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# Contact Network Structure Explains the Changing Epidemiology of Pertussis

Pejman Rohani,<sup>1,2,4\*</sup> Xue Zhong,<sup>1,2†</sup> Aaron A. King<sup>1,3,4</sup>

The epidemiology of whooping cough (pertussis) remains enigmatic. A leading cause of infant mortality globally, its resurgence in several developed nations—despite the availability and use of vaccines for many decades—has caused alarm. We combined data from a singular natural experiment and a detailed contact network study to show that age-specific contact patterns alone can explain shifts in prevalence and age-stratified incidence in the vaccine era. The practical implications of our results are notable: Ignoring age-structured contacts is likely to result in misinterpretation of epidemiological data and potentially costly policy missteps.

Understanding the epidemiology of pertussis (whooping cough) has become a public health priority (1). This is partly because of the continued toll exacted in developing countries, where pertussis is estimated to account for more than 295,000 infant and childhood deaths per year (2), and partly because, despite high vaccine uptake levels for decades, a number of developed countries have reported a resurgence in the incidence of pertussis over the past decade (1, 3, 4). Most recent research effort has focused on hypotheses that have emphasized genetics (5), antigenic divergence as a result of vaccination (6), immunology and waning protection especially after immunization (7, 8), improvements in diagnostic methodology and surveillance systems (4), and variability in vaccine uptake (9) and efficacy (3, 10). In pertussis, as in all other directly transmitted infections, the structure of the contact network can play an important role, yet has not been quantitatively characterized.

Here, we examine the epidemiological dynamics of pertussis using age-stratified annual incidence data from Sweden. As shown in Fig. 1A, after almost three decades of vaccination, the whole-cell (wP) pertussis vaccine was withdrawn from the Swedish childhood immunization program in 1979, after concerns over safety and efficacy (11–13). There ensued a 17-year hiatus in pertussis vaccination, ending with the introduction of the acellular (aP) vaccine in 1996. Throughout this period, the Swedish Institute for Infectious Disease Control collected incidence data stratified by age (13) (Fig. 1, B and C). We combined these data with contact network information from the European POLYMOD study (14) via an age-structured model with the principal aim of assessing the role of age-specific contacts in pertussis epidemiology.

The data presented in Fig. 1, B and C, reveal shifts in the age-specific incidence of pertussis after the introduction of the aP vaccine; these shifts are similar to those reported elsewhere (15). Despite annual variation in prevalence, there was little variability in the distribution of cases among different age groups from 1986 to 1996. More than 95% of cases were found in children aged 10 and younger, with the largest fraction of cases among 1- to 5-year-olds (Fig. 1B). The onset of immunization in 1996 led to a decline in pertussis cases in preschool children and an increase in all other age groups, especially infants (younger than 1 year), who

account for almost 25% of cases in the recent vaccine era. At the same time, there have been changes in both the distribution and magnitude of incidence: Immunization coincides with a factor of 10 reduction in the number of reported cases, consistent with strong herd immunity effects (13) and an increase in the mean age at infection (from 4.1 to 10.1 years). The shift in age distribution has been observed elsewhere and has been attributed to changes in the epidemiology of pertussis (15, 16), loss of immunity, or aspects of case diagnosis and reporting fidelity (4). Here we show that the observed shifts in incidence and age distribution of pertussis cases can be more simply explained as a direct consequence of vaccination once correct age-specific social mixing is taken into consideration. This remains true even in the absence of the aforementioned epidemiological and immunological complexities, as we show here.

We first derive an expression relating infection prevalence to the age-specific risk of infection. If the hazard of infection in age class  $i$  is denoted by  $\lambda_i$ , then

$$\lambda_i = \sum_j q c_{ij} \frac{I_j}{N_j}$$

where  $I_j$  is the number of infectives, and  $N_j$  the population size, of age class  $j$ ;  $c_{ij}$  is the rate of contacts between age classes  $i$  and  $j$ ; and  $q$  is the probability of infection given contact. In earlier models, the “who acquires infection from whom” (WAIFW) matrix,  $\beta_{ij} = q c_{ij}$ , has been parameterized under ad hoc assumptions on the matrix structure (17–19). Key epidemiological determinants, including the basic reproduction ratio  $R_0$ , are known to be highly sensitive to these assumptions (20–22). We estimated the contact matrix  $c_{ij}$  using self-reported contact data from a large-scale study (14) that revealed the actual age-specific pattern of contacts in a number of European countries. By combining the Sweden incidence data  $I_j$  (scaled to account for infectious period and reporting fidelity), known population sizes  $N_j$ , and the contact network structure  $c_{ij}$  (Fig. 2D), we obtain an estimate of the number of risky contacts,  $K_i = \sum_j c_{ij} I_j / N_j$  (Fig. 2B). We can test this model by directly comparing the model-predicted number of risky contacts

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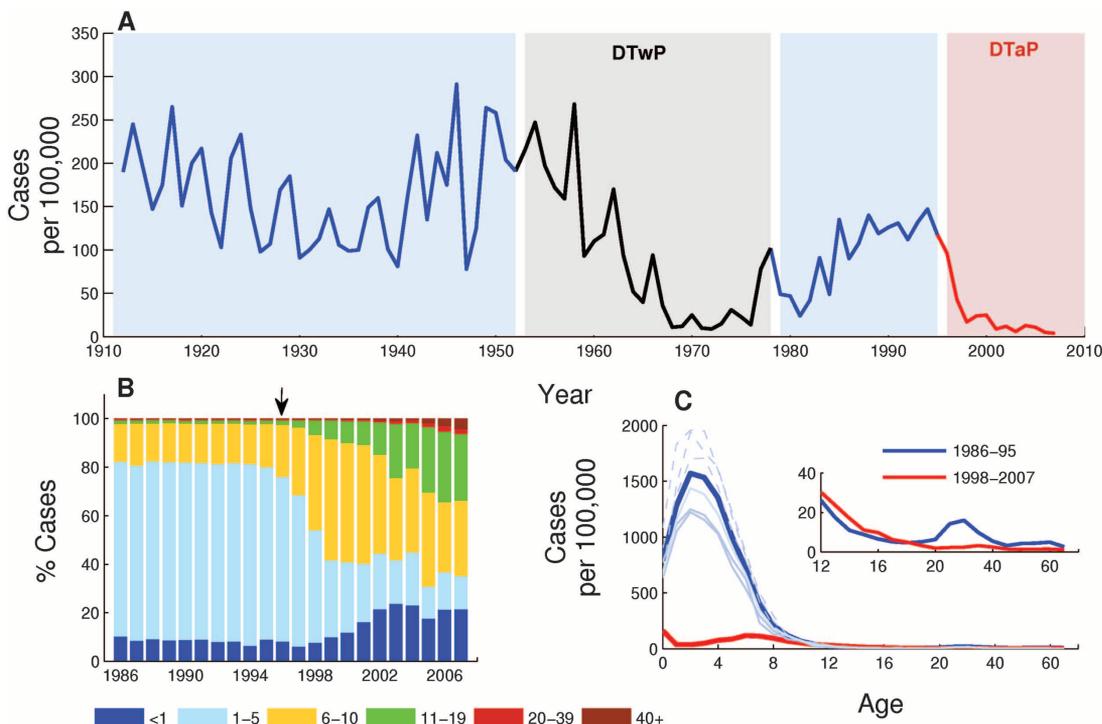
to the empirically determined age-specific force of infection,  $\lambda_i$  (Fig. 2A) (20). Specifically, our model predicts that  $\lambda_i/K_i$  should equal the constant  $q$ . Therefore, to the extent that  $\lambda_i/K_i$  is independent of  $i$ , the assumed contact structure provides a complete explanation of the data. As Fig. 2C shows,  $\lambda_i/K_i$  varies surprisingly little

across ages. The variation is smooth, with fluctuations likely to be due to age-specific biases in the contact data and age-specific variation in detectability, susceptibility, and nature of contacts as related to transmission. By making additional assumptions regarding the dependence of the above effects on age, we might achieve a

deceptively high degree of model-data agreement, at the expense of robustness. In the absence of independent data quantifying the extent of these effects and in keeping with our central goal of assaying the impact of contact structure, we instead make the parsimonious assumption that  $\lambda_i/K_i$  and reporting probability are inde-

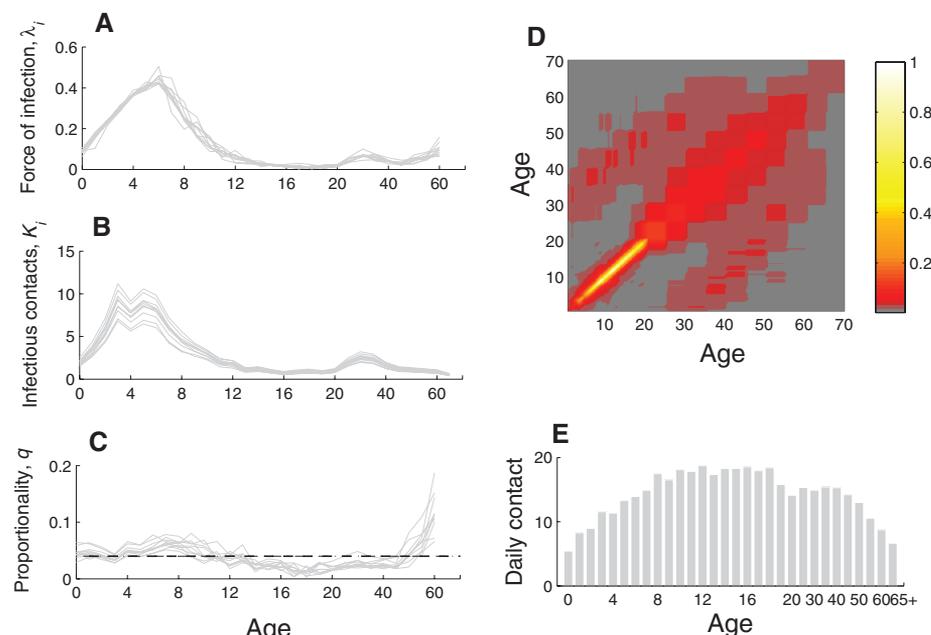
**Fig. 1. Pertussis in Sweden.**

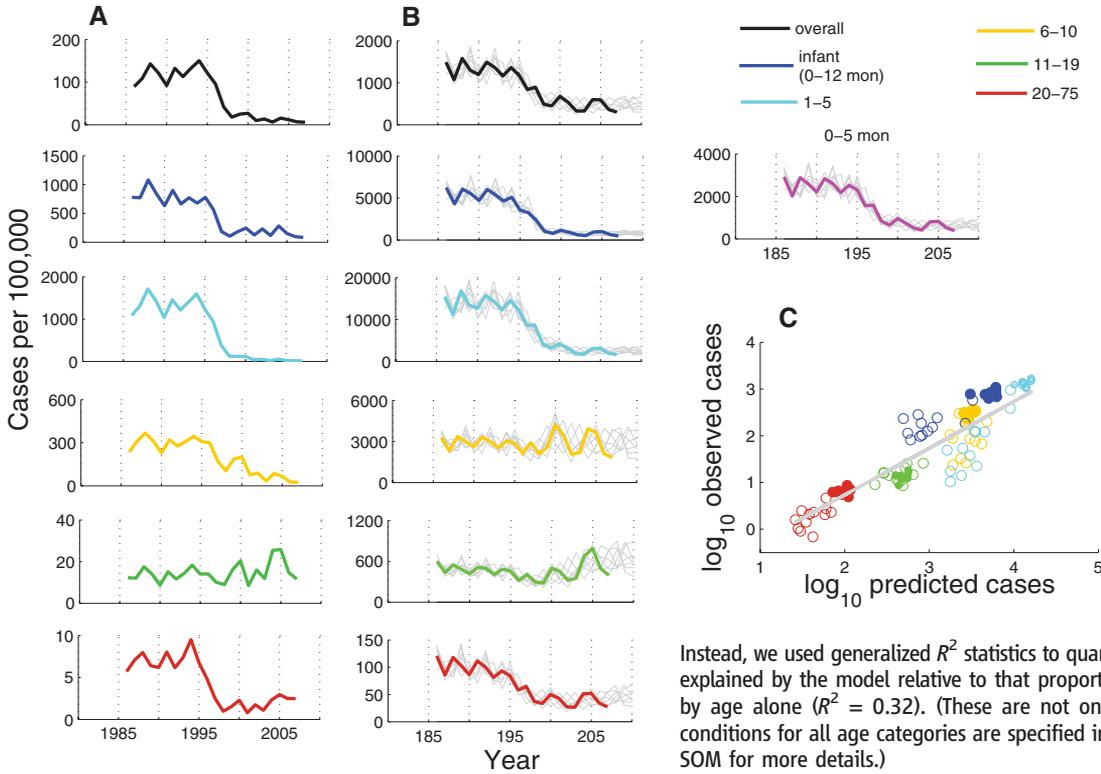
**(A)** Long-term incidence data from four distinct eras: pre-vaccination era 1910 to 1952 (shaded light blue); vaccination era with whole-cell pertussis vaccines, ending in 1979 (shaded gray); vaccine-free era (shaded light blue); and the resumption of nationwide vaccination in January 1996 with acellular pertussis (aP) vaccines (shaded pink). aP vaccine coverage instantly exceeded 98% of infants with a schedule of doses at 3, 5, and 12 months. **(B)** Case percentage among age groups: infants (<1 year), preschool children (aged 1 to 5 years), primary-school children (aged 6 to 10), adolescents (aged 11 to 19), young adults (aged 20 to 39), and older than 40. The onset of aP vaccination is marked with the arrow. **(C)** Age-specific incidence of pertussis. We present the mean in the 10 years preceding (thick dark blue line) and after (thick red line) the resumption of vaccination. For the vaccine-free era, we also plot incidence data for epidemic (thin dashed lines) and non-epidemic (thin solid lines). The disease burden among young children (aged



<6 years) has been reduced by 90% after vaccination. The inset shows shifts in incidence among adolescents and adults after the 1996 resumption of vaccination. [Redrawn from data in table 3 in (13)]

**Fig. 2. (A)** Age-specific force of infection,  $\lambda_i$ , for pertussis in Sweden from 1986 to 1895, calculated according to Anderson and May (20, 21):  $\lambda_i = -[1/(\Delta a)] \ln[(1 - p_i)/(1 - p_{i-1})]$ , where  $\Delta a$  is the width of the age class and  $p_i$  is the proportion of cases by age class  $i$ . The force of infection initially increases with age, peaking in the 6-year-old age class followed by a decline to a plateau during adolescence, with a small subsequent peak among 30- to 40-year-olds. **(B)** Age-specific rate of risky contacts,  $K_i$ . Determined by annual disease prevalence ( $I_i/N_i$ , corrected for 10% assumed reporting probability) and the assumed matrix of population contacts. Upon an in-danger contact, a susceptible is exposed to infection. **(C)** Age-specific probability of transmission given risky contact,  $q$ , which is markedly constant, around a value of 0.04 (dashed line). In fig. S6, we show that this estimate is robust to realistic age-specific notification biases. **(D)** The normalized age-specific contact rates ( $c_{ij}$ ) as estimated by averaging the data across all eight countries and correcting for reciprocity:  $c_{ij} = m_{ij}/w_j$ , where  $m_{ij}$  is the contact rate and  $w_j$  is the proportion of the population in age class  $j$ . The intensity of contacts is scaled to vary from 0 to 1. As shown in the SOM, our results are not sensitive to the pooling of data across the eight countries in the Mossong *et al.* (14) study. **(E)** Number of daily contacts per person.





**Fig. 3.** (A) Age-specific pertussis incidence in Sweden from 1986 to 2007, compared with (B) model simulations. Ten stochastic realizations are presented (gray lines), with one highlighted for comparison (color bold lines). The y-axis scales differ between panels in (A) and (B). This is most readily attributable to age-specific reporting bias (32), as we discuss in the SOM. (C) Quantitative comparison between model simulation and data (log-log scale); the line shows regression with a slope of 1. Color of symbols according to age group, with filled (open) circles representing incidence in the prevaccine (vaccine) era. Due to the correlation among ages and between years, standard linear regression statistics are not appropriate here.

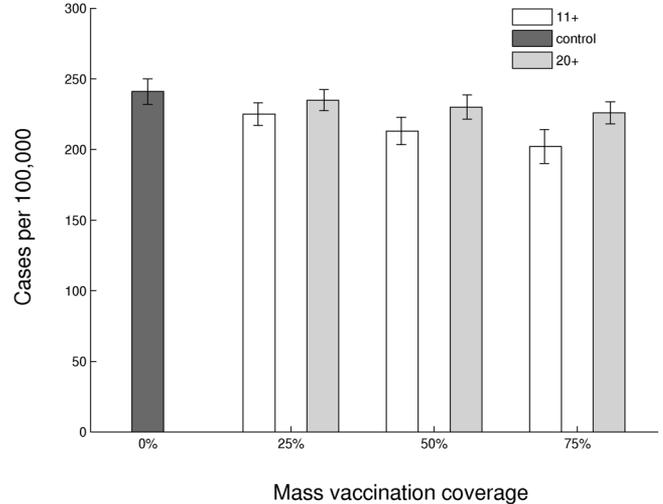
pendent of age. As we next show, this yields a model that explains the disease dynamics well. In figs. S5 and S6, we demonstrate that our parameterization is only weakly sensitive to the relaxation of these assumptions.

We parameterized a stochastic seasonally forced SEIR model of transmission dynamics (18), using the contact matrix derived above and demographic and immunization data from Sweden [see Supporting Online Material (SOM)]. In Fig. 3, we present the comparison of the incidence data (column A) with our model output (column B), broken down by age. Despite the simplicity of our model, we find quantitative agreement between model predictions and data (Fig. 3C). Overall, the model captures the sudden decline in incidence observed in the infant, toddler, and adult classes in the recent vaccine era. The model also demonstrates that in the short term, pediatric immunization has little or no impact on pertussis in the adolescent groups and predicts an uptum in cases among teenagers, which in other settings has been attributed to changes in pertussis epidemiology due to waning of vaccine- or infection-induced immunity, but is here revealed to be a consequence of the age-structured transmission dynamics.

The most pronounced discrepancy between model and data occurs in the 6- to 10-year age class. Specifically, according to the contact network data, 6- to 10-year-olds should be epidemiologically similar to teenagers, but the incidence data portray them as intermediate between toddlers and teenagers.

These findings have policy implications; several national health agencies currently recom-

**Fig. 4.** Modeling the impact of adolescent and adult booster vaccination. Simulations were run for 196 years, at which point pediatric immunization was introduced, as reported for Sweden (23). Then, starting at year 210, boosters were administered to 25, 50, or 75% of individuals aged 11 and over (white bars) or aged 20 and over (light gray bars) every 5 years over the next decade. Total cumulative incidence (assuming 10% reporting) over the 10-year period was compared to the scenario without booster vaccination (dark gray bar). In the SOM, we show the robustness of these results to changes in the mean duration of immunity.



mend the administration of pertussis boosters for ages 11 and up, based on the presumed epidemiological impact of adolescent and adult infections (23, 24). Specifically, the observation that pertussis infection in many adolescents and adults can be asymptomatic (25, 26) has led to the suggestion that circulation of the bacterium in the population is driven by infections among older age groups (23, 27). Our simple model reproduces most of the features of the data, despite its assumption that secondary and later infections have no epidemiological impact at all. If this assumption is even approximately correct, then the policy of administering even very frequent adult boosters may be inef-

fective. To see this, we titrate the effectiveness of adolescent and adult booster campaigns on reducing pertussis burden (Fig. 4). We assume that in addition to the routine immunization of infants, boosters are administered to a proportion of the population every 5 years. We then calculate the reduction in the cumulative number of cases over a 10-year period compared with a no-booster scenario. Our findings are emphatic: Even if half the population aged 11 and above receive boosters every 5 years, the reduction in pertussis burden is modest in the short term, ranging from 5 to 10% (Fig. 4). The reduction is most modest among infants (fig. S13, C and D), the age group at greatest risk of mor-

tality or severe complications after pertussis infection. In the extreme (and logistically unfeasible) situation where 75% of the 11 and older population are immunized at 5-yearly intervals, incidence reduction approaches only 15%. These results raise important questions about the epidemiological effectiveness and financial prudence of booster programs for adolescents and adults.

Our model ignores the myriad complexities that have been proposed as explanations for recent pertussis epidemiology. Critically, it ignores loss of immunity. This assumption is reasonable and has its basis in empirical evidence. Equivalent parameterization of an SIRS model that assumes temporary immunity reveals  $q$ —the probability of infection given contact—to be age dependent and to decay exponentially beyond ages 4 to 5 (fig. S5). Hence, the age-specific Sweden data provide strong support for the stated minimal transmission impact of repeat asymptomatic infections (28), which has been inferred from aggregate epidemiological data in other countries (8, 29, 30). It remains to be seen whether the explanatory power of our simple yet predictive model will substantially increase with the inclusion of additional complexities, be they age-dependent effects (e.g., differential transmissibility, susceptibility, and observability) or refinements of the contact network (e.g., household and spatial structuring).

Since the pioneering work of Fine and Clarkson, the impact of pertussis vaccines has been the subject of much debate (31). The focus of contention has been whether vaccination protects against transmission or merely disease. Our

analysis strongly points to the former: The pronounced drop in incidence in the infant, toddler, and adult groups after infant immunization is indicative of reduced pertussis circulation and increased herd immunity (13). Our findings also point toward a minimal transmission role for adults, due to the strong assortativity of contacts among the young (Fig. 2D). Hence, we conclude that adults are not the missing piece of the puzzle they have been made out to be (23). Our results suggest that contact structure is the pivotal element for understanding the epidemiology of pertussis and, it is likely, other directly transmitted infectious diseases.

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#### Supporting Online Material

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Methods  
Figs. S1 to S14  
References

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## Essential Regulation of CNS Angiogenesis by the Orphan G Protein–Coupled Receptor GPR124

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The orphan G protein–coupled receptor (GPCR) GPR124/tumor endothelial marker 5 is highly expressed in central nervous system (CNS) endothelium. Here, we show that complete null or endothelial-specific GPR124 deletion resulted in embryonic lethality from CNS-specific angiogenesis arrest in forebrain and neural tube. Conversely, GPR124 overexpression throughout all adult vascular beds produced CNS-specific hyperproliferative vascular malformations. In vivo, GPR124 functioned cell-autonomously in endothelium to regulate sprouting, migration, and developmental expression of the blood-brain barrier marker Glut1, whereas in vitro, GPR124 mediated Cdc42-dependent directional migration to forebrain-derived, vascular endothelial growth factor–independent cues. Our results demonstrate CNS-specific angiogenesis regulation by an endothelial receptor and illuminate functions of the poorly understood adhesion GPCR subfamily. Further, the functional tropism of GPR124 marks this receptor as a therapeutic target for CNS-related vascular pathologies.

Organ-specific vascular beds form through angiogenesis, followed by substantial anatomic and molecular differentiation to

support various physiologic requirements (1, 2). The central nervous system (CNS) vasculature is highly specialized, with a blood-brain barrier (BBB),

extensive pericyte coverage, reciprocal interactions with neurons and glia, and function as a neural stem cell niche (3–5). In the developing CNS, the perineural vascular plexus (PNVP) surrounds the ventral neural tube at embryonic day 7.5 (E7.5) to E8.5. By E11.5, angiogenic endothelial sprouts invade the neuroepithelium from the pial surface to periventricular areas and branch, generating the periventricular vascular plexus

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