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Review article

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Pertussis vaccines, epidemiology and evolution

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Abstract

Pertussis, which is caused by *Bordetella pertussis*, has plagued humans for at least 800 years, is highly infectious and can be fatal in the unvaccinated, especially very young infants. Although the rollout of whole-cell pertussis (wP) vaccines in the 1940s and 1950s was associated with a drastic drop in incidence, concerns regarding the reactogenicity of wP vaccines led to the development of a new generation of safer, acellular (aP) vaccines that have been adopted mainly in high-income countries. Over the past 20 years, some countries that boast high aP coverage have experienced a resurgence in pertussis, which has led to substantial debate over the basic immunology, epidemiology and evolutionary biology of the bacterium. Controversy surrounds the duration of natural immunity and vaccine-derived immunity, the ability of vaccines to prevent transmission and severe disease, and the impact of evolution on evading vaccine immunity. Resolving these issues is made challenging by incomplete detection of pertussis cases, the absence of a serological marker of immunity, modest sequencing of the bacterial genome and heterogeneity in diagnostic methods of surveillance. In this Review, we lay out the complexities of contemporary pertussis and, where possible, propose a parsimonious explanation for apparently incongruous observations.

Sections

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Introduction

The disease whooping cough is primarily caused by the bacterium *Bordetella pertussis*, with genomic evidence indicating an association with humans that dates back thousands of years[1]. The earliest medical record comes from 1484 in Herat, Persia, followed by the 1578 account of a whooping cough outbreak in Paris by de Baillou (reviewed in ref. 2). By the nineteenth century, whooping cough was considered one of the deadliest illnesses afflicting humanity and a leading cause of infant mortality[3]. As summarized by one of the pioneers of the study of pertussis, "In emphasizing the importance of whooping cough as a cause of death, Gordon and Hood[3] (1951) pointed out that in the United States during the period 1940–1948, whooping cough killed almost three times as many infants less than one year of age as measles, mumps, chicken pox, rubella, scarlet fever, diphtheria, poliomyelitis, and meningitis all together"[4]. The mortality and morbidity burden of pertussis focused efforts towards the development of vaccines, which led to the first generation of whole-cell (wP) vaccines — so called because they contain entire chemically inactivated bacteria — that have been available since the 1920s. Widespread vaccination campaigns started in the 1950s, with wP vaccines included in the World Health Organization (WHO) Expanded Programme on Immunization, which began in 1974 (ref. 2). The broad adoption of routine pertussis vaccination was associated with plummeting cases and mortality[5–7], which led to calls for whooping cough to be considered as a candidate for eradication[4]. However, beginning in the 1980s, a resurgence in pertussis cases was reported in some countries with persistently high vaccination coverage. Starting in the late 1990s, a number of countries switched to acellular vaccines in their routine schedule. Today, pertussis accounts for ~161,000 annual deaths and is a leading cause of childhood mortality owing to a vaccine-preventable disease[8].

In this Review, we explore the contemporary epidemiology of pertussis and discuss the controversies surrounding the mechanisms responsible for the re-emergence of pertussis, including the effectiveness and duration of natural immunity and vaccine-derived immunity, the ability of vaccines to prevent transmission and severe disease, and the impact of *B. pertussis* evolution (especially gene loss and genomic shuffling) on evading vaccine immunity. The article aims to lay out the complexities of contemporary pertussis and attempts to arrive at a parsimonious explanation for apparently incongruous observations.

To illustrate these complexities, we conduct a global analysis of pertussis vaccination policies, vaccine coverage and incidence, based on publicly available data provided by the WHO[9–11] (see Supplementary Texts 1 and 2 for complete details about data extraction, pre-processing and analysis). Altogether, except for the uniform recommendations for the primary series (Fig. 1a), these analyses portrayed a heterogeneous picture of pertussis vaccine policies and implementation worldwide. This spatial heterogeneity was strongly associated with variability in income, with higher-income areas recommending later vaccination ages for the primary series in infants (Fig. 1a) and more boosters in older age groups (Fig. 1b), and achieving higher diphtheria tetanus toxoid and pertussis (DTP3) coverage (Fig. 1c). In particular, the extensive booster vaccination effort in some high-income regions illustrates the difficulty of effectively controlling pertussis.

Our analysis of incidence trends in 45 countries depicted a similarly complex picture of pertussis epidemiology worldwide (Fig. 2). Especially noteworthy is the heterogeneity in trends, which persisted even in the most recent period and among high-income countries with sustained high vaccine coverage and multiple recommended boosters. This heterogeneity illustrates the intricacies of pertussis epidemiological dynamics, resulting from an interaction between regional variations in past and current vaccination policies, sociodemographic factors, social contact patterns, and the ecology and evolution of *Bordetella* pathogens, in addition to observation biases that result from differences in pertussis diagnosis, reporting and surveillance across countries. A recent addition to this list is the COVID-19 pandemic, the consequences of which led to a reduction in the circulation of *B. pertussis* (because of the nonspecific effects of non-pharmaceutical interventions[12–14]) and the coverage of pertussis vaccines[15]. Continued epidemiological surveillance will thus be essential to assess the ongoing impact of the pandemic and adapt pertussis control strategies.

Recent developments and putative explanations

B. pertussis evolution

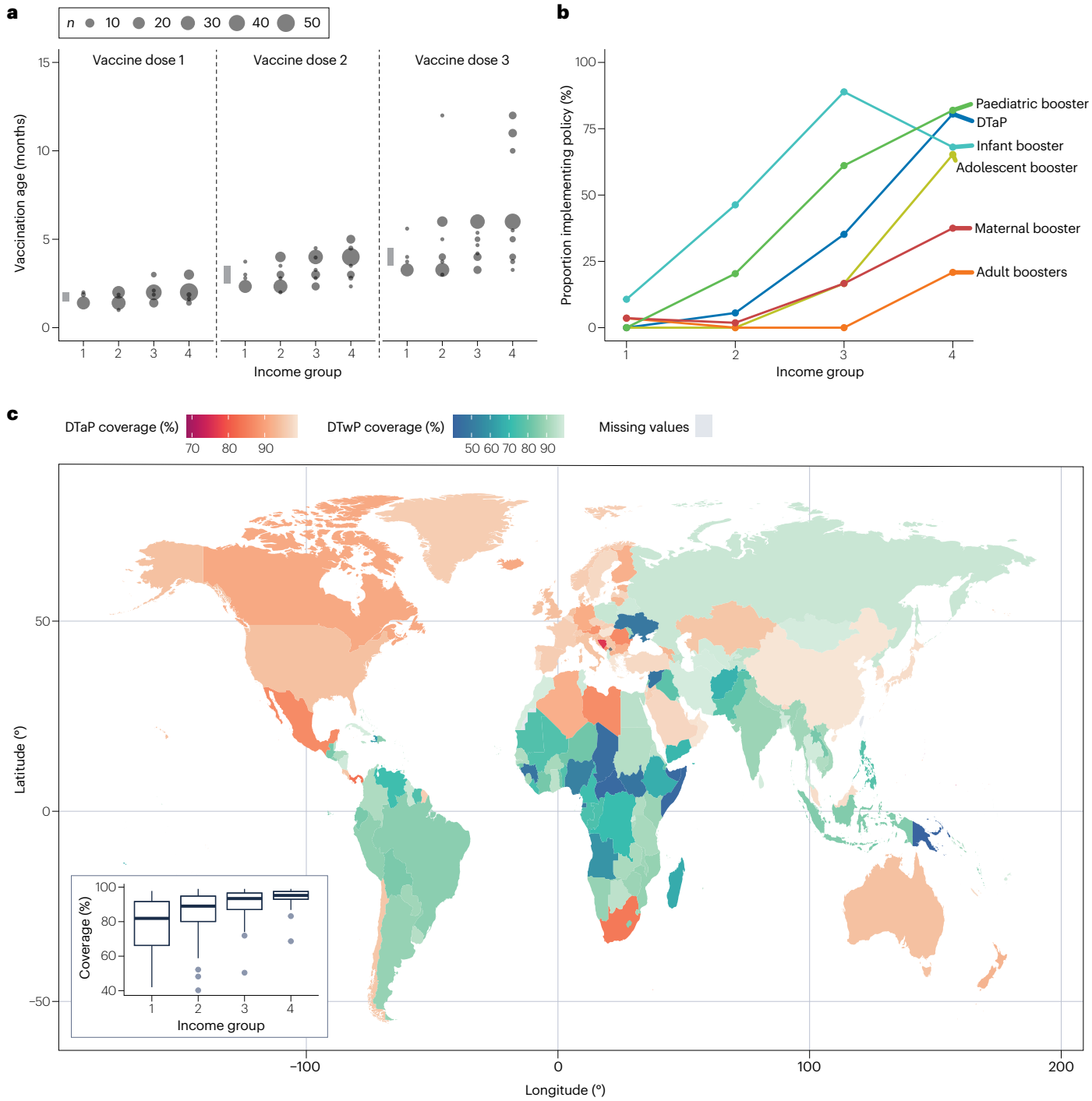
Although *B. pertussis* is broadly recognized as a monomorphic bacterium, the existence of and change in phenotypic diversity has been known for many decades. An early serotyping system[16] categorized *B. pertussis* isolates primarily according to possession of heat-labile agglutinogens, fimbriae (Fim)[17,18], with factors 1, 2 and 3 considered major and factors 4, 5 and 6 considered minor[19]. It was generally considered that the Fim2 serotype was associated with more severe disease than Fim2,3 or Fim3. Serotype diversity in fimbriae was documented in the pre-vaccine era with isolates reported in many countries corresponding to a mixture of Fim2 and Fim2,3 types, including the UK, USA, the Netherlands and Sweden[20–22]. However, the introduction of the wP vaccine coincided with a geographically consistent shift towards Fim3. This pattern of serotype replacement was argued to be owing to a lack of Fim3 serotypes in most of the early vaccines[22]. Since then, newer methods have been considered including multilocus variable number tandem repeat analysis (MLVA) and multilocus sequence typing (MLST) for characterizing trends in the circulating bacterial population[23]. A classic study[24] has used these methods to illustrate the evolution of *B. pertussis* in the USA from 1935 to 2009,

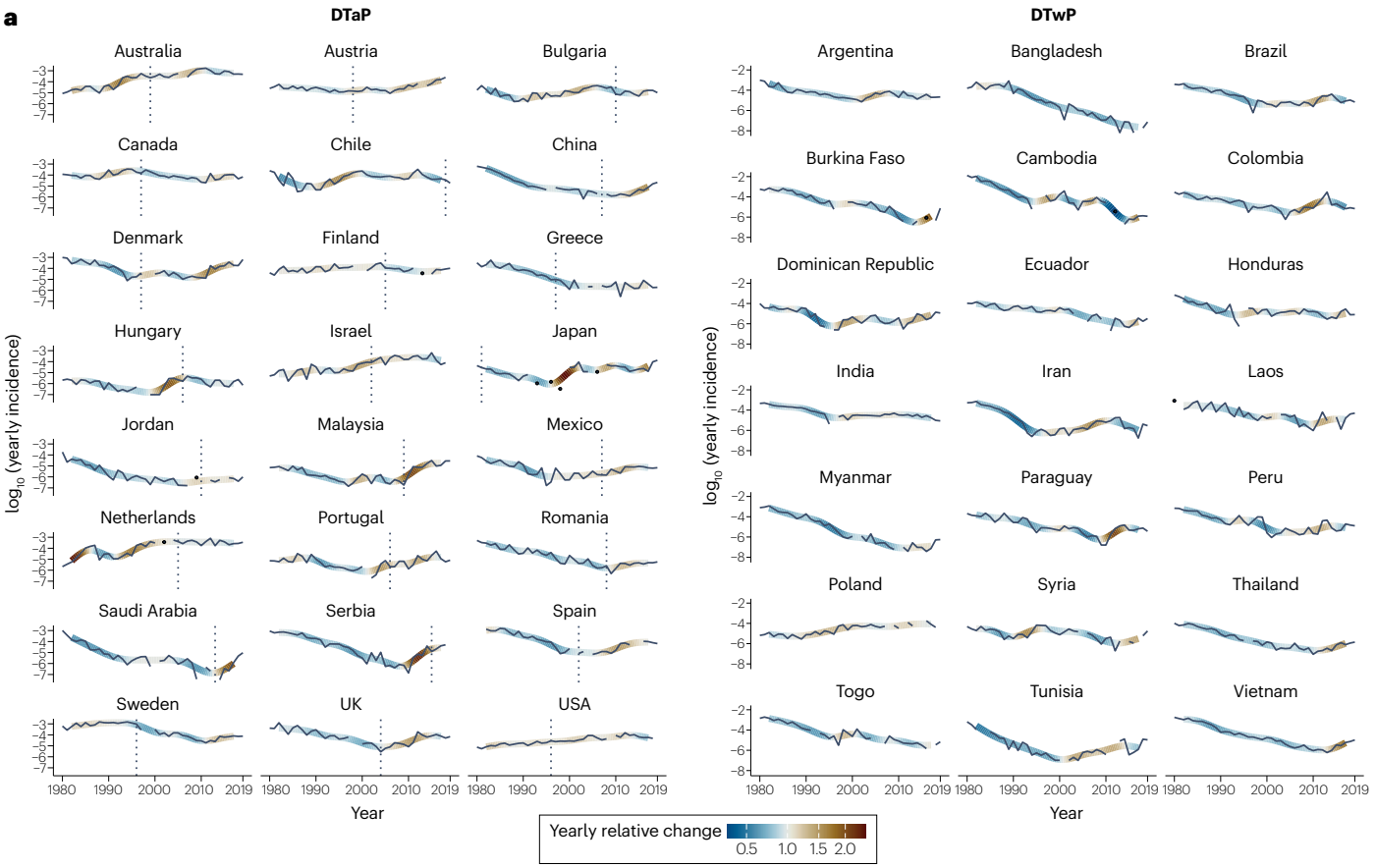
Fig. 1 | Summary of pertussis vaccination policies and vaccine coverage worldwide. a, Recommended vaccination age for the primary course (defined as the first three doses of pertussis vaccines in infants). The grey rectangles indicate the age range recommended by the WHO[55] for each vaccine dose. The numbers on the *x*-axis indicate the income groups of the geographical area, as defined by the 2022 World Bank income groups: low-income group (1), lower-middle-income group (2), upper-middle-income group (3) and high-income group (4). **b**, Proportion of geographical areas in each income group using diphtheria, tetanus and acellular pertussis (DTaP) vaccines for primary immunization (dark blue line) and implementing additional vaccine booster strategies (other colours). Income groups are the same as in part **a**. **c**, Map of average diphtheria tetanus toxoid and pertussis coverage during 2015–2019. The different geographical areas are coloured according to the type of vaccine used for primary immunization (red colours for DTaP vaccines; blue colours for diphtheria, tetanus and whole-cell pertussis (DTwP) vaccines). The inset represents vaccine coverage distribution in the different income groups. The data presented were extracted from WHO databases[9,10] and covered 208 geographical areas (corresponding to countries, overseas territories, or special administrative regions) in the different income groups (low-income group, 28 areas; lower-middle-income group, 54 areas; upper-middle-income group, 54 areas; and high-income group, 72 areas). See Supplementary Text 1 for full details about the data extraction and analysis. All data and R programming codes to reproduce Fig. 1 are freely available from Edmond, the Open Data Repository of the Max Planck Society.

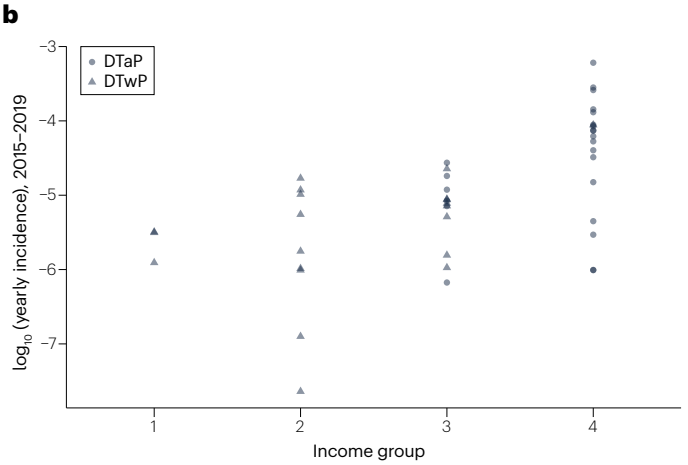
clearly demonstrating the push and pull dynamics that led to the eventual dominance of a multilocus sequence comprising the immunogen pertactin 2 (prn2), pertussis toxin promoter 3 (ptxP3), pertussis toxin subunit 1A (ptxS1A) and Fim3B – generally referred to as type prn2–ptxP3–ptxS1A–fim3B. Surprisingly, the expected selection pressures imposed by fluctuations in immunization coverage, vaccine composition and schedule were not obviously associated with allele changes in *B. pertussis*[24].

Genomic reshuffling – what does it mean for epidemiology?

Most recently, studies of pertussis evolutionary dynamics have focused on genomic sequencing, identifying a small number of mutations in a subset of genes, coding for immunogenic proteins. This includes genes for fimbriae, pertussis toxin (ptxA) and its promoter region (ptxP). Specifically, in a number of populations, *B. pertussis* has moved away from antigens used in contemporary acellular (aP) vaccines, which has been put forward as evidence for vaccine-driven evolution[25]. Interestingly,







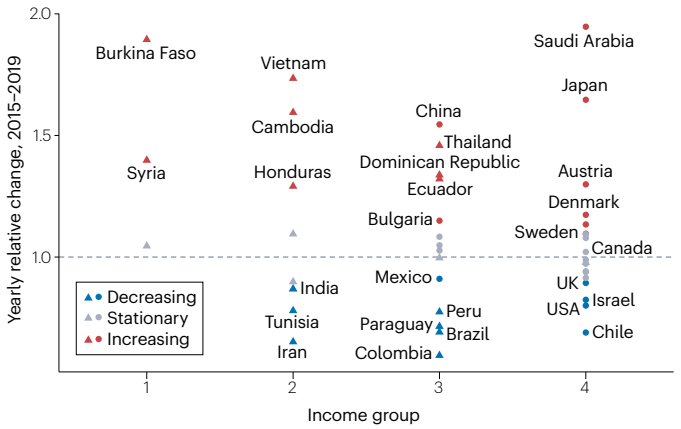


Fig. 2 | Global trends in the reported incidence of pertussis infections. a, Yearly incidence (per 100,000) of pertussis infections during 1980–2019 in countries that use diphtheria, tetanus and acellular pertussis (DTaP) vaccines (left panel, $n = 21$ countries) or whole-cell pertussis (DTwP) vaccines (right panel, $n = 24$ countries) for primary immunization. In the left panel, the vertical dotted line indicates the date of the switch to DTaP (see Supplementary Table 2 for the data sources). For every country, the coloured lines represent the yearly relative change of pertussis incidence, estimated from fits of generalized additive models (GAMs) to the 5-year moving average of pertussis incidence, thus covering the period from 1980–1984 to 2015–2019. The colour scale for yearly change in incidence is square-root transformed to better visualize the low values. **b**, Average yearly incidence of pertussis during 2015–2019 (estimated from GAMs) in different income groups. The numbers on the *x*-axis indicate the income groups of the geographical area, as defined by the 2022 World Bank income groups: low-income group (1), lower-middle-income group (2), upper-middle-income group (3) and high-income group (4). **c**, Average yearly relative change of pertussis incidence during 2015–2019 (estimated from GAMs) in different income groups. The colour of the points indicates the sign of the trend: decreasing (blue), stationary (grey) or increasing (red), based on data from the WHO[11] in 45 countries (low-income group, 3 countries; lower-middle-income group, 9 countries; upper-middle-income group, 14 countries; high-income group, 19 countries). Full details about data extraction, pre-processing and analysis can be found in the Supplementary Text 2. All data and R programming codes to reproduce Fig. 2 are freely available from Edmond, the Open Data Repository of the Max Planck Society.

the introduction of more than 16 mutations in the virulence factor pertactin has led to the loss of functionality, with pertactin-deficient isolates predominating in a number of populations[26–28]. The deficiency may confer a fitness advantage during infection[29], especially when hosts are vaccinated with the aP vaccine[30], though there is no evidence that it affects vaccine effectiveness[31].

One interesting observation from genomic studies has been evidence for frequent and repeated patterns of genome rearrangement in *B. pertussis*[27] (Fig. 3). The most comprehensive study of *B. pertussis* genomics to date has focused on data from 2000 to 2016, concluding that although there was little gene sequence diversity, the "chromosome of *B. pertussis* displays structural fluidity"[32]. In 469 complete genomes, 107 unique chromosome structures have been detected, with evidence that "structural diversity remains undersampled"[32]. This pattern of rearrangement is thought to be a source of mutational diversity[33], though whether it also has phenotypic consequences remains unclear.

Allelic divergence from vaccine strains and vaccine development

B. pertussis has been evolving, with evidence of changing frequencies in polymorphic genes such as pertactin, pertussis toxin, pertussis toxin promoter and Fim[24]. Although in some locations, multi-decadal shifts in serotype dominance do not seem to be driven by changes in vaccines or the immunization schedule[24], there is increasing evidence in support of the pathogen's adaptation in response to vaccine-induced immunity[29]. Specifically, the frequency of pertactin-deficient isolates has been increasing in populations that solely use aP vaccines in the primary schedule, with the frequency of pertactin-deficient isolates highest in countries that switched to aP vaccines earliest[26]. In addition to the loss of the pertactin gene, a diversity of pertactin gene mutations has been identified, highlighting the vaccine-driven selection on pertactin[34]. It has been speculated that differential selection in pertactin may be in part owing to potential functional redundancy, longer functional persistence of antibodies against it, and its close location to the surface membrane for productive complement fixation[35]. By contrast, pertussis toxin has a central, non-redundant role in pathogenesis, requires a complex operon to assemble and export and has no paralogs in the genome that can replace it[36,37]. Finally, additional evidence for vaccine-driven selection is provided by a genomic analysis of *B. pertussis* isolates in the UK, with faster evolution of genes encoding aP vaccine antigens than other surface proteins[38]. At present, there is little compelling evidence regarding the consequences of evolution on *B. pertussis* virulence and pathogenicity. Although a paper suggested the transition from ptxP1 to ptxP3 allele is associated with greater toxin production[39], the small sample sizes and absence of confirmation from follow-up studies preclude a definitive conclusion in this regard.

Other bordetellae – evidence for misdiagnosis?

The genus *Bordetella* belongs to the family of Alcaligenaceae and is composed of 16 species, infecting humans and animals, as well as environmental colonizers. The *Bordetella* species that have received the most attention are *B. pertussis, Bordetella parapertussis* and *Bordetella bronchiseptica*, which were considered as subspecies differentiated by host adaptation. *B. pertussis* is restricted to humans and is the primary causative agent of whooping cough (pertussis), whereas *B. bronchiseptica* and *B. parapertussis* can cause respiratory disease in humans but primarily infect dogs and sheep, respectively. The remaining species are phylogenetically more distantly related but some, in particular *Bordetella holmesii* and *Bordetella hinzii*, have been detected in humans, at surprising frequencies[40,41]. For example, during a 2010 pertussis outbreak in Ohio, USA, *B. holmesii* was detected in 32% of patients with *Bordetella*-confirmed respiratory infection, including 45% of adolescents aged 11–18 years (ref. 42). There remains a large number of unknowns regarding the epidemiology of bordetellae such as *B. holmesii*, including the mechanism of transmission, seasonality and the extent of cross-protective immunity. It is interesting to note that in the Ohio outbreak, five instances of *B. pertussis* and *B. holmesii* coinfection were reported. A complicating factor is the possession of insertion sequence 481 (IS481) in both the genomes of *B. pertussis* and *B. holmesii*, which increases the risk of pertussis false positives using standard PCR because IS481 is the target sequence[40]. Fortunately, recent advances in diagnostic protocols have led to multiplex qPCR kits for *Bordetella* detection, which detect IS481 for *B. pertussis* and pIS1001 for *B. parapertussis*, or hIS1001 for *B. holmesii*[43]. This development will enable a careful quantification of trends in detections of *B. pertussis, B. parapertussis* and *B. holmesii*[43].

Whether increasing detections of *B. parapertussis* and *B. holmesii* reflect evolutionary adaptations in these bacteria or perhaps a shift in the *Bordetella* community assemblage remains unclear. Infection experiments indicate that aP vaccines induce much lower immunity to other *Bordetella* species[44,45]. Therefore, as previously pointed out[46], it is probable that the introduction of aP vaccines changed the competitive landscape among *B. pertussis* and related species.

Asymptomatic infections

The prevalence of asymptomatic infections and their contribution to overall transmission dynamics remains a serious bone of contention in pertussis epidemiology. The disagreement has largely stemmed from a lack of consensus about the total burden of pertussis infections, which can be evaluated by multiple laboratory diagnostic methods. These methods include culture of nasopharyngeal swabs, PCR and serological assays to titrate host antibodies against various *B. pertussis* antigens (typically the pertussis toxin)[47]. Although laboratory culture or PCR is the gold standard for pertussis diagnosis[48], a widespread view is that serological assays are better suited for gauging the true burden of recent or past infections, especially in demographics like adults, in which infection may lead to atypical or no symptoms. Tentatively supporting this view, epidemiological studies have reported large differences in the incidence rate and the age distribution estimated from notification data and cross-sectional seroepidemiological surveys[49]. For example, in a study during 1994–1996 in the Netherlands[50], the incidence rate estimated from notification data (with case definition based on clinical symptoms and laboratory confirmation by culture or two-point serology) peaked in young children and totalled 0.01% per year in the overall population. By stark contrast, the incidence rate estimated from a concomitant cross-sectional survey (with case definition based on one-point serology only) peaked in adults and totalled 6.6% per year – a 660-fold difference. Schematically, these discrepancies have led to a polarization of the pertussis community into two camps: the first one positing that pertussis vaccines (especially diphtheria, tetanus and acellular pertussis (DTaP) vaccines) confer only short-term protection against infection, resulting in a large pool of asymptomatically infected adults, who then transmit to susceptible children (see ref. 51 for a full presentation of this view), and the second one estimating long-lasting effectiveness of vaccines (including DTaP) with a modest transmission contribution of adults[52].

Seroepidemiology has become a frequent study design in the field of pertussis epidemiology[49] and beyond[53]. Because such studies only

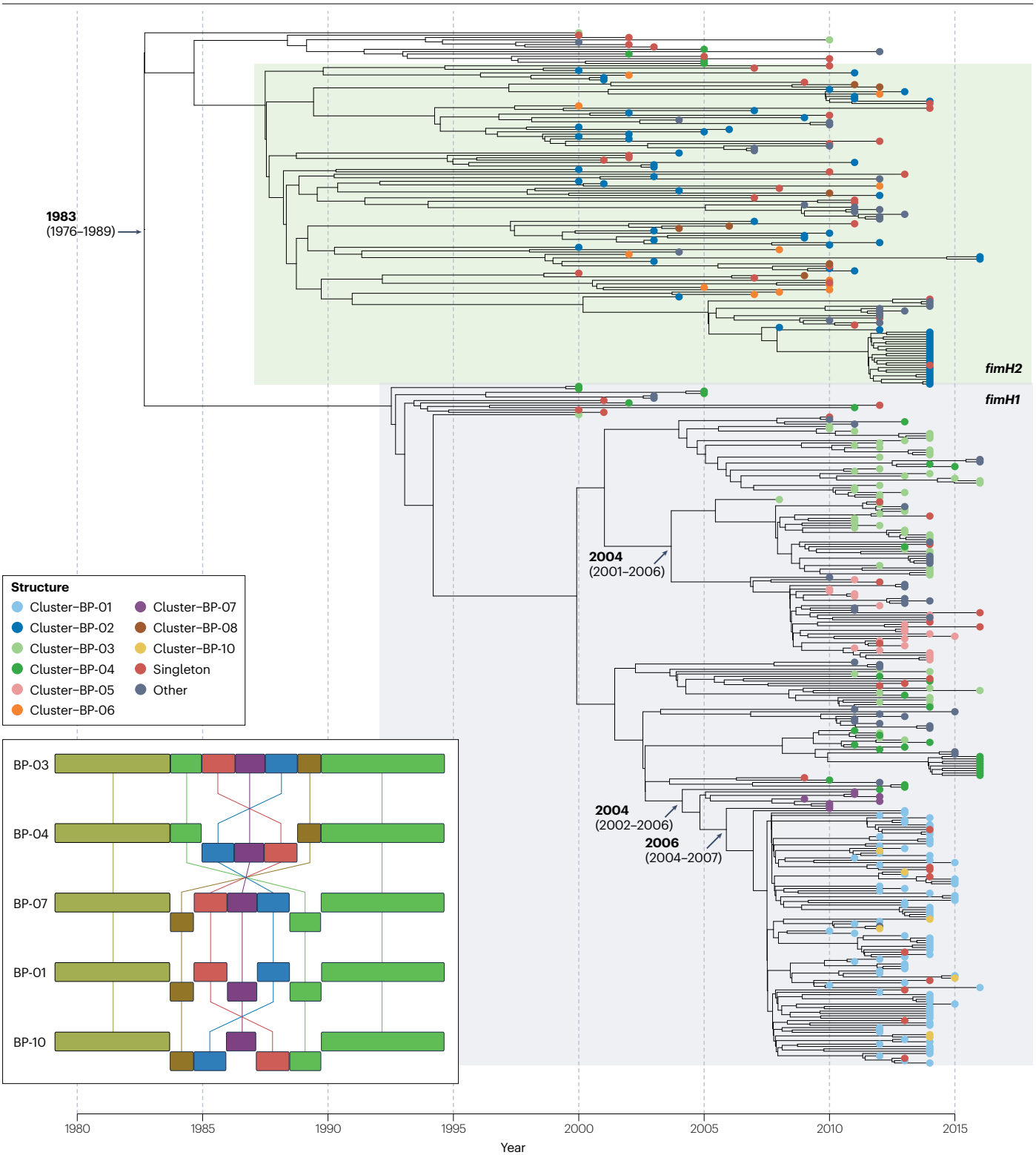


Fig. 3 | Pertussis evolution and genome shuffling. Bayesian timescaled phylogenetic reconstruction of *Bordetella pertussis* isolates from the *ptxP3-prn2-ptxA1* background was calculated using 908 variable, core nucleotides, with tip colours denoting predominant chromosomal structures (see key). The green and grey shadings highlight subclades corresponding to *fimH1* (*fim3-1*) and *fimH2* (*fim3-2*) alleles. The tree also presents estimates of the divergence date for internal nodes, together with the upper and lower bounds of highest posterior density intervals (95% HPD). To illustrate genome shuffling, the inset demonstrates that select structures could be connected by symmetric inversions. Adapted with permission from ref. 32, ASM.

require a collection of blood samples (typically, with no further information on clinical symptoms of seropositive cases), they are also easy to implement and seemingly adequate to capture the true burden of infection. Close scrutiny, however, suggests major difficulties in interpreting such studies. First, owing to the lack of definite serological correlates of protection against pertussis[54], seropositivity does not provide evidence of immunity but suggests recent infection[55]. Estimating the recency of infection, however, requires detailed models of antibody kinetics, which may vary by age and population. Although such models have been developed to back-calculate the infection time and convert seropositivity fractions to seroincidence rates[56,57], they are rarely, if ever, used in practice (Box 1). Hence, only the seropositivity fraction is typically reported, but this fraction is an ill-defined measure of pertussis burden. More fundamentally, second, seropositivity with no clinical evidence of infection may simply represent an anamnestic immune response in the absence of transmissible infection, such that serology may be unable to distinguish between infection and immune boosting[58]. Supporting this hypothesis, seropositivity without culture positivity was frequently observed in a household study part of the DTaP clinical trial in Sweden[59]. Hence, the inconsistent causal link between seropositivity and infection may severely reduce the specificity of serology-only diagnosis of recent or past infections, a concern already voiced decades ago[60,61]. This concern is also implicit in some published guidelines, which recommend attempting serological diagnosis of presumed recent infection only in the presence of symptoms compatible with pertussis, like a prolonged cough[62,63]. In addition to the evidence outlined previously[52], two recent studies have provided new insights into the unreliability of diagnosis based on serology only. The first — a case–control study to assess the effectiveness of Tdap (that is, formulations of DTaP vaccines with lower doses of diphtheria and pertussis antigens) in adults aged ≥45 years during 2006–2008 in New South Wales, Australia[64] — demonstrated a vast difference in vaccine effectiveness estimates between cases confirmed by PCR only (52, 95% CI 15–73%) and by serology only (−55, 95% CI −177 to 13%). This striking discrepancy led the authors to comment on the substantial risk of false positives (that is, low specificity) when basing the diagnosis of pertussis solely on serology. The second study — a newly developed human challenge experiment in 34 adults aged 18–45 years and vaccinated with DTwP in their infancy — provided information about the characteristics of post-vaccine infections[65]. In a dose-escalation design, the lowest dose (of 10^3 cfu) did not cause infection in any participant, whereas the highest dose (of 10^5 cfu) caused seroconversion and mostly asymptomatic infection in all participants (though we highlight uncertainty regarding how bacteria cultured on defined growth medium relates to natural transmission). Strikingly, however, extensive environmental sampling (including samples collected from masks, fomites, fingertip cultures and bedroom air after aerosol-provoking procedures such as talking or coughing) could not demonstrate any *B. pertussis* shedding from any of the infected participants. This study thus demonstrated that achieving an asymptomatic pertussis infection is possible given a sufficiently high inoculum dose, but the absence of subsequent shedding by these participants raises questions about the potential onward transmission impact of asymptomatic infections, as discussed previously[66,67]. Altogether, the collective evidence suggests that, even though asymptomatic infections can undoubtedly occur (even in infants[68]) and be detected by serology, their transmissibility and impact on pertussis population dynamics is unclear. Hence, asymptomatic infections may currently be portrayed as the 'dark matter' (ref. 69) of pertussis — a potentially large but poorly characterized mass of infections purported to explain pertussis epidemiology.

To characterize asymptomatic infections, several epidemiological study designs are possible, such as vaccine studies to estimate the infectiousness of vaccinated breakthrough cases[70]. Such studies, however, are difficult to implement and have remained rare in the pertussis literature[71]. Alternatively, mathematical models of pertussis transmission can be formulated and compared with epidemiological data to test a range of hypotheses about asymptomatic infections. This comparison has been aided by recent advances in statistical inference methods[72,73], which now enable the estimation of increasingly realistic population-based models that can include seasonality, demography, age-specific contact patterns and multiple sources of stochasticity while correcting for case underreporting (known to be substantial for pertussis[74–76]). When challenged to explain longitudinal incidence data, these models have provided robust evidence for a minimal impact of asymptomatic infections across multiple locations, including Thailand[77], Sweden[78], England and Wales[79], and the USA[80,81]. It should be noted, however, that none of these studies considered data from seroepidemiological studies. Mirroring the dissimilarities between pertussis burden estimates reported above, comparable models fitted to seroprevalence data (or both notification and seroprevalence data, but without addressing the potential lack of specificity of the latter) have arrived at different conclusions[82,83]. Hence, developing transmission models that simultaneously incorporate multiple data streams is a promising line of future research to settle the persisting uncertainties about asymptomatic infections (see Supplementary Texts 3 and 4 for an illustration of such models). Extending the human challenge model to

Box 1 | Checkpoints for conducting and reporting seroepidemiological studies of pertussis

Study design

- If possible, collect clinical information to support the presence of pertussis infection in putative cases detected by serology. If not possible, the seroepidemiological burden estimates should be interpreted with caution because of the possibility of false positives caused by anamnestic responses (see discussion in the main text and Supplementary Texts 3 and 4).
- Collect pertussis notification data in the source population for comparison with seroepidemiological burden estimates.

Estimation

- Use the formula $p_{est} = S_e p_{true} + (1 - S_p)(1 - p_{true})$ to estimate the true burden of infection p_{true} from the study's estimate p_{est} and external estimates of sensitivity S_e and specificity S_p, for $p_{est} > S_p$. For $p_{est} \leq S_p$, the study's estimate is consistent with no pertussis ($p_{true} = 0$). Ideally, the estimates of sensitivity and specificity should be derived from the source population, to avoid spectrum bias.
- For studies based on one-point serology, test multiple cut-offs for the antibody titre separating cases and non-cases and report the resulting range of seropositivity estimates.
- On the basis of the antibody titres measured in the study population, back-calculate the infection times and estimate the resulting seroincidence rate of infection in the study population. These calculations, based on existing methodology[56], are implemented in the R package seroincidence[57].

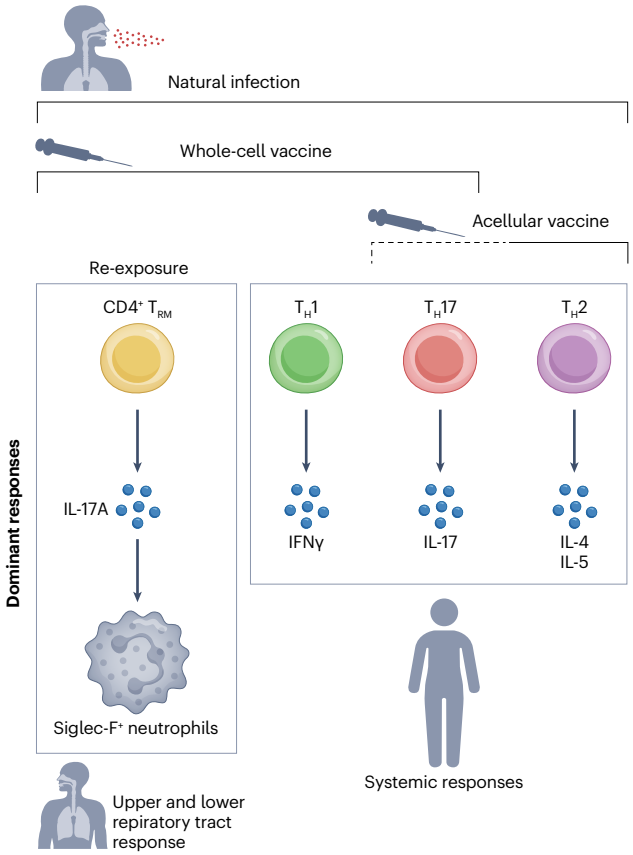


Fig. 4 | Differential immune responses to natural *Bordetella pertussis* infection and immunization with whole-cell and acellular vaccines. During *B. pertussis* infection, specific tissue-resident memory T (T_{RM}) cells accumulate within the upper and lower respiratory tract, including the nasal cavity. These $CD4^+$ T_{RM} cells secret IL-17A, which is involved in the clearance of *B. pertussis* from the nasopharynx and, upon reinfection, promotes the recruitment of neutrophils (in particular Siglec-F^+) to the nasal mucosa[118]. In contrast to immunization with an acellular vaccine, immunization of mice with a whole-cell vaccine results in the accumulation of $CD69^+CD4^+$ T_{RM} cells within the upper respiratory tract following re-exposure to *B. pertussis*[120]. Studies in baboons show that whole-cell vaccines significantly reduce the *B. pertussis* loads within the nasopharynx and prevent transmission to non-infected animals whereas an acellular vaccine protects the animals from disease symptoms, without reducing the *B. pertussis* dwell times within the nasopharynx or preventing onward transmission[85]. These differences may be owing to the absence of an increase in T_H1 and T_H17 lymphocyte activity in individuals receiving an acellular vaccine. By contrast, the expansion of T_H1 and T_H17 cells was described in individuals immunized with whole-cell vaccine and boosted with either whole-cell or acellular vaccines[131]. Reprinted from ref. 37, CC BY 4.0.

individuals vaccinated with aP will also be essential to better characterize post-aP infections and resolve the disagreement between the experimental evidence from animal models and the epidemiological evidence from human populations[84–86].

Waning immunity — how long-lasting is protection?

The issue of immunity to pertussis infection and vaccines has been long-standing, dating back many decades[87–90]. This is in part because of the absence of serological markers of protection[91,92] and the documented instances of reinfection following infection[93] and immunization[94].

Discussion of pertussis immunity has focused on the dual questions of nature and duration: does immunity protect against infection or disease[81,95]? And how long-lasting is immunity[96]? Until about 15 years ago, there was much concern among pertussis clinicians and immunologists that infection-derived and wP vaccine-derived immunity primarily affected disease severity (and not transmission) and were short-lived[89,96,97]. These conclusions were at odds with the epidemiological evidence. Studies aiming to explain the patterns of extinction or epidemic frequency have pointed towards transmission-blocking protection that is long-lasting[79,80,98]. A population-based study in California, USA, in 2017 confirmed the rarity of repeat infections with 0.1% of children becoming reinfected within 4 years of follow-up[99].

The introduction of the baboon model of *B. pertussis* infection was instrumental in causing a widespread rethink, pointing out that the immunological response to pertussis infection and vaccination with wP are similar (both T_H1 and T_H17 dominated) and are associated with substantially reduced risk of breakthrough infection[85,100] (see below).

The protective effects of acellular vaccines remain much more controversial. Resurgent pertussis outbreaks in some countries with high vaccination coverage (for example, the UK) followed a few years after the switch to aP vaccines[101], fuelling suspicion that these vaccines not only offer significantly weaker protection against transmission than wP vaccines, but their protective effects wane rapidly[102]. Evidence from animal models has identified differences in the immune response to aP vaccination, compared with infection or immunization with wP vaccines. Specifically, as illustrated in Fig. 4, it is now understood that the immune response to aP vaccines is T_H2 dominated, with increased production of cytokines IL-4, IL-9 and TGFβ, as well as reduced production of opsonizing and neutralizing IgG antibodies[37,85,103]. Together, these observations have led to a general narrative that aP vaccines are associated with transient protection against disease (not colonization nor onward transmission) and permit circulation of the bacterium via asymptomatic infections. This conclusion was bolstered by phylodynamic analysis of pertussis sequences that suggested higher bacterial diversity than would be expected by disease incidence[101], though it is unclear whether this result is because of substantially higher numbers of available sequences in the aP vaccine era.

A number of authors have attempted to examine the duration of protection afforded by aP vaccines by quantifying vaccine effectiveness as a function of time since the last vaccine dose. One study examined pertussis incidence among a cohort of children in California, USA, and calculated that the odds of acquiring pertussis increased by 42% per annum for ~8 years following the fifth dose of DTaP[102]. This study has been criticized on grounds that the absence of a non-vaccinated control group means that its conclusions were based on relative rather than absolute vaccine effectiveness, which is better than the authors appreciated[104]. Elsewhere, it has been demonstrated that the observations reported in the study[102] may parsimoniously arise from a combination of very slow waning of DTaP protection and children entering school where contacts and exposure rates to pertussis are high[105]. A recent retrospective cohort study of children in King County, Washington, USA, concluded that there was no evidence for waning of vaccine effectiveness for up to 4 years after five doses of the aP vaccine[106]. Finally, the pitfalls of attempting to compare estimates of pertussis waning among studies given differences in controls have been demonstrated[107]. Controls may be either identified through laboratories in a test-negative design (TND) or obtained via administrative databases in a frequency-matched design (FMD). Using data from Ontario, Canada, from 2005 to 2015, the controls in each group were

examined and significant confounders between cases and controls were noted in the TND but not FMD, including age, vaccination history, comorbidities and higher healthcare use. These differences affected vaccine effectiveness estimates. Within 3 years of immunization, vaccine effectiveness estimates were comparable (TND: 84%; FMD: 89%). Whereas FMD vaccine effectiveness estimates declined slowly with time since immunization, TND estimates decreased rapidly, such that 8 years post-vaccination the vaccine effectiveness estimates were 41% and 74% for TND and FMD, respectively.

Other attempts to quantify the duration and effectiveness of aP vaccines have relied on confronting age-specific pertussis incidence data with mechanistic models of transmission dynamics[79–81,108,109] (Table 1). In this case, the hope is to use computational models to extract information efficiently on vaccine traits that is implicitly embedded within the statistical characteristics of incidence reports[110], including the frequency and duration of extinction events, temporal trends in the size and frequency of outbreaks and the dynamics of the age distribution of cases. These features of the data are well known to be shaped by factors that determine the pool of individuals susceptible to pertussis, including demographic factors (per capita birth rates) and vaccine traits (duration of protection, probability of failure to take[111]). Modelling studies have fitted different kinds of models to data from different populations using a diversity of statistical methods and, in the process, have arrived at different conclusions. Studies using less formal approaches to model fitting have identified rapid loss of aP vaccine-derived immunity with estimates in the range of 5–10 years (refs. 108,109). Other research using formal computational statistics methods has instead estimated protection that lasts, on average, many decades[80,81,112] Of note, the estimation of aP vaccine-derived duration of protection against infection may be biased if unobserved natural exposures to *B. pertussis* frequently boost immunity. However, the collective evidence from modelling studies indicates that the epidemiological impact of immune boosting is limited[77,79–81,113], especially in well-vaccinated populations with low rates of natural exposure.

An intriguing explanation for the differences in the estimated effectiveness of aP vaccines relates to the complexities associated with these vaccines and their interactions with other vaccines. As demonstrated in Fig. 2, there is considerable geographic heterogeneity in the pattern of pertussis resurgence. In particular, a number of countries with long-standing aP immunization programs and high coverage have not experienced resurgence[52,114]. One intriguing proposed explanation for this variation in the experience of populations with aP vaccines is the potential interaction with other vaccines. One such example is the potential nonspecific impact of the BCG vaccine. It has been demonstrated that BCG vaccination of mice before the administration of DTaP can trigger a T_H1-dominated immune response[115]. This effect may have important population-level effects. Comparison of the incidence of pertussis in countries with existing BCG vaccination to those without indicates a 10-fold lower incidence of pertussis in countries where the DTaP vaccine follows the BCG vaccine, comparable with the incidence observed in countries using diphtheria, tetanus and whole-cell pertussis (DTwP)[115]. The protective effects of BCG-induced trained immunity have recently been confirmed in a human clinical trial[116]. A second possible interaction among vaccines is between Tdap and the inactivated poliovirus when combined in the Tdap-IPV vaccine. A recent study reported vaccines containing IPV led to an enhanced innate immune activity that was associated with persistent pertussis-specific antibody responses[117].

An important new development in pertussis immunity has been a move away from antibody-focused approaches leading to the identification of tissue-resident memory (T_{RM}) $CD4^+$ T cells in the lungs, stimulated by pertussis antigen-induced IL-17 production, that determine vaccine-derived and infection-derived mucosal immune

Table 1 | DTaP properties estimated from age-structured transmission models fitted to incidence data

Study	Model type	Estimation method	Vaccine effectiveness (%)	Waning immunity distribution, *D*	Waning immunity, *E*(*D*) (years)	Waning immunity[a], *E*(*D*|*D*<τ) (years)	Waning immunity, *p*(*D*<5) (%)	Leakiness (%)	Model fit
Ref. 154, Norway 1996–2010	Static deterministic	Maximum likelihood optimization (full parameter search)	82	Non-parametric[b]	9.6	NA	15–30	0 (F)	NA
Ref. 80, USA 1950–2009	Dynamic deterministic	MCMC (full parameter search)	80 (78–82)	Exponential (F)	55.6 (50.0–66.7)	30.7 (29.8–32.2)	9 (7–10)	0 (F)	Good (Fig. 3)
Ref. 108, England and Wales 1954–2013	Dynamic deterministic	Grid sampling (limited parameter search)[c]	100 (F)	Exponential (F)	IQR: 7.5–17.5	IQR: 7.5–16.7	IQR: 25–49	IQR: 20–50	Very poor (Supplementary Fig. 2)
Ref. 81, Massachusetts, USA, 1990–2005	Dynamic stochastic	Maximum iterated filtering algorithm (full parameter search)	95 (86–98)	Exponential (F)	58.9 (25.6–500)	31.2 (21.9–38.9)	8 (1–18)	5 (1–7)	Good (Fig. 2)

Unless otherwise stated, ranges represent 95% confidence intervals. DTaP, diphtheria, tetanus and acellular pertussis; F, fixed parameters (not estimated from the data); IQR, interquartile range; MCMC, Markov Chain Monte Carlo; NA, not available. [a]For estimates of DTaP waning, $E(D|D<\tau)$ represents the average duration of immunity conditioned on survival, assuming a constant lifespan $\tau = 80$ years (see ref. 155 for the mathematical derivation); $p(D<5)$ represents the probability that immunity wanes within 5 years after receipt of DTaP. [b]A non-parametric distribution with two modes at 7 and 12 years post-DTaP resulted in the best fit; gamma distributions were also fitted but did not explain the data as well, and the corresponding estimates were inconsistent across time periods (see Supplementary Fig. 5 and Table 2 in ref. 154). [c]The likelihood was evaluated on a pre-specified grid of parameters (nine leakiness values in the range 10–90% and 11 waning rate values in the range 0.03–0.2 per year). Because of the curse of dimensionality, such an approach does not tend to identify the maximum likelihood estimates in a high-dimensional parameter space (six parameters estimated in ref. 108).

protection[103,118]. Interestingly, experiments in mice have revealed the suppression of mucosal T_H17 memory responses by aP vaccines facilitates nasal *B. pertussis* carriage[119,120]. A challenge to assessing immune status through the detection of T_{RM} is the difficulty in accessing human respiratory mucosal tissue, though a recent study has demonstrated the feasibility of detecting T_{RM} cells from nasal tissue cells suggesting a plausible means of assessing individual immunity[121].

Countering pertussis resurgence

Booster programs

As reviewed in the previous section, despite the ongoing debates about DTaP immunity[81,85,86,122,123], as a whole the current evidence indicates that these vaccines confer initially high but slowly waning protection against infection[80,104,105], and suggests that observed resurgences may be owing to other causes, such as incomplete vaccine coverage (Supplementary Text 5), vaccine composition, increasing incidence of other bordetellae and bacterial evolution. According to theoretical predictions, supported by the observation that pertussis remains endemic in many, if not all, parts of the world (Fig. 2), this gradual loss of vaccine protection and the high transmissibility of pertussis — with basic reproduction numbers estimated at around 10 in realistic age-structured models[78,80,81] — make elimination via primary immunization alone with existing aP vaccines impossible[81]. Hence, as previously demonstrated for the USA[81,105], these effective but imperfect vaccines can still result in a high burden of pertussis, with periodic epidemics in school-aged children and teenagers even in well-vaccinated populations. Exacerbating this control problem, the complex epidemiological dynamics of pertussis may result in transient effects such as the 'end-of-honeymoon' effect, characterized by a resurgence and a shift of infections to adolescents and adults decades after the start of primary immunization[81,124]. Therefore, a limitation of current DTaP vaccines is the need for additional booster doses to supplement immunity from primary immunization and to control pertussis more effectively.

Available since the early 2000s, Tdap vaccines are now recommended in multiple countries for booster immunization, predominantly in adolescents (Fig. 1b). To establish a scientific basis for choosing target age groups for Tdap boosters, two main questions must be addressed. First, what is the general control objective — specifically, in which age group one aims to reduce pertussis? Indeed, because the benefits of boosters in a target age group may not extend beyond that group, no universally best strategy may exist, but only multiple strategies with different trade-offs between age groups. When the control goal is to confer indirect protection (for example, to unvaccinated newborns), identifying an effective booster strategy becomes more difficult because it requires a detailed understanding of the sources of infection to the target age group and, more generally, of transmission dynamics across age groups. Second, what is the degree of protection conferred by booster vaccination? Intuitively, this question is also critical, as, for instance, more rapid waning immunity would necessitate more frequent boosters to sustain protection. Mathematically, the answers to these two questions then translate the choice of age groups receiving Tdap boosters into an optimization problem, in which the cost function (potentially combining economic and health costs) and the impact of any boosting strategy can be unambiguously defined.

Following this approach, a prior study combined an empirically validated age-structured model of pertussis transmission with a genetic algorithm to identify cost-effective booster vaccination strategies[125]. A key finding was that not only the overall effectiveness of vaccine boosters but also the mechanism of vaccine failure predicted the optimal boosting strategies, with a single preschool booster needed for vaccines failing in take (owing to either incomplete coverage or low effectiveness) and multiple boosters in adolescents and adults for vaccines failing in duration (that is, conferring transient protection). These large differences in predicted boosting strategies emphasize that a prerequisite to the optimal deployment of Tdap vaccines is detailed knowledge of the immunity they confer.

Previous studies have shed some light on the properties of Tdap vaccines. In a clinical trial in the USA in adults aged 15–65 years, monitored for 2.5 years after vaccination, the effectiveness of the GSK Tdap vaccine was estimated at 92% (32–99%)[126]. Three subsequent observational studies in the USA have shown that, in populations of adolescents having received their full five-dose DTaP series, the extra protection conferred by a Tdap booster was high <1 year after receipt (~70% reduction in pertussis risk) but declined rapidly to become negligible 3–4 years after[127–129]. A limitation of these studies was the absence of a fully unvaccinated control group (that is, not vaccinated with DTaP nor Tdap), such that the reported estimates of Tdap effectiveness were relative, not absolute. In a meta-analysis of the three USA studies, this interpretation subtlety was pointed out and, after careful modelling to convert relative vaccine effectiveness estimates into absolute vaccine effectiveness estimates, it was estimated that the absolute vaccine effectiveness after adolescent boosting (that is, after five doses of DTaP and one dose of Tdap) was initially 85% and declined by ~12% every year[104]. In addition to the clinical trial[126], observational studies, including the study in Australia discussed above[64], also demonstrated the effectiveness of Tdap in adults.

Altogether, the current epidemiological evidence suggests that Tdap boosters confer initially high but gradually waning protection in adolescents and adults. However, the evidence from immunological studies offers additional lines of epidemiological research to characterize Tdap immunity fully. Of particular relevance is the observation that the immune response to boosters depends on the host's vaccination history, in particular the type of vaccine used for primary immunization (with wP vaccine-primed individuals mounting more robust antibody and memory B cell responses[130–132]). Assessing the epidemiological consequences of these immunological complexities will, thus, be essential to develop more realistic models of pertussis transmission and vaccination and to predict optimal Tdap boosting strategies.

Maternal immunization

The first dose of the currently licensed pertussis vaccines is generally recommended a few months after birth (Fig. 1a). An undesired consequence of this schedule is that it results in a window of susceptibility, during which newborns remain unvaccinated and vulnerable to pertussis infection. This susceptibility window is particularly problematic for pertussis because unvaccinated newborns suffer the highest risks of infection, hospitalization, and death. Indeed, according to 2014 estimates from a modelling study, pertussis resulted in approximately 5 million cases and 86 thousand deaths in children <1 year old worldwide, predominantly in low-income countries[133]. More direct observations have confirmed a large burden of pertussis in infants <6 months, with pertussis-related hospitalization rates of 100–1,000/100,000 per year, even in well-vaccinated populations of high-income countries[134]. Although vaccinating at birth could theoretically close this susceptibility window, none of the current vaccines is licensed for this purpose. More generally, such a strategy may not be advisable, given the robust evidence showing that vaccinating too early reduces the immune response to pertussis vaccines and other vaccines — potentially as a consequence of interference with maternal antibodies and incomplete maturation of the newborn's

immune system[135]. Hence, a central goal of pertussis control has been to devise other strategies to protect unvaccinated newborns and reduce their risk of pertussis until receipt of the first vaccine dose.

The so-called cocooning strategy, that is, Tdap vaccination of adult family members and other adult close contacts of newborns, was the first implemented to protect unvaccinated newborns[136]. Although successful in some settings[137], this strategy generally had little impact on the burden of pertussis in unvaccinated newborns[138,139]. Various hypotheses have been put forth to explain this lack of impact, such as the practical challenges of forming the cocoon[55], the lack of vaccine protection against asymptomatic infections[101], or the fact that siblings are the predominant source of transmission to infants[81]. A promising alternative strategy (first deployed in 2012 in the UK and the USA) is to give a Tdap booster to mothers during their pregnancy, so they can transfer their antibodies that will provide passive protection to the newborns during their first months of life. Compared with the cocooning strategy, this so-called antenatal maternal immunization strategy is easier to implement (as it requires only one dose of Tdap) and is expected to provide more direct, though passive, protection to the newborn. Indeed, a robust body of epidemiological evidence demonstrated the effectiveness of this strategy, with 70–95% reductions in laboratory-confirmed disease of unvaccinated newborns estimated in Australia[140], the UK[141,142] and the USA[143,144]. These encouraging figures have led the WHO[55] and multiple countries (Fig. 1b and ref. 145) to recommend maternal immunization, now considered a pivotal intervention for controlling infant pertussis.

Despite these undeniable successes, the possibility of immunological blunting (that is, immunological mechanisms whereby maternal antibodies interfere with the infant's immune response to primary vaccination) has caused concern. The current pieces of evidence have revealed an intriguing discrepancy. On the one hand, immunological studies have provided unequivocal proof that, after primary immunization, infants born to mothers vaccinated during pregnancy developed lower immunity to various *B. pertussis* antigens than infants born to unvaccinated mothers[146]. On the other hand, epidemiological studies have provided mixed evidence about the relative risk of pertussis after primary vaccination in infants born to vaccinated mothers versus unvaccinated mothers, with no indication of blunting in some studies and suggestion of it in others[140,142,143]. A meta-analysis of these studies confirmed the large remaining uncertainty in the available relative risk estimates[147]. Using a transmission model to interpret this evidence, it was shown that transient dynamics could mask the impact of blunting for many years after the roll-out of maternal immunization. In all scenarios, however, maternal immunization was predicted to remain effective at protecting unvaccinated newborns, supporting current recommendations. Altogether, this study suggests that the current epidemiological evidence is too limited to rule out a clinical impact of immunological blunting, calling for more research to resolve the remaining uncertainties.

New vaccines

As reviewed in ref. 92, given existing narratives regarding the duration and effectiveness of aP vaccine-derived protection, attempts to halt the re-emergence of pertussis have inevitably focused on the development of new vaccines. Candidate new wP vaccines have explored two independent avenues. First, they have examined ways to ameliorate endotoxic activity and hence reactogenicity by reducing the quantity of lipopolysaccharide[148]. Second, they have striven to find ways in which greater mucosal and systemic immunity may be induced. An example of this is BPZE1, a new molecularly attenuated live vaccine that is intranasally delivered[149,150]. In parallel, the development of a new suite of aP vaccines is focused on the following: the inclusion of additional antigens[92], the inclusion of novel adjuvants with the aim of promoting a T_H1 or T_H17 immune response[151], vaccines with genetically (rather than chemically) detoxified pertussis toxin to induce a higher immune response[92], and new vaccine delivery mechanisms including microparticles and outer membrane vesicles[92]. Finally, a promising study has demonstrated that intranasal administration of an experimental aP vaccine formulated with a more potent adjuvant than aluminium salt can induce respiratory T_{RM} cells in mice[152]. To afford long-term protection against infection, it is imperative that any new vaccine avoids blunting the T_{RM} response in the nasopharyngeal mucosa. We expect it will be a number of years until a cost-effective and safe alternative to existing wP and aP vaccines is identified. Until then, improving our understanding of the protectiveness of contemporary vaccines and their efficient deployment as part of the routine schedule and booster programs remains a priority.

Discussion and conclusions

In this Review, we presented an up-to-date picture of global pertussis epidemiology and the heterogeneity in immunization practices and coverage. Our analyses identify considerable variability in trends across countries and stress the importance of understanding the complexity of pertussis population biology, which stems from the interplay between country-specific immunization policies, vaccine components, regional variations in sociodemographic factors and in the genetic make-up of the aetiological agents, and heterogeneities among individuals in transmission and disease. Nevertheless, the burden of pertussis makes it worthwhile to reconsider received wisdom in the context of all available evidence.

Our synthesis of the available empirical evidence has focused on the prevailing explanations for pertussis resurgence, control and evolution, paying particular attention to promising ideas that may help explain some of the complexities of pertussis, with implications that can be tested by integrating computational models with appropriate data. Overall, we find compelling evidence for the impact of evolution on pertussis epidemiology. This stems from increasing support for vaccine-driven evolution away from antigens contained in aP vaccines, as well as the improved understanding of the epidemiology and detection of other bordetellae, especially *B. holmesii*. There continues to be much attention focused on bringing to bear available methodologies from biometrics and computational statistics for estimation of key parameters from longitudinal cohort and incidence data to illuminate the mechanisms and duration of immunity conferred by infection and by wP and aP vaccines. These issues will increasingly be testable using the recently pioneered human challenge system. Ultimately, this information will be critical for the design of cost-effective and efficient immunization strategies, including teenage and adult boosters.

In 1988, discussing the consequences of the apparent contradictions in pertussis biology, Preston commented that "However, controversy abounds–mainly because so many of us have a blinkered approach. If our various ships are to reach the haven of pertussis eradication, their captains and pilots and navigators might do well to read each other's maps and exchange each other's compasses!"[153]. In the intervening 35 years, the importance of adopting an integrative approach to pertussis has become even more apparent. We submit that achieving Preston's vision of a holistic understanding of pertussis will require interdisciplinary collaboration to reconcile immunological, epidemiological, serological and phylogenetic data.

Data availability

All data and R programming code for Figs. 1 and 2 and Supplementary Fig. 2 are freely available from Edmond, the Open Data Repository of the Max Planck Society.

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Author contributions

The authors contributed equally to all aspects of the article.

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