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Core pertussis transmission groups in England and Wales: A tale of two eras

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ABSTRACT

The recent resurgence of pertussis in England and Wales has been marked by infant deaths and rising cases in teens and adults. To understand which age cohorts are most responsible for these trends, we employed three separate statistical methods to analyze high-resolution pertussis reports from 1982 to 2012. The fine-grained nature of the time-series allowed us to describe the changes in age-specific incidence and contrast the transmission dynamics in the 1980s and during the resurgence era. Our results identified infants and school children younger than 10 years of age as a core group, prior to 2002: pertussis incidence in these populations was predictive of incidence in other age groups. After 2002, no core groups were identifiable. This conclusion is independent of methodology used. Because it is unlikely that the underlying contact patterns substantially changed over the study period, changes in predictability likely result from the introduction of more stringent diagnostics tests that may have inadvertently played a role in masking the relative contributions of core transmission groups.

1. Introduction

Pertussis (whooping cough) is an extremely contagious vaccine-preventable respiratory disease [1–4]. In England and Wales, following the introduction of routine immunization in the 1950s, pertussis incidence decreased dramatically [5–7] and although not eradicated, steadily faded from the public consciousness [2,7]. However, a national pertussis outbreak was announced in April 2012, despite high vaccine coverage [4,8–11], characterized not only by increased incidence but also a spate of pertussis-related infant deaths [8,10,12].

An interesting feature of this resurgence has been the notable shift in the age-distribution of cases: what had historically been regarded as primarily a childhood disease, is now encompassing all age groups, with increasing incidence trends in adolescents and adults [2,4,11,13,14]. These events have reignited a debate regarding changes in those key age groups that may contribute disproportionately to transmission, with teenagers proposed as the new "drivers" of recent epidemics [11,15–18]. The concern over the transmission contribution of teenagers was, in part, responsible for the roll out of the Tdap booster vaccine in the US and other countries [10,18,19].

A greater contribution to transmission by core groups, perhaps due to higher contact rates or lower immunity, may consequently translate into their over-representation in incidence reports as an epidemic takes off. Thus, identifying potential sentinel age cohorts that may be driving transmission could be central for a re-evaluation of control strategies. Hence, we attempted to harness this information from age-stratified incidence reports in order to quantify the relative transmission contribution of different age cohorts [20]. We analyzed pertussis case reports in England and Wales, collected through the Notifications of Infectious Diseases (NOIDs), for the period 1982–2012, during which a pre-school booster was introduced (late 2001) and the whole cell vaccine was replaced by an acellular vaccine (2004) [7]. We submit that systematic shifts in the transmission network of pertussis would translate into detectable changes in the age-stratified patterns of its incidence through time. In this regard, NOIDs data by virtue of their longitudinal span across changes in vaccine type used may be especially informative.

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We applied three independent statistical techniques, each aimed at identifying potential core groups driving outbreaks. These methods were: (I) Correlation analysis – which quantifies linear associations between reported incidence in different age groups [21]; (II) Transfer entropy – developed in the field of information theory [22], provides a measure of predictability in the incidence of each age group, given information regarding the kinetics of other age classes; and (III) Relative risk analysis - which calculates the ratio of the probability of an event occurring in one group to the probability of it occurring in another group [20,23].

Using all three methods, we contrast potential changes in age-specific drivers of pertussis transmission by exploring incidence records before and after the introduction of the acellular vaccine booster in October 2001, and the introduction of serological and PCR diagnostic methods in late 2001. This highly resolved, long-term epidemiological dataset allows us to determine transitions and patterns, that otherwise might have been overlooked. Key groups may vary in time due to many factors; from behavior changes that impact actual transmission patterns, to changes in reporting fidelity and statistical artifacts.

2. Methods

2.1. Data sets

We used the Notifications of Infectious Diseases (NOIDs), collected by Public Health England (PHE) – weekly incidence data stratified by age (in months if under 1 year old, in years otherwise) reported in England and Wales from 1982 to 2012. The weekly cases in each age group are plotted in Fig. 1, along with the total cases by week, and the mean cases in each age group and estimated vaccine coverage (available from Public Health England [11]). During the time period (1982–2012) of our study, two vaccines were in use for routine immunization: the whole cell vaccine (1982–2004) and the acellular vaccine (2004 onwards) [7]. An accelerated primary schedule was introduced in England and Wales in June 1990, shifting from a 3, 5, 11 month schedule to a 2, 3, 4 month schedule [7]. In 2001, a pre-school booster was introduced for children between 3½ and 5 years of age [7].

An enhanced surveillance scheme for pertussis infection (based on laboratory-confirmed cases with epidemiological follow-up) was established in 1994. Since 2001, serology and PCR have been used routinely to diagnose pertussis, especially in adults and adolescents [7,34]. Prior to this date, cases were conventionally confirmed by culture only, a method not as sensitive as the newer ones, but more specific [34].

2.1.1. Wavelet analysis

In order to investigate the periodicity of pertussis epidemics over this period, we used wavelet analysis [24,25] to decompose time series and to detect the dominant frequencies through time. Wavelets are especially powerful when time series data are inherently non-stationary [26–28]. For this analysis, we used the Morlet wavelet of log-transformed total weekly cases. Further details provided in the supplementary material.

2.2. Statistical analysis

We used three independent statistical approaches, each subject to assumptions and limitations (for details refer to [21,22,29]). The purpose of these methods was to identify the existence of key age groups driving outbreak waves, as well as, how incidence in specific age groups may provide information regarding changes in other age groups.

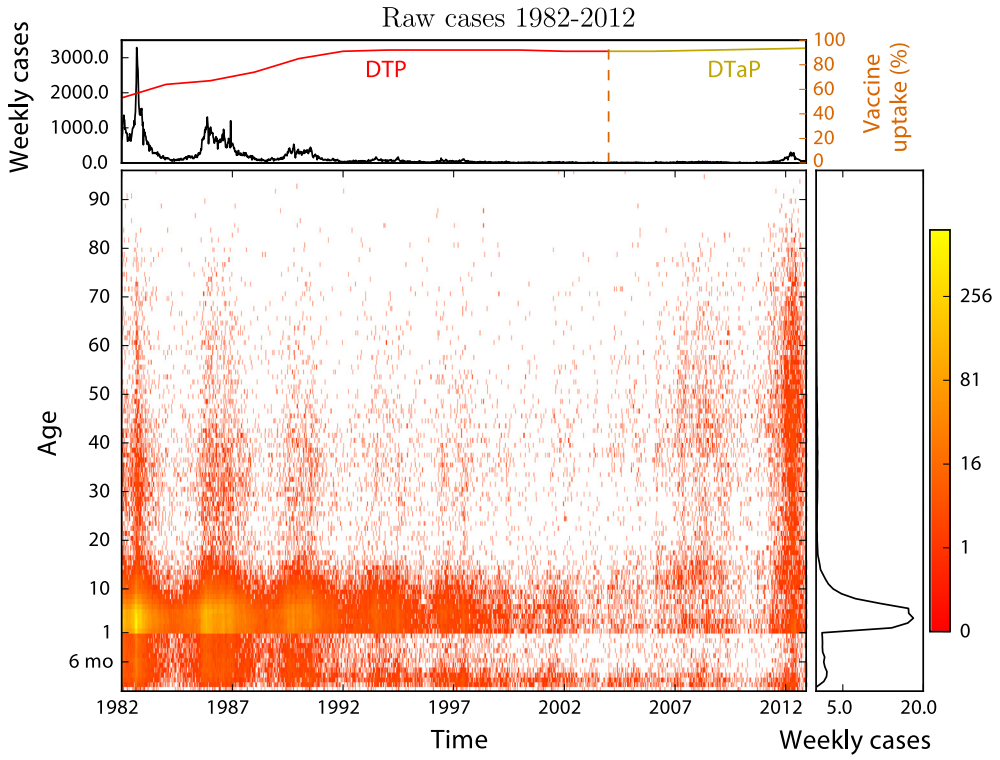

Fig. 1. Weekly cases of pertussis by age in England and Wales. The total cases each week and vaccine coverage for both DTP and DTaP are plotted in the top panel. The heat map in the bottom left panel depicts the cases reported each week and age group, with white indicating zeros, and the colors from red to yellow with increasing cases. The mean weekly cases in each age group are plotted in the bottom right panel. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.2.1. Rolling windows

We calculated the mean and standard deviation of pertussis incidence using a four-year rolling window [29], to assess the time series stationarity over time and to illustrate possible structural differences between distinct time periods.

2.2.2. Correlation structure

Let $X_i(t+\mathrm{L})$ be the incidence at week $(t+\mathrm{L})$ in age group i and $X_j(t)$ be the incidence at week t in age group j, where $L \in \{0,1,2,3,4\}$ is the time lag in weeks. We calculated the correlation coefficients [21] between age group i and age group j, using the range of values of L, in an attempt to identify the signal of transmission. For details on the Pearson's correlation, see supplementary information (Eq. S1).

2.2.3. Transfer entropy

The transfer entropy [22] from incidence in age group i ($X_i(t)$) to age group j ($X_j(t)$) quantifies the improvement in predictions about $X_i(t)$ that result from knowledge of the history of $X_j(t)$, given prior knowledge of $X_i(t)$. It relies on the Shannon entropy, which measures the expected information value of a signal [30], in this case a time series of pertussis incidence in an age group. This concept can then be extended to consider the difficulty of predicting $X_i(t)$, given the additional information in $X_j(t)$, which is the conditional entropy of $X_i(t)$ given $X_j(t)$. For simplicity of notation we rename $X_i(t)$ as $X(t)$ and $X_j(t)$ as $Y(t)$. Conditional entropy is thus:

$$H(X_t|Y_t) = \sum_{(x,y)\in(X_t,Y_t)} -p(x,y)log_2p(x|y) \quad (1)$$

The transfer entropy is expressed in terms of conditional entropies of the time series $X(t)$ and $Y(t)$

$$TE_L(X_t,Y_t) = H(X_{t+L}|X_t) - H(X_{t+L}|X_t,Y_t) \quad (2)$$

where $L \in \{0,1,2,3,4\}$ is the time lag of interest. For each pair of age groups, we calculated the transfer entropy with a history of a single week, binned into categories from zero to very high (See supplementary materials for details of the calculation). For example, the transfer entropy from infant case data to adults informs whether we can better predict future adult incidence given the past week's incidence among infants in addition to information gained from the number of cases in adults over the past week. However, if the Shannon entropy of that time series is very low to start with, additional clues will not provide further information. This may occur if, for instance, adult and infant cases track each other perfectly, since the adult incidence time series already contains all the information. Finally, in the event transfer entropy from infants to adults is greater than zero, the past cases in infants predicts future adult incidence better than past adult cases alone.

2.2.4. Age specific relative risks during an outbreak

We further attempted to characterize the role of different age groups by comparing the patterns of incidence before and after the epidemic peak, as recently proposed by Worby et al. [20]. It relies on identifying the pre- and post-peak phases of an outbreak.

2.2.4.1. Defining periods. We defined the peak week, as the calendar week in two specific outbreak years, 1982 and 2012, with the highest total number of recorded cases. Because the data are noisy and do not have a consistently timed annual peak, we characterized the pre- and post-peak periods by smoothing the data using a cubic spline with 3 knots. The pre-peak represents the "take off" period before the peak of the epidemic. The post-peak is the "tail" of the epidemic and was determined by the same method using the cut off week with the emergence of a smaller peak in incidence. We confirmed that our choice of the pre- and post-peak periods was robust to alternative methods such as a generalized additive model (GAM) [31] and segmented regression [32] (see Fig. S9).

2.2.4.2. Relative risk calculation. We estimated the relative role that different age groups play in the transmission of pertussis infection by splitting the population into groups. The relative risk for each age group was defined as:

$$RR(i) = \frac{B(i)}{A(i)} \quad (3)$$

where $B(i)$ is the proportion of cases in age group i over the total cases in the pre-peak period and $A(i)$ is the proportion for the cases in that same age group i over all cases during the post-peak period. The 95% confidence intervals were calculated for relative risk following Lachin [23], where $\ln(RR(i))$ is approximately normal.

In the pre- and post-peak periods, we calculated the fraction of cases which occur in each age group. We estimated the relative risk for each age group according to Eq. (3), which quantifies the probability of a specific group being at high risk before the epidemic takes off compared to post peak period. Thus, comparing the periods before and after the epidemic's peak. This allows us to account for the difference in overall incidence between age groups and between pre- and post-peak periods.

2.2.4.3. Odds ratio calculation. In order to compare the extent to which different age groups are overrepresented in the pre-peak period, we can look at the odds-ratio between pairs of these relative risks of two different age groups. This gives us a relative measure of effect, allowing us to compare between age groups. We estimate the odds ratio to characterize which age group, when compared with another age group, shows a more pronounced susceptible depletion during the period approaching the outbreak - pre-peak period [20]:

$$OR(i,j) = \frac{RR(i)}{RR(j)} \quad (4)$$

where i and j are age groups as defined for the previous methods. The 95% confidence intervals were calculated for odds ratios following Lachin [23], where $\ln(OR(i,j))$ is approximately normal.

3. Results

3.1. Data and wavelet analysis

In Fig. 1, we present weekly pertussis cases between 1982 and 2012, together with the estimated whole cell (DTP) and acellular vaccine (DTaP) vaccine coverage (top panel). Vaccine uptake in England and Wales recovered from a low of 31% in 1976 to reach 93% in 1991, and has subsequently continued to increase. A predictable association is observable between vaccine coverage and pertussis periodicity. Up until the early '90s, pertussis presented 3½ -year epidemic cycles. As vaccine coverage steadily increased, however, there was both a decline in the amplitude of pertussis epidemics and a reduced propensity for cyclicity.

The heat map (Fig. 1, bottom panel) depicts weekly incidence through time by age group. During the first decade, prominent recurrent 3½-year cycles - synchronized across all age groups – are apparent. When incidence was high, young children between 1 and 10 years of age were the most affected. After 2002, notification numbers were lower and more evenly spread between age groups. This is especially obvious in the latter years, with 2012 showing increased incidence in older age classes. The bottom right panel shows the mean weekly cases across age, reflecting age of infection with increased incidence in ages between 1 and 10 years old.

The mean and variance of total weekly case reports varied markedly over the three decades of data. In Fig. 2A, we plot the mean and standard deviation of weekly cases, calculated in a rolling window. There is a steady decline in mean weekly cases over time, reaching a nadir in 2004, after which a steady increase was evident. In addition, the age distribution of cases also changed considerably (Fig. 2B). Before 2002, most cases were among young children. Post-2002 there was a marked increase in pertussis notifications in older individuals. While proportions are still higher in school-age children, increased proportions of cases in infants, adolescents and adults were observed (Fig. 2B). Wavelet analysis identified distinct periods, with 1982 until the early 2000 s characterized by 3.5-year cycles and low-amplitude aperiodic fluctuations afterwards (Fig. 2C). Through the calculation of the number of weeks with zero reported cases, particularly among older age groups, clear changes in the age distribution of cases were visible, with a shift in incidence to older age groups post-2002 (Fig. 2D).

3.2. Correlation structure

To remove effects of periodicity and synchrony in the correlation structure presented in Fig. 2C, we calculated these correlations by age in a four-year rolling window and plotted the average correlation found pre-2002, post-2002, and overall for each pair of age groups (Fig. 3).

In the pre-2002 period, 1–10 year olds dominated the correlation structure in the raw data (Fig. 3A). The cases among any of the 10 age groups within the 1–10 year olds were strongly correlated with future cases in other 1–10 year olds. Cases in 1–10 year olds also correlated with cases in other age groups. The strongest correlations were among school aged children and between cases in unvaccinated infants and future cases in unvaccinated infants, school aged children, and adults (Fig. 3B). In the post-2002 era, the correlations between age groups were weaker overall (Fig. 3B). There was also some correlation between cases in adults and future cases in adults, toddlers and unvaccinated infants (Fig. 3B). Correlation structure in these two periods were similar at 2–4 week lags (see Figs. S4, S5, and S6).

3.3. Transfer entropy

The pair-wise transfer entropy among age groups before 2002 (Fig. 4A), illustrated a "bowtie" shape centered around 5 year olds. Thus, in order to predict the cases in an age group, it is useful to know recent cases in any age group closer to 5 year olds. This is

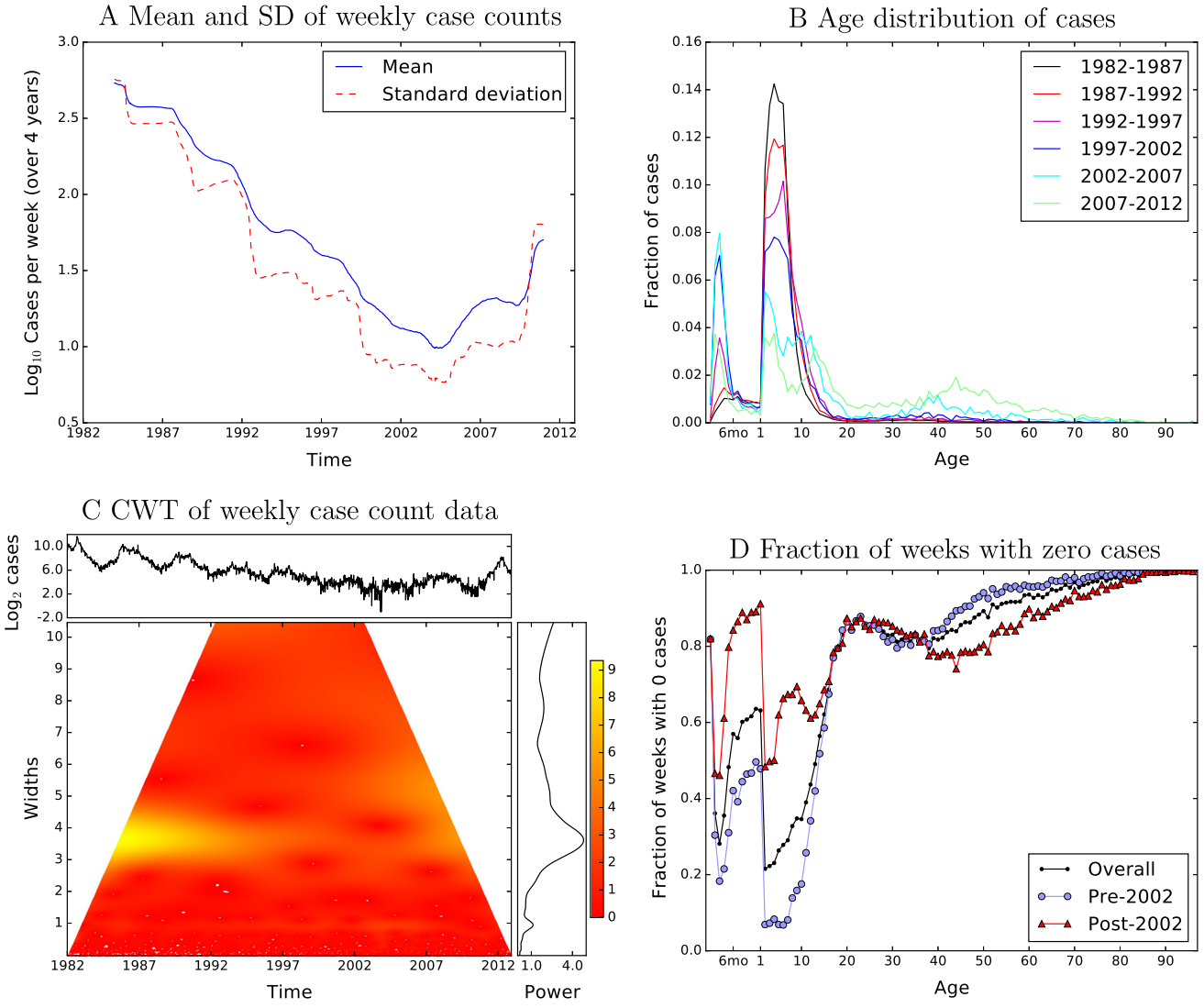

Fig. 2. (A) The mean and standard deviation in the number of weekly cases over a four-year rolling window plotted against time. (B) The age distribution of cases for 5-year intervals (with specific colors) from 1982 to 2012. (C) Continuous wavelet transform of log transformed total weekly cases (using the Morlet wavelet). (D) Plot of the fraction of weeks with zero cases in each age group. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

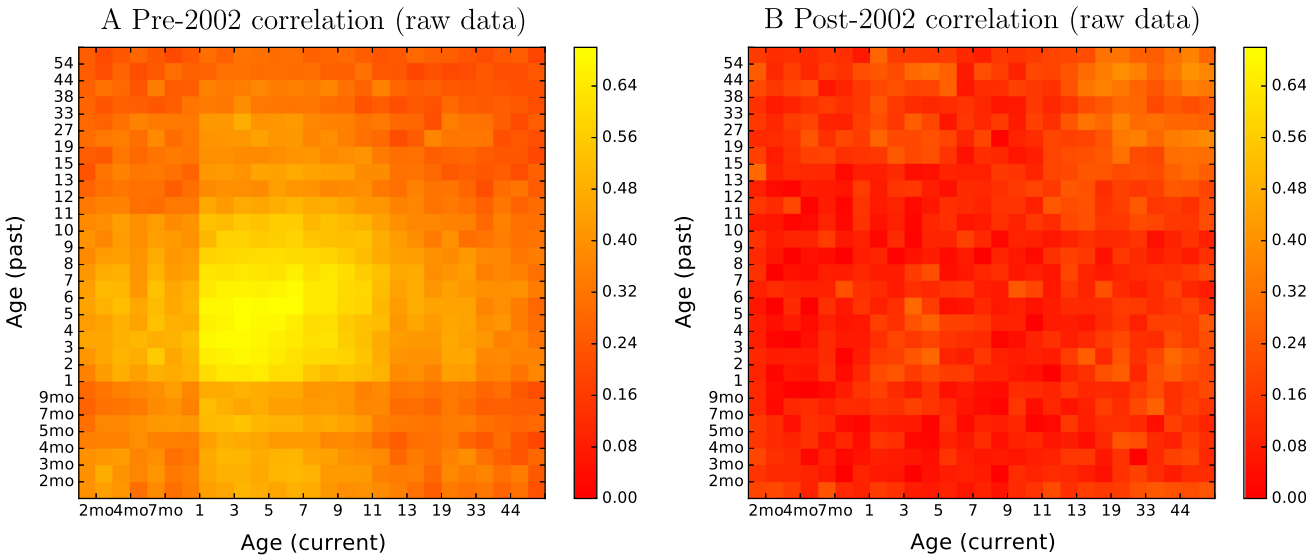

Fig. 3. Correlation coefficient between cases at a lag of one week in a rolling 4-year window, averaged before 2002 (A), and after 2002 (B).

consistent with scrutiny of weekly case reports, where 5 year olds were on the leading edge of outbreaks, with other age groups fanning out behind (Fig. S1).

In the post-2002 era, the number of cases in adults was informative in predicting future incidence in toddlers, unvaccinated infants and other adults (Fig. 4B).

3.4. Age specific relative risk

Table 1 presents the estimates of the relative risk (*RR*) in each age group. High values of *RR* were estimated for children between 1 and 10 years of age, with the highest values for 6–10-year-olds for the 1982 outbreak.

Table S1 provides a pairwise comparison of age groups, the odds ratios (*OR*), possibly indicating that young children (1–10-year-olds) were a key group in the epidemic. Worby et al. [20] described this higher risk as a measure for experiencing a significant depletion of susceptible pool during the outbreak take-off (pre-peak) period when compared to the other age groups, with risks among 6–10 years old significantly higher. Like the pre-2002 transfer entropies, in 1982 the pre-peak relative risk of an age group was higher the closer that group was to ages 6–10 years old, suggesting that school-aged children were on the leading edge of the outbreak

Table 1
The total number of cases, relative risk RR and 95% confidence interval for each age class in the pre- versus post-peak periods during the 1982 national outbreak.

Age group (years)	Pre-Peak	Post-Peak	RR
<1	1341	1751	0.85 (0.79, 0.91)
[1–3)	4017	4662	0.95 (0.92, 0.99)
[3–6)	7259	7465	1.08 (1.05, 1.11)
[6–10)	2858	2764	1.14 (1.09, 1.20)
[10–15)	432	560	0.85 (0.75, 0.97)
[15–20)	61	141	0.48 (0.35, 0.65)
[20–40)	228	452	0.56 (0.48, 0.65)
>40	92	212	0.48 (0.38, 0.61)
Total	16,288	18,007	–

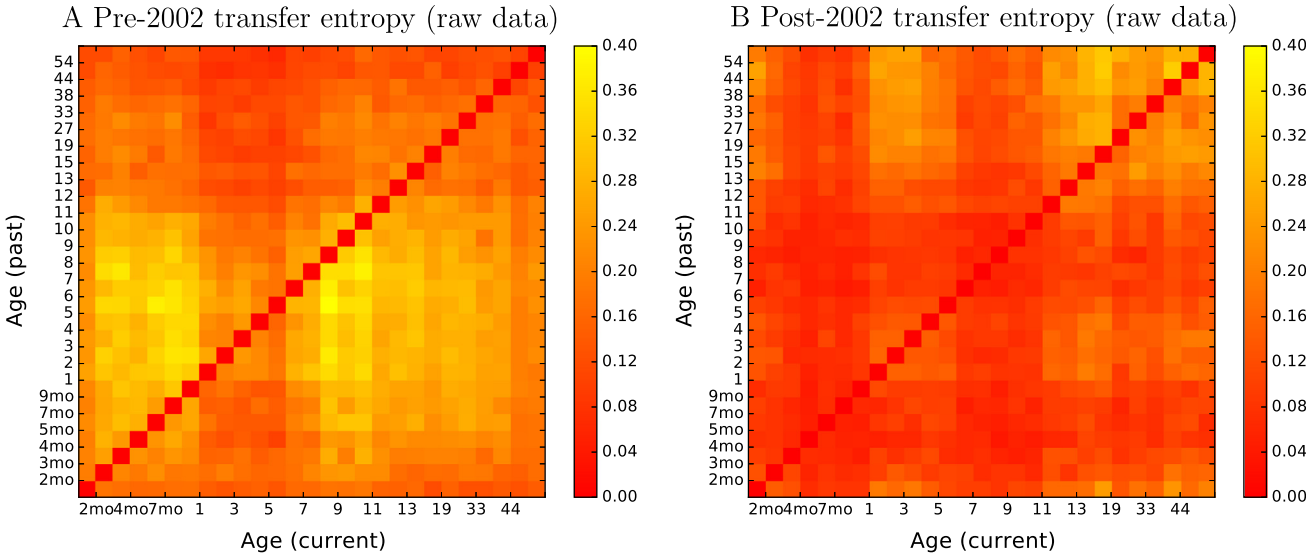

Fig. 4. Transfer entropy at a lag of 1 week, before 2002 (A) and after 2002 (B). For the purposes of calculating transfer entropy, case data is binned into 9 bins: one bin for zeros, and eight equally dividing the remaining non-zero week.

(Table S1). Similar to the transfer entropy analysis for post-2002, for the 2012 outbreak the relative risk and odds ratio no trends were observed (Tables S2 and S3).

4. Discussion

In recent years, England and Wales has witnessed an alarming rise in whooping cough incidence. Trying to understand the underlying mechanisms responsible for the resurgence is only a part of the puzzle [35]. Successful countermeasures will require pinpointing the optimal age groups to be targeted. Presently, there is no consensus on which age group is driving pertussis epidemics, presenting a challenge to public health practitioners [7,8,33]. One clue may lie in the changing age-distribution of pertussis (Figs. 1, 2, S1 and S2), characterized by a shift to higher incidence among teens and adults, with infants too young to be vaccinated remaining at risk [10].

The NOIDs dataset allowed us to document changes in age-specific epidemiological patterns over time (1982–2012) in response to changes in surveillance and vaccination policy. In general, outbreaks were highly synchronized among age groups (Figs. 1 and S9). In addition to synchrony among age groups, pertussis notifications in England and Wales during the vaccine era have previously been shown to be highly spatially synchronized [5].

The correlation and entropy methods clearly show that before 2002, children 1–10 years old were the most useful sentinel age-group for making short-term predictions about pertussis incidence in other age groups (Figs. 3A, 4A, S4A, S5A, S6A). Subsequently, the relative risk and odds ratio analyses examined the relative change, in the proportion of each group pre- and post- the 1982 epidemic peak, allowing us to further understand the roles of age groups (Table 1, S1, S2, S3). Our results suggest that, in the 1982 outbreak, school children, specifically 6–10-year-olds, played a greater role in the outbreak (Table 1 and S1), leading us to propose that school children with higher *RR* statistic may have played a driving role in the outbreak. This result is in keeping with our core group hypotheses from the entropy analysis (Fig. 4A).

The picture is not so clear post-2002. In this period, pertussis cases in unvaccinated infants, toddlers, and adults were better predicted by recent cases in adults, while cases in 1-10-year-olds were relatively uninformative (Figs. 3B, 4B, S4B, S5B, S6B). Both correlation structure and transfer entropy agree (Figs. 3 and 4). The relative risk and odds ratio method complements these results. The 1982 trend is absent in the 2012 outbreak (Tables S2 and S3). There are of course limitations to the relative risk analysis; we can only compare these two periods if we assume that reporting rate within each age class over time and locations remain constant. While this assumption seems reasonable within one outbreak, between outbreaks less so. These national findings might also not reflect all areas of the country.

In both time periods, the best predictors of future cases were also age groups with a large number of reported cases (and a relatively small number of zero weeks) during that period (Figs. 2D and 4). One possible explanation for this pattern is that, with such highly synchronized outbreaks, an age group's ability to be predictable may be largely determined by data quality. In the early stages of an outbreak, if the timing of peaks and troughs in pertussis incidence is driven by age groups with high enough overall case counts where the troughs in incidence are not "flattened" by the presence of zeros, this will prove to be informative. Further, it is not always easy to disentangle the differences between age cohorts, in terms of sentinel qualities. In a given group, there might be actual increased incidence of pertussis or simply higher age-specific reporting rates.

Potential explanations for the patterns we observed in England and Wales include changes in contact structure of the population, asymptomatic transmission – the latter associated with the acellular vaccine introduction – or changes in diagnostics, vaccine schedule and uptake. We elaborate further below.

The structure of contacts within a population can account for changes in age-specific incidence in the vaccine era [36]. However, we have no reason to believe that the social patterns would have substantially changed after 2002, such that they would have affected the underlying transmission dynamics.

Another proposed factor in the changing epidemiology of pertussis is asymptomatic transmission as a consequence of the acellular pertussis vaccine [11,37–40]. In a recent baboon model study, Warfel et al. [41] found that the acellular pertussis vaccine prevented symptomatic disease without affecting transmission. Therefore, these authors speculated that individuals receiving the acellular vaccine could still acquire a transmissible but asymptomatic infection. If this were the case in England and Wales, the increase among adult notifications could have been due to both the transmission from infected children who were vaccinated with the acellular vaccine as well as through higher reporting rates. To attempt to disentangle those mechanisms, in a separate modelling study [42], we developed an age-structured transmission model and found that permitting asymptomatic carriage after DTaP vaccination accounted for the increase in incidence in adults. However, there were knock-on effects on the age distribution of cases among other age groups, as reflected in the age-specific relative risk patterns (quantified via the RR statistic and odds ratio analysis). In such a scenario, age groups 1–15 years of age remained at higher risk, with 10–15 year olds most at risk. These patterns are not consistent with those observed in England and Wales after 2002.

Finally, it is possible that both the shifting age-distribution in reported cases we reported (Figs. 1, S1 and S2) and the absence of a signal for a core age group in the latter period, are consequences of changes in diagnostics and surveillance rather than underlying epidemiology. The newer serological methods are more sensitive but less specific than bacterial cultures used historically for diagnosing pertussis infection in children [43]. Since the introduction of serological tests in 2001, it is likely that there was an increase in the rate at which pertussis was diagnosed and reported in the less symptomatic infections among adults, e.g. a persistent cough without the characteristic whoop [1–3,40].

A simultaneous increase in pertussis in unvaccinated young infants does, however, signal a surge in transmission perhaps resulting from greater actual incidence in older age groups rather than an increased surveillance artifact (Fig. 2B). Modeling studies suggest that an increase in the actual incidence of pertussis in adults would be unsurprising after several decades of incomplete routine vaccination with an imperfect vaccine, even in the absence of changes in vaccination and surveillance [9,40,44].

Pertussis transmission is a complex, nonlinear dynamical system and, because the immunization and infection histories of individuals have the potential to impact their immunity for a lifetime, it is a system with a long-term memory. Thus, analyzing England and Wales age-specific incidence from 1982 to 2012, allowed us to contrast two periods, pre- and post-2002, and identify transitions and patterns, that could easily be overlooked. The three statistical methods we employed were consistent in describing the data and depicting idiosyncrasies in the time series. This knowledge is crucial in the context of dynamical public health adaptive management strategies, as determining the core transmission groups through time will be helpful for implementation of age-targeted surveillance and control strategies. Under a complicated set of ever-changing drivers from demography and contact patterns to vaccination, evolution, surveillance and diagnostics sensitivity and technology, it is no surprise that the vaccine-era dynamics of pertussis are far from equilibrium.

Extracting information about transmission parameters and immunity from long-term, finely grained datasets requires particularly careful attention to the statistical properties of the data [45]. Given the level of under-reporting from routine surveillance, accurate estimates of pertussis incidence and burden in specific age classes are paramount to inform policy. Thus, using the information available cautiously, is critical when devising optimal strategies depending on the goal: from minimizing transmission in the overall population to targeted risk reduction in specific vulnerable age groups. Our results provide a useful cross-period comparison, drawing attention to the marked differences between the two periods and to changes in surveillance and, in sensitivity and specificity of diagnostic methods, as potential underlying reasons for the notable and substantial increase in the number of reported cases in older age classes.

Notes

Author contributions: AIB and MAR designed the study with PR. AIB and MAR carried out the analysis. YHC provided the data. AIB drafted the manuscript. All authors reviewed and edited versions of the manuscript. All authors agree with the conclusions of the manuscript.

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Potential conflicts of interest information for all authors

All authors: no reported conflicts.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2018.01.046.

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