
pertussis notifications for the 48 contiguous US states and Washington D.C. from 1951 to the end of 2009 (Fig. 1A). Historical incidence data represent clinical case diagnoses. Since 1997, case confirmation has involved either an acute cough illness of any duration, with isolation of the bacterium from a clinical specimen, or a cough illness lasting ≥2 weeks, with either one of the following symptoms: (i) paroxysms of coughing, (ii) inspiratory “whoop”, or (iii) post-tussive vomiting or at least a polymerase chain reaction (PCR) positive for pertussis, or contact with a laboratory-confirmed case of pertussis. Parallel demographic data on population sizes were obtained from The US Census Bureau (Fig. 1B). Historical vaccine uptake estimates are obtained from Simpson et al. (2001), with uptake data since 1995 downloaded from the Centers for Disease Control & Prevention’s National Immunization Survey website (http://www.cdc.gov/vaccines/stats-survey/nis/default.htm#nis).

Statistical analyses

To statistically establish the presence of trends (decline, resurgence and downturn), we converted monthly case notifications (denoted by $N_t$) in each state to prevalence estimates ($P_t$) by dividing by the annual state population size ($N_t$). These prevalence data were then log10-transformed. To extract long-term trends, we used non-parametric seasonal decomposition and smoothing (function “stl” in the statistical software R, version 2.10.0) to extract seasonal ($S_t$), trend ($T_t$), and residual ($U_t$) components such that $P_t = S_t + T_t + U_t$.

An interesting outcome of this analysis was considerable variability in the pattern and timing of resurgence across states. We therefore next estimated the turning point in each state from 1951 to 2005 using segmented linear regression analysis of the nonseasonal components of transmission ($Z_t = U_t + T_t$), wherein the independent variable (in this case, time) is partitioned into intervals joined at unknown but estimated breakpoints with independent slopes fitted to each interval. Thus, for each state, pertussis prevalence from could be separated into two intervals separated by a state-specific turning point. Periods of statistically significant increase or decreases in incidence are defined as those segments of the piecewise regression model with slope coefficients different than zero. Significance of changes in slope was determined using the Davies’ test, which is based on Wald statistics. In this case, the $p$-value is an upper bound.

Results

Patterns of pertussis prevalence through time

As expected from more casual analyses (Hewlett and Edwards, 2005), the single most consistent and uniform feature of these data is a pronounced and steady decline in reported pertussis cases in each state from 1951 until a turning point occurred, typically 20 or more years later. As shown in Fig. 2, national prevalence reached its minimum in 1976 (Davis et al., 1992), after which a pronounced and statistically significant rise was detected.

This broad national trend masks substantial state-by-state variation. Segmented regression showed that 89.7% of the national variation in case notifications between 1951 and 2005 can be explained by representing pertussis epidemiology as having two
phases. The timing and severity of the transition between these phases varied considerably among states, however. As shown in Fig. 2B–G, in some states (such as Louisiana and Florida) there was a notable decline in pertussis until the turning point (1960 for Louisiana and 1976 for Florida), after which incidence remained steady until 2005 since which point incidence has decreased. In a number of states, including Texas, there was a very slight (though statistically significant) rise in prevalence during the 1980s, which gave way to increases in the 1990s. By contrast, in other, primarily large populous states (e.g., New York, California and Massachusetts), resurgence has been steady since the turning point. Although the national pattern has been noted, these differences among states have been previously overlooked.

Our analyses further reveal, as far as we are aware for the first time, that pertussis reports in many large states have declined significantly over 2004–2007 (inset, Fig. 2A). While the resurgence has received considerable attention in the pertussis literature, the recent downturn appears to have gone surprisingly unnoticed. This national pattern is the result of declines in 24 out of 48 states, including Massachusetts and New York. Nationally, this downturn represents a reduction in total reported cases of 59% between 2005 and 2007. Fifteen states not conforming to this pattern are concentrated primarily in the Deep South, where the initial resurgence was notably less pronounced. Despite this overall downturn, prevalence in 2007 was an order of magnitude greater than the minimum reached in 1976. Over the past four years, pertussis prevalence has increased in many states, including California, where a large outbreak was reported in 2010. It remains to be seen whether changing pertussis epidemiology over the past 10 years is indicative of a shift to a new, predictable oscillatory regime, with a five-year period.

Finally, to quantify the spatial variation in pertussis epidemiology, we mapped transmission trends (decreasing, flat or increasing)
over successive intervals (Fig. 3). This figure decomposes the national trends illustrated in Fig. 2 into space-time components. Consistent with the temporal pattern shown in Fig. 2, reported pertussis cases were declining in all states but Louisiana during the 1960s (Fig. 3A). The resurgence started with a handful of states in the 1970s (Fig. 3B), specifically New Jersey, Georgia, Kansas and New York. By the 1980s, pertussis cases in most states were increasing (Fig. 3C), a pattern that continued into the 1990s with the exception of a group of Southeastern states (Fig. 3D). The contrast between Fig. 3E and F illustrates that the reversal in case notifications was synchronized across most of the country, in sharp contrast to the earlier resurgence of the 1970s.

For comparison, the variation in this earlier turning point may be quantified by inspecting the fit coefficients from the segmented regression analysis. The would describe when the turning point occurred in each state and the regression slopes before and after this event. As shown in Fig. 4A, there was substantial variation in the timing of the turning point in pertussis trends, though the most commonly observed breakpoint (observed in twenty states) occurred in 1976. We emphasize that breakpoints characterize the time at which a significant change in pertussis trends occurred and that the shift may be from declining to flat (e.g., Florida; Fig. 2B), or from decreasing to increasing (e.g., California and New York; Fig. 2A and E) or simply reflect a reduced rate of decline (e.g., Louisiana; Fig. 2C). Fig. 4B quantifies the change in case notification trends from before to after the turning point. Finally, to examine possible spatial clustering, we map breakpoints in Fig. 4C, which illustrates the absence of geographical structuring in the turning point.

Conclusions

Understanding the epidemiology of pertussis is urgent because it remains a major cause of infant morbidity and mortality worldwide (Crowcroft et al., 2003). Worryingly, over the last twenty years, a number of countries with high vaccine uptake levels have reported an increase in pertussis incidence, with the US perhaps the most frequently cited among them (Bamberger and Srugo, 2006; Celentano et al., 2005; Forsyth et al., 2007; Mooi, 2009; Wood and McIntyre, 2008). Furthering our understanding of the reasons for the observed increase in incidence is crucial because it will
In the US (Cherry, 2003). (IV) Finally, the waning of infection- and especially vaccine-induced immunity has been thought to be culpable. Some argue that infection-induced immunity is typically long lasting, while the immunity resulting from vaccination is much shorter (Wendelboe et al., 2005), while others suggest that waning of immunity has become more common in recent years due to decreased transmission and thereby decreased natural boosting (Águs et al., 2006). The assumptions inherent in these explanations are not universally accepted (Cherry, 2005) and the determinants of protective immunity (Hallander and Gustafsson, 2009; Mills, 2001) and its duration (Broutin et al., 2004, 2010; Rohani et al., 2010; Wearing and Rohani, 2009; Wendelboe et al., 2005) are both important research questions that continue to receive attention.

In this paper, we have made use of incidence data from the NNDS in an attempt to paint the most accurate picture of pertussis in the US to date. We report a number of consistent features of these data, including an almost universal decline in pertussis incidence throughout the 1950s and 1960s, a dramatic increase in the 1980s and a striking downturn 2005–2007. Despite these broad natural patterns, we have documented substantial variation between states in the onset of the resurgence, with a delay exceeding two decades between the states exhibiting the earliest and the latest turning points. We conclude that if improvements in diagnostic capabilities and reporting fidelity were primarily responsible for the resurgence in pertussis cases, we would have expected a reasonably consistent pattern of re-emergence across states. Similarly, observation-based explanations would not have predicted the occurrence of a turning point in pertussis notifications, let alone the most recent downturn. Therefore, we are led to conclude that pertussis resurgence in the US is most likely due to biological conditions. The distribution of estimated state-by-state turning points (Fig. 4C) rules out efficacy-related concerns over acellular vaccines as a general explanation since all states showed a resurgence a decade before the acellular vaccine was licensed for use in the US. It is worth pointing out that mouse models demonstrate that acellular vaccines do not protect against Bordetella parapertussis Long et al. (2010), leaving open the possibility that some cases post-1991 attributed to pertussis may in fact be due to parapertussis. Hence, of the candidate explanations, the evolution of the bacterium (II), vaccine efficacy (III) and waning immunity (IV) remain.

A concern with any based on reported cases, including ours, is the impact of under-reporting and systematic biases in notification fidelity. Indeed, this is precisely the claim of explanation (I) and recent research has estimated that reported pertussis cases in the US may represent only 11.6% of true infections (Sutter and Cochi, 1992). However, an arbitrary or ad hoc reporting process would lead to scattered and unstructured data, whereas the NNDS data contain several clear patterns: (i) strong and consistent trends in incidence; (ii) a pronounced periodic signature, with a statistically significant inter-epidemic period of four-years in most states from 1950 to 1970 and 1980s onwards (Choisy and Rohani, in preparation); (iii) spatially structured outbreaks, with clear waves of epidemics sweeping across the continent (Choisy and Rohani, in preparation). For these reasons we believe our overall qualitative conclusions to be robust, despite imperfections in the data.

Finally, to the list of potential explanations we add a fifth candidate: population demography. Standard epidemiological theory (Anderson, 1991; Keeling and Rohani, 2008; Anderson and May, 1982; Anderson et al., 1988; Nguyen and Rohani, 2008) predicts substantial changes in disease incidence as a function of systematic changes in the rate of recruitment of infection-naïve individuals. In the context of the resurgence in the US, this would point to the examination of factors including state-specific birth rates, population expansion (resulting from immigration), trends in vaccine uptake and access to non-medical exemptions (Omer et al., 2006). Direct evidence for this explanation is not yet available. The severe
decline in per capita birth rate between the late 1950s and early 1970s coincides almost exactly with the rollout of the first pertussis vaccines (Fig. 1B), precluding meaningful statistical analysis. Similarly, the only event that might enable statistical detection of effects due to gross immigration is a spike in immigration around 1990 (Fig. 1B). But this burst is believed to reflect primarily legalization of illegal immigrants that arrived over the previous decade. However, indirect support for this explanation comes from the study of Tanaka et al. (2003), which found that patterns of immigration and aspects of ethnic and economic disparities correlate with a differential in the incidence of pertussis in infants in the US. Identifying the sources of data (both epidemiological and demographic) to enable a rigorous statistical analysis of these potential explanatory variables is a research priority.

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