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Impact of vaccination and birth rate on the epidemiology of pertussis: a comparative study in 64 countries

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Bordetella pertussis infection remains an important public health problem worldwide despite decades of routine vaccination. A key indicator of the impact of vaccination programmes is the inter-epidemic period, which is expected to increase with vaccine uptake if there is significant herd immunity. Based on empirical data from 64 countries across the five continents over the past 30–70 years, we document the observed relationship between the average inter-epidemic period, birth rate and vaccine coverage. We then use a mathematical model to explore the range of scenarios for duration of immunity and transmission resulting from repeat infections that are consistent with empirical evidence. Estimates of pertussis periodicity ranged between 2 and 4.6 years, with a strong association with susceptible recruitment rate, defined as birth rate $\times$ (1 $-$ vaccine coverage). Periodicity increased by 1.27 years on average after the introduction of national vaccination programmes (95% CI: 1.13, 1.41 years), indicative of increased herd immunity. Mathematical models suggest that the observed patterns of pertussis periodicity are equally consistent with loss of immunity that is not as rapid as currently thought, or with negligible transmission generated by repeat infections. We conclude that both vaccine coverage and birth rate drive pertussis periodicity globally and that vaccination induces strong herd immunity effects. A better understanding of the role of repeat infections in pertussis transmission is critical to refine existing control strategies.

Keywords: pertussis; vaccination; birth rate; periodicity; comparative approach

1. INTRODUCTION

Bordetella pertussis infection remains an important public health threat worldwide, causing recurrent epidemics associated with an estimated 45 million cases and approximately 300 000 paediatric deaths annually (Plotkin *et al.* 2008). The incidence of pertussis dramatically declined in developed countries following childhood vaccination programmes initiated in the 1940s–1960s. However, doubts remain over the consequences of pertussis immunization for *transmission*, as opposed to disease (Das 2002), with concerns about whether declining incidence in the vaccine era truly reflects reduced transmission or reduced clinical symptoms following infection (Fine & Clarkson 1982; Aguas *et al.* 2006). This distinction is especially important for understanding and managing the recent rise in reported cases that has been recently documented in countries with long vaccination history, together with an increasing proportion of cases in adolescents and adults, including those previously vaccinated (Wirsing von König *et al.* 1995; Guris *et al.* 1999; Senzilet *et al.* 2001; Gilberg *et al.* 2002; Hellenbrand *et al.* 2009). The increase in age at infection may be the result of reduced pertussis circulation after prolonged vaccination, waning of vaccine- and infection-induced immunity, lack of immune boosting from reduced pathogen circulation, and greater recognition of the potential etiologic role of pertussis in adults with a chronic cough. In developing countries, pertussis vaccination was included in the expanded programme of immunization initiated by the World Health Organization (WHO) in 1974. Despite a decline in the global burden of pertussis, vaccine uptake has remained low in developing countries, and the impact of vaccination programmes has not been well studied in this setting.

Pertussis vaccination strategies are heterogeneous both across and within countries over time, resulting in a diversity of epidemiological patterns globally, which have yet to be systematically studied. A complete pertussis vaccination schedule includes at least three doses received during the first year of life. In most developed countries, a fourth dose is recommended before the age of 5, and a few countries have adopted additional booster vaccination in teenagers and adults (Heininger 2008). Acellular vaccines are the most commonly used in many developed countries, while whole-cell vaccines are still used in many developing countries.

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Table 1. Details of the non-WHO data obtained through a review of literature and direct contacts. Country names are in bold when the time series covers both the pre- and post-vaccination periods.

country	data range	year of starting of vaccination[a]	source
Brazil	1980–2000	before 1980	Luz *et al.* (2003)
Canada	1924–1999	1943	Public Health Agency of Canada (www.publichealth.gc.ca)
Chile[b]	1952–2005	1950s	Ministry of Health (Dr A. Olea and Dr D. Rajs)
Denmark	1901–1997	1961	Nielsen & Larsen (1994)
France	1945–1985	1959	Broutin *et al.* (2005*a*)
Italy[b]	1976–1996	before 1976	Broutin *et al.* (2005*a*)
Japan	1947–1998	1945	Broutin *et al.* (2005*a*)
Poland	1950–1999	1966	Gzyl *et al.* (2004)
Portugal[b]	1954–1999	1966	Broutin *et al.* (2005*a*)
Switzerland[b]	1943–1973	1940s	Broutin *et al.* (2005*a*)
UK	1940–1999	1957	Broutin *et al.* (2005*a*)
USA	1922–2000	1940s	Broutin *et al.* (2005*a*)

[a]Last year of the pre-vaccination period.
[b]Monthly data.

An indicator of the effectiveness of vaccination programmes in reducing transmission is the inter-epidemic period, which is expected to increase with vaccine uptake (Keeling & Rohani 2007). For a strongly immunizing infection, multi-year epidemic cycles are explained by the period necessary for the replenishment of the susceptible pool above a threshold, so that disease periodicity varies with the rate of recruitment of susceptibles (Anderson & May 1991). Births, then, represent a direct influx of susceptible individuals in a population, delayed by maternal immunity, whereas vaccination decreases the rate of susceptible recruitment (SR) by providing immunity. In the case of pertussis, waning immunity in previously infected or vaccinated individuals is thought to contribute to the replenishment of the susceptible class. If, as has been postulated, pertussis vaccination reduces disease incidence but not transmission, then waning immunity may overwhelm herd immunity effects (Fine & Clarkson 1982). However, observed changes in pertussis epidemic periodicities in England and Wales, and in Niakhar, Senegal, are consistent with significant herd immunity (Rohani *et al.* 2000; Broutin *et al.* 2005*b*).

While periodicity estimates range from 2 to 5 years in Europe and North America in the pre-vaccine and vaccination eras (Hethcote 1998; Gomes *et al.* 1999; Rohani *et al.* 1999; Skowronski *et al.* 2002; Broutin *et al.* 2005*a*), there is a paucity of estimates from South America, Asia and Africa, where vaccine coverage has dramatically increased over recent decades. Here, we apply time series methods to long-term epidemiological data from 64 countries across five continents to quantify the impact of vaccination on pertussis periodicity, and examine the global signature of herd immunity effects. Further, we compare the observed relationship between disease periodicity, birth rate and vaccine coverage with results from an epidemiological model, and explore different scenarios about waning immunity and transmission characteristics of repeat infections.

2. MATERIAL AND METHODS

(a) *Epidemiological and vaccination data*

The annual number of reported pertussis cases and vaccine coverage for DTP3 (three doses of diphtheria–tetanus–pertussis vaccine) by country were compiled from the WHO database from 1974 to 2005 (http://www.who.int/immunization_monitoring/data/data_regions/en/index.html). We restricted the analysis to 61 countries in the database that provided epidemiological and vaccination data for at least 15 consecutive years. Since pertussis vaccination programmes started between 1940 and 1974 in these countries, all time series extracted from the WHO database covered the vaccination era (we illustrate time series for South American countries in the electronic supplementary material, appendix S1).

We also performed a literature review to identify longer case time series that covered the pre-vaccination era, and contacted the authors of relevant publications and Ministries of Health. We retrieved additional data for 12 countries (table 1), nine of which are also in the WHO database. We kept these partially redundant time series since they were longer than those extracted from the WHO database, and they allowed comparison of data from original sources and WHO reports. Of note, eight of those additional time series covered both the pre- and post-vaccination periods, and four were available by month.

Overall, our combined pertussis database from WHO and original sources included 64 countries in five continents.

(b) *Birth rate and susceptible recruitment rate*

To study the impact of vaccination on disease periodicity, we first estimated the SR rate, defined as SR = birth rate × (1 − vaccine coverage). In the absence of country-specific data on vaccine efficacy over time, we assumed that vaccine efficacy was 100 per cent, which would under-estimate SR values but not introduce a systematic bias towards one particular country. For each of the 64 countries, we calculated the mean SR during the vaccination period; for eight of those countries with pre-vaccination disease data, we also calculated a mean pre-vaccination SR.

The average annual number of births per 1000 and deaths under 1 year of age were extracted from the United Nations World Population Prospects database (http://esa.un.org/unpp/), by 5-year periods. For each country, we computed the mean birth rate over the study period, corrected by the mean infant mortality rate. We applied this correction because infant mortality rates differed substantially between countries, and disregarding

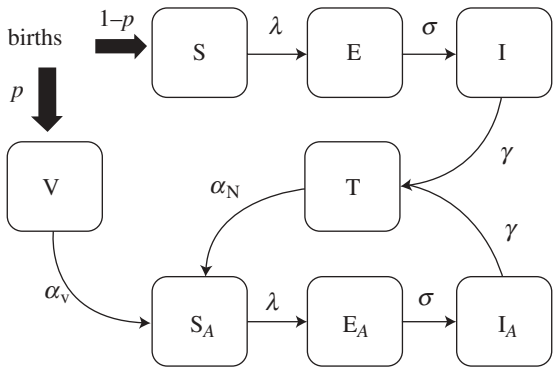

Figure 1. Diagram of the epidemiological model.

infant mortality rates could have overestimated SR, especially in low income countries.

(c) *Periodicity estimates*

The mean periodicity of pertussis epidemics was estimated for eight countries in the pre-vaccine era and 64 countries in the vaccination era. Case time series were first detrended by fitting a loess function to 5 years of data and subtracting the trend from the raw data. Periodicity was defined as 1/frequency, where frequency corresponded to the maximum spectrum value of spectral analysis (R software, v. 2.5.0). We tested the accuracy of periodicity estimates derived from annual data by comparing estimates with those derived from monthly data in 4 countries and found similar values (within 8%). The association between periodicity, SR rate, vaccine coverage and birth rate was tested by linear regression.

(d) *Mathematical model*

Following the statistical analysis of epidemiological data, we used a modelling approach to examine various assumptions concerning loss of infection- and vaccine-induced immunity, and transmission characteristics of repeat infections. We analysed a stochastic compartmental model of pertussis transmission including births, vaccination and waning immunity (van Boven *et al.* 2005), parameterized using previously assumed estimates for the duration of latent and infectious periods, and transmission parameters (figure 1 and table 2; electronic supplementary material, appendix S2; Anderson *et al.* 1984; Nguyen & Rohani 2008; Wearing & Rohani 2009). We considered a generic homogeneously mixed model that was applicable to 64 countries with unknown age-mixing patterns. Predicted periodicity estimates from the modelling approach were compared with the observed estimates in 64 countries.

Table 2. The table below explains the epidemiological meaning of model parameters along with whatever information is known about them.

parameter	epidemiological description	value
ν	*per capita* birth rate	variable
μ	*per capita* death rate	0.02 y^{-1}
N	population size	5×10^5
β_0	mean transmission rate (I)	450 y^{-1}
β_A	mean transmission rate (IA)	225 y^{-1}
b_1	amplitude of seasonality	0.05
m	shape parameter, I and IA classes	4
$1/\sigma$	latent period	8 days
$1/\gamma$	infectious period	14 days
$1/\alpha_N$	infection-derived immune period	variable
$1/\alpha_V$	vaccine-derived immune period	variable
p	vaccination probability	variable

3. RESULTS

(a) *Periodicity estimates*

Across the 64 countries studied, SR varied from 0.2 to 36.8 per 1000 annually, while the mean periodicity of pertussis epidemics ranged between 2 and 4.6 years (see electronic supplementary material, appendix S3). Disease periodicity decreased with increasing SR, as suggested by figure 2*a* (R^2 for linear trend = 0.39, $p < 0.001$). Two distinct epidemiological groups emerged from the global periodicity patterns ($p < 0.001$): the first group was associated with locations experiencing frequent epidemics (mean periodicity = 2.72 years; 95% CI: 2.61, 2.84 years) and included African countries ($n = 11$) in the vaccination era, and countries in Europe and the Americas in the pre-vaccination period ($n = 8$). The second group ($n = 62$) was associated with less frequent epidemics (mean periodicity =3.83 years; 95% CI: 3.77, 3.89 years) and included all countries in the vaccination period, except those in Africa. In addition to these global patterns, we quantified temporal changes in periodicity estimates in eight countries with disease data in the pre-vaccine and vaccination eras. Periodicity increased by a mean of 1.27 years (95% CI: 1.13, 1.41) following the initiation of vaccination programmes ($p = 0.007$; figure 2*b*).

A multiple regression analysis demonstrated that birth rate and vaccination coverage are both statistically significant predictors of periodicity ($p < 0.001$ and $p = 0.04$ for vaccine coverage and birth rate, respectively). Next, we dissected the specific determinants of periodicity, considering the separate relationships between periodicity and birth rates, and periodicity and vaccine coverage. There was a significant but weak association between birth rates and periodicity (R^2 for linear trend = 0.15, $p < 0.001$). Birth rates in African countries remained high in recent years, in particular as compared with Europeans countries in the pre-vaccination era (not shown). As regards the relationship between SR and vaccination, low periodicity estimates in African countries were consistent with lower vaccine coverage than other regions of the world; however, geographical variation in vaccination coverage alone could not fully explain the global patterns of disease periodicity (R^2 for linear trend = 0.16, $p < 0.001$; not shown). We conclude that both birth rate and vaccine coverage drive the observed geographical variation in the global epidemiology of pertussis.

(b) *Mathematical modelling*

Next, we used a modelling approach to explore in a qualitative sense how dynamics resulting different assumptions concerning loss of immunity and transmission characteristics of repeat infections fared against our empirical periodicity estimates (figures 3 and 2*a*). In the absence of precise estimates on the average duration of immunity

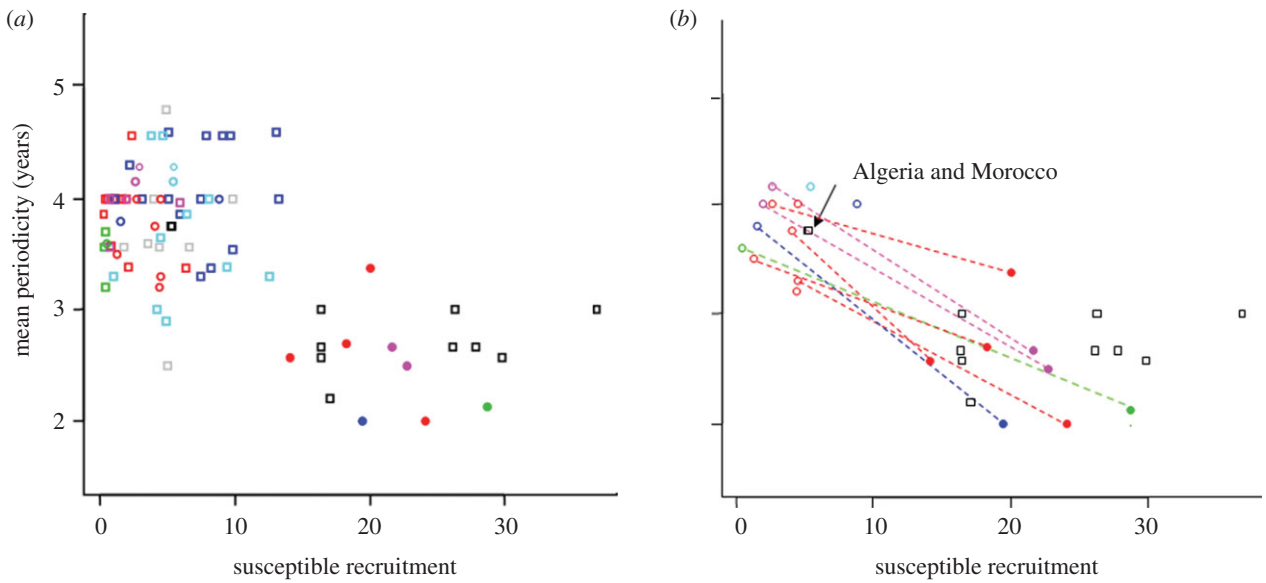

Figure 2. (*a*) Periodicity against SR for 64 countries ($R^2 = 0.39$, $p < 0.001$). Colours represent geographical regions (red, western Europe; pink, North America; grey, Middle East; cyan, Asia; green, eastern Europe; blue, South America; black, Africa). Squares correspond to the WHO database and circles to non-WHO data (see electronic supplementary material S2 for details). Open symbols represent post-vaccination eras and filled symbols represent pre-vaccination era. (*b*) As for (*a*) except with WHO database African countries (black squares) and non-WHO data in pre-vaccination (filled circles) and post-vaccination (open circles) periods ($R^2 = 0.58$, $p < 0.001$). The dashed lines link the pre- and post-vaccination eras for the same country.

(resulting from both infection and immunization) and contribution of repeat infections to the force of infection, we are forced to explore a range of possible values with the intention of drawing general conclusions about their plausibility. In figure 3, we present the predicted relationship between periodicity and SR for a variety of scenarios that differ in their assumed duration of natural and vaccine-derived immunity, ranging from 10 years to lifelong. We found the model dynamics were broadly consistent with empirical patterns when the duration of immunity from infection was long (spanning many decades) and the duration of immunity from immunization was at least 10 years.

A key assumption in this analysis is that individuals experiencing repeat pertussis infections are 25 per cent as infectious as those experiencing the disease for the first time (figure 3). If, instead, the infectivity of repeat infection is assumed to be only 10 per cent of primary infection, periodicity is nearly independent of duration of immunity (see electronic supplementary material, appendix S4, D–F). In this case, individuals experiencing repeat infections generate so little transmission that they are ineffective in modifying the inter-epidemic period, and in essence this is dynamically equivalent to the extreme scenario of a perfectly immunizing infection. In contrast, if we assume that infectivity of repeat infections is 50 per cent that of primary infections, periodicity is predicted to be very sensitive to the duration of immunity (see electronic supplementary material, appendix S4, A–C). In summary, the strong statistical association between epidemic period and SR derived from the global pertussis dataset was equally consistent with two distinct scenarios in our model: (i) slow loss of natural immunity, and (ii) nearly negligible disease transmission from individuals experiencing repeat infection. In either case, the dynamical signature of herd immunity is very strong (Rohani *et al.* 2000).

4. DISCUSSION

In this comparative study, we have documented pertussis periodicity patterns in 64 countries over more than 30 years, covering regions with little prior information on the epidemiology of the disease, such as Africa and Asia. We applied the same methodological approach to all countries and provided the first global picture of pertussis multi-annual epidemic cycles. Our results are in agreement with previous studies from a limited number of countries, mostly in Europe and North America, suggesting a mean periodicity of 3–4.5 years in the vaccine era (Hethcote 1998; Gomes *et al.* 1999; Rohani *et al.* 1999; Skowronski *et al.* 2002; Broutin *et al.* 2005*a*,*b*).

Further, we showed that the periodicity of outbreaks increased by 1.27 years (95% CI: 1.13–1.41 years) following vaccination ($p < 0.001$), based on eight countries with sufficiently long epidemiological records. This observation is in clear contrast with the classic study of Fine & Clarkson (1982), who examined cyclicity of pertussis in national England and Wales case notification data. They interpreted the failure of immunization to increase pertussis inter-epidemic periods in these data to mean that vaccines are more effective in reducing disease rather than transmission. As echoed by Cherry (1996), the implications of such a conclusion for pertussis control are substantial. Our finding that immunization programmes consistently increase the inter-epidemic period point to reduced disease transmission, in line with strong herd immunity effects (Rohani *et al.* 2000).

A key finding of this global study is the demonstration that pertussis periodicity is associated with both birth rate

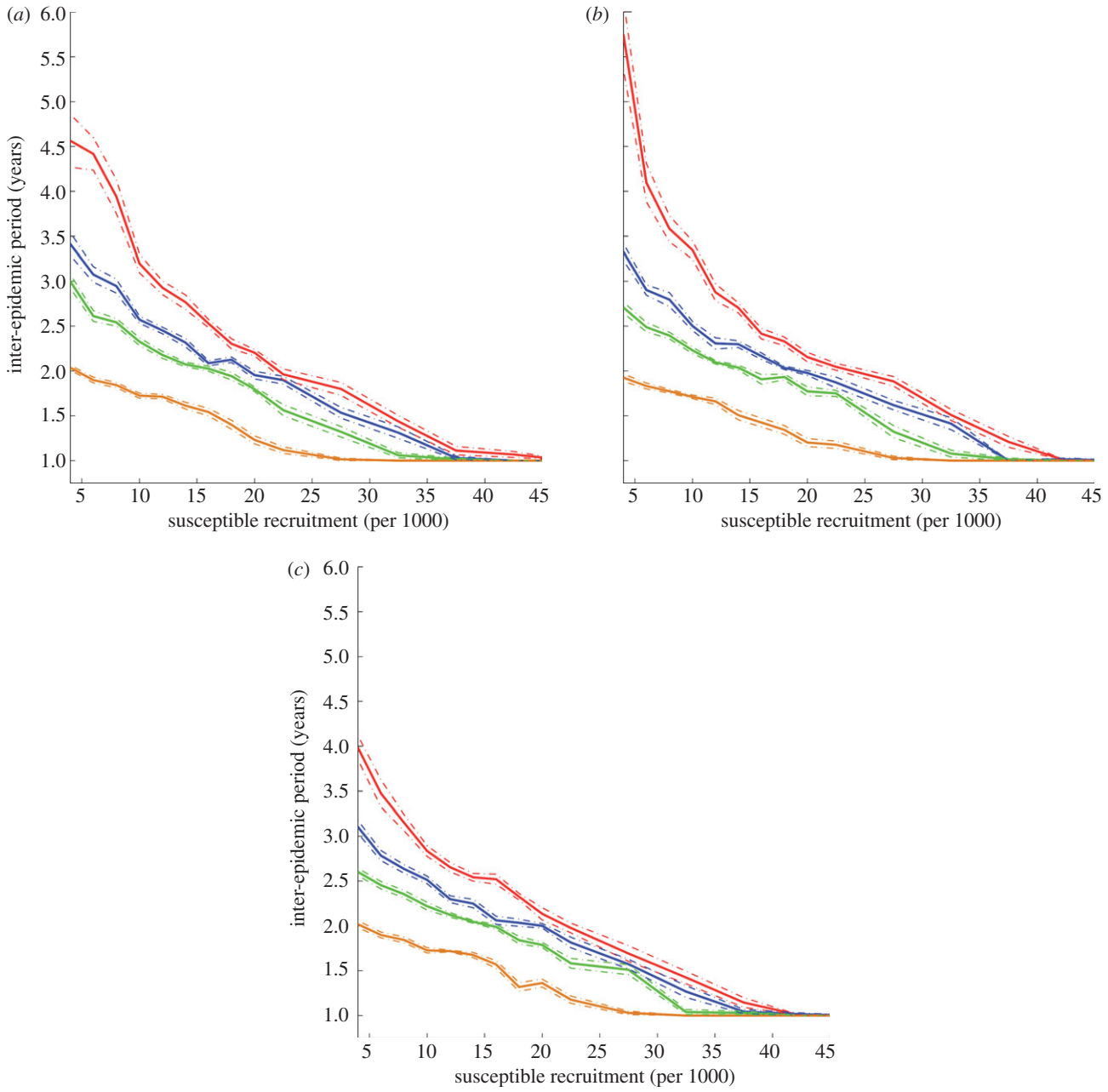

Figure 3. Results of the model simulations. In all scenarios, we assume that $\beta = 4\beta_A$ (i.e. that a repeat infection is 25% as infectious as a primary infection). In (*a*) we assume the duration of infection-derived immunity (denoted by T_I) and vaccine-derived immunity (denoted by T_V) are identical (red line, lifelong; blue line, 50(50) years; green line, 25(25) years; brown line, 10(10) years). In (*b*) we assumed T_V is half T_I (red line, lifelong; blue line, 50(25) years; green line, 25(12.5) years; brown line, 10(5) years) and in (*c*) we fixed T_V at 10 years (red line, lifelong; blue line, 50(10) years; green line, 25(10) years; brown line, 10(10) years). The dashed lines correspond to the standard error limits for each curve. We used 30 stochastic simulations of the model for each value of SR. For each simulation we ran the model for 20 years and analysed the output for another 20 years of weekly cases. Periodicity was analysed by running the data through a wavelet spectrum. In each panel, model simulations are most consistent with empirical patterns when a long duration of immunity (in excess of 25 years) is assumed.

and vaccine coverage, as predicted by theory for strongly immunizing diseases (Anderson & May 1991; Keeling & Rohani 2007). This relationship is clearly indicative of what may be termed 'supply-side' epidemiology: namely, that outbreak frequency is determined by susceptible births. It is clearly in direct contradiction of the assertion that waning of immunity is the main driver of SR dynamics and thus determines transmission. However, an increasing number of cases in adolescents and older people, including those who have been vaccinated in infancy, has been described during the last 10 years in different countries with long vaccination history (Guris *et al.* 1999; Strebel *et al.* 2001; Skowronski *et al.* 2002; Hellenbrand *et al.* 2009). One potential explanation for that discrepancy between our results and case studies is that by estimating the mean periodicity over several decades, our results probably reflect a long-term trend without capturing the possible recent changes. Detailed investigation of these pronounced and age-related increases in incidence has become urgent, though is currently hampered by limited age-stratified longitudinal records.

Interpretation of our results requires a number of caveats. A first limitation relates to heterogeneities in epidemiological data, due to differences in diagnostics tools

(i.e. clinical, culture, PCR, serology), case definitions and survey efforts between countries. Under-reporting can be expected and may vary geographically and over time. In particular, detection of disease in adolescents and adults is not necessarily systematic since pertussis was considered a childhood disease until recently. Moreover, diagnostic sensitivity is poor in older age-groups (as well as in vaccinated children) because of non-specific and mild clinical symptoms. As a result, numbers of reported cases are probably much lower than the true number of clinical cases. However, under-reporting should not affect estimates of the mean periodicity, since years considered as epidemic by our method probably reflect a true increase in disease incidence compared with surrounding years, even if the magnitude of reported epidemics may be uncertain. Moreover, most time series used in this study are annual and do not allow us to quantify the seasonal patterns of the disease, potentially leading to overestimation of periodicity in countries where annual outbreaks persist. However, our modelling approach suggests that annual outbreaks are not expected in the 64 countries studied, given the range of SR rates. In addition, the majority of our time series comprise more than 20 years of data, producing robust periodicity estimates for multi-annual cycles.

Finally, for the sake of simplicity, we did not take into account heterogeneity in vaccine types, schedules (timing of vaccination and number of doses) and efficacy across countries or within the same country over time, or between administrative units of the same country. For the period of interest here, ending in 2005 or earlier, whole-cell vaccines were most commonly used, with acellular vaccines phased in at the very end of our study period (with Japan being the only exception; Watanabe & Nagai 2005). Globally, almost all our time series span the era with no vaccination or when only three doses were recommended. In fewer than 10 countries, a fourth dose is recommended (with USA and Canada being the two exceptions that have recommended five doses) for decades but we do not have access to specific vaccine coverage data for this booster. The impact of boosters on pertussis periodicity remains an interesting and open question. Finally, we used an average estimate of vaccine coverage during the vaccination period, and do not capture short-term time trends in vaccine coverage. However, coverage did not change much over the study period, except in the UK (Rohani *et al.* 2000), Japan and Sweden. We note that further research should focus on heterogeneity in disease dynamics and vaccine coverage between administrative units of large and economically diverse developing countries such as Brazil or India, which we could not investigate here. Taken together, both data heterogeneity and methodological issues are expected to obscure the true relationship between vaccination and disease periodicity, but would not lead to spurious and statistically significant associations.

In addition to quantifying the global periodicity patterns of pertussis, we used a stochastic model to qualitatively explore the relationship between periodicity and SR rate, for different scenarios regarding loss of immunity and transmissibility of repeat infections. Simulations showed that two assumptions were equally consistent with periodicity patterns detected in the global disease dataset: (i) reasonably long duration of natural immunity and (ii) very slight transmissibility of repeat infections. Epidemiological studies documenting duration of immunity are scarce and provide imprecise estimates, typically 4–20 years for natural infection and 4–12 years for vaccination (Wendelboe *et al.* 2005). Our modelling approach suggests that natural immunity could last longer than previously thought, consistent with strong herd immunity effects, if repeat infections do contribute to the overall transmission of pertussis. While our modelling exercise is intended to provide a general comparison, our overall conclusions are in strong agreement with the work of Wearing & Rohani (2009), who used the method of moments (specifically the inter-epidemic period and the extinction profile) to explore parsimony between model predictions and the epidemiology of pertussis in England and Wales. Future work needs to attempt to use statistical inference methods to estimate these parameters of key interest, though this represents a formidable technical challenge.

Our study reinforces the need for more quantitative information on the transmission consequences of repeat infections. Along these lines, a prospective study suggested that adults are responsible for 76 to 83 per cent of transmission of *B. pertussis* to young infants in the household in Germany, France, US and Canada (Wendelboe *et al.* 2007), implying that teenagers and adults may play a role in pertussis transmission. These values are likely to represent an overestimate, however, since these studies are focused on households with infant cases but do not consider 'control' group by including households with no infant case.

Long-term vaccination efforts will inevitably increase the mean age of infection, leading to proportionately more cases in adolescents and adults. In fact, older pertussis cases have become more commonly described in Europe and North America, although they are still probably under-reported (Deville *et al.* 1995; Schmitt-Grohe *et al.* 1995; Wirsing von König *et al.* 1995; Cherry 1999; Guris *et al.* 1999; Senzilet *et al.* 2001; Gilberg *et al.* 2002; Park *et al.* 2005; Rothstein & Edwards 2005). It is plausible, therefore, that our estimates of inter-epidemic periods from the data are based predominantly on typical primary pertussis cases. It is worth highlighting that primary and repeat infections have highly correlated incidence in our model dynamics, suggesting that periodicity of pertussis outbreaks in adults and children is similar, and that our periodicity estimates are robust. Further, mixing patterns may affect disease periodicity; for instance, adults could be substantially infectious, but mixing may occur preferentially among children. Our model did not take into account age-specific mixing patterns, which are likely to vary geographically; instead, we focused on a generic model that could be applied to all settings.

In this context, future research on the global epidemiology of pertussis should focus on (i) estimation of disease burden in adults, controlling for diagnostic issues; (ii) quantification of the role of adults in pertussis transmission, in particular to infants; and (iii) studies of geographical variation in disease dynamics in large countries where vaccine coverage and demographics are heterogeneous. These issues represent crucial questions to address in order to understand changes in pertussis epidemiology in the vaccination era and move towards a global control of pertussis.

More broadly, our study underlines the power of large-scale multi-national epidemiological analyses, bolstered by mathematical modelling, in clarifying infection dynamics and the impact of vaccination.

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