Taylor & Francis
Taylor & Francis Group

Human Vaccines & Immunotherapeutics

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/khvi20

# Understanding the impact of adult pertussis and current approaches to vaccination: A narrative review and expert panel recommendations

**Peter Kardos, Jaime Correia de Sousa, Ulrich Heininger, Andreas Konstantopoulos, C. Raina MacIntyre, Donald Middleton, Terry Nolan, Alberto Papi, Adrian Rendon, Albert Rizzo, Kim Sampson, Alessandro Sette, Elizabeth Sobczyk, Tina Tan, Catherine Weil-Olivier, Birgit Weinberger, Tom Wilkinson & Carl Heinz Wirsing von König**

**To cite this article:** Peter Kardos, Jaime Correia de Sousa, Ulrich Heininger, Andreas Konstantopoulos, C. Raina MacIntyre, Donald Middleton, Terry Nolan, Alberto Papi, Adrian Rendon, Albert Rizzo, Kim Sampson, Alessandro Sette, Elizabeth Sobczyk, Tina Tan, Catherine Weil-Olivier, Birgit Weinberger, Tom Wilkinson & Carl Heinz Wirsing von König (2024) Understanding the impact of adult pertussis and current approaches to vaccination: A narrative review and expert panel recommendations, Human Vaccines & Immunotherapeutics, 20:1, 2324547, DOI: 10.1080/21645515.2024.2324547

**To link to this article:** https://doi.org/10.1080/21645515.2024.2324547

HUMAN VACCINES & IMMUNOTHERAPEUTICS
2024, VOL. 20, NO. 1, 2324547
https://doi.org/10.1080/21645515.2024.2324547

Taylor & Francis
Taylor & Francis Group

REVIEW

OPEN ACCESS Check for updates

# Understanding the impact of adult pertussis and current approaches to vaccination: A narrative review and expert panel recommendations

Peter Kardos[a], Jaime Correia de Sousa[b], Ulrich Heininger[c], Andreas Konstantopoulos[d], C. Raina MacIntyre[e], Donald Middleton[f], Terry Nolan[g], Alberto Papi[h], Adrian Rendon[i], Albert Rizzo[j], Kim Sampson[k], Alessandro Sette[l], Elizabeth Sobczyk[m], Tina Tan[n], Catherine Weil-Olivier[o], Birgit Weinberger[p], Tom Wilkinson[q], and Carl Heinz Wirsing von König[r]

[a]Group Practice & Center, Allergy, Respiratory and Sleep Medicine, Maingau Hospital of the Red Cross, Frankfurt am Main, Germany; [b]Life and Health Sciences Research Institute, School of Medicine, University of Minho School of Medicine, Braga, Portugal; [c]Pediatric Infectious Diseases and Vaccinology, University of Basel Children's Hospital, Basel Switzerland; [d]Department of Pediatrics, University of Athens, Athens, Greece; [e]Kirby Institute, UNSW Medicine, University of New South Wales, Sydney, Australia; [f]Department of Pediatrics, University of Pittsburgh Medical Center, Pittsburgh, USA; [g]Department of Infectious Diseases, University of Melbourne, Melbourne, Australia; [h]Department of Translational Medicine, University of Ferrara, Ferrara, Italy; [i]Pulmonary/Critical Care Division, Autonomous University of Nuevo León, San Nicolás de los Garza, Mexico; [j]American Lung Association, Chicago, USA; [k]Immunisation Coalition, Melbourne, Australia; [l]Center for Infectious Disease and Vaccine Research, La Jolla Institute for Immunology, San Diego, USA; [m]AMDA – The Society for Post-Acute and Long-Term Care Medicine, Denver, USA; [n]Feinberg School of Medicine, Northwestern University, Chicago, USA; [o]Department of Pediatrics, University of Paris, Paris, France; [p]Institute for Biomedical Aging Research, Universität Innsbruck, Innsbruck, Austria; [q]Faculty of Medicine, University of Southampton, Southampton, UK; [r]Clinical Microbiology Consultant, Cologne, Germany

**ABSTRACT**

Pertussis has several notable consequences, causing economic burden, increased strain on healthcare facilities, and reductions in quality of life. Recent years have seen a trend toward an increase in pertussis cases affecting older children and adults. To boost immunity, and protect vulnerable populations, an enduring approach to vaccination has been proposed, but gaps remain in the evidence surrounding adult vaccination that are needed to inform such a policy. Gaps include: the true incidence of pertussis and its complications in adults; regional variations in disease recognition and reporting; and incidence of severe disease, hospitalizations, and deaths in older adults. Better data on the efficacy/effectiveness of pertussis vaccination in adults, duration of protection, and factors leading to poor vaccine uptake are needed. Addressing the critical evidence gaps will help highlight important areas of unmet need and justify the importance of adult pertussis vaccination to healthcare professionals, policymakers, and payers.

**ARTICLE HISTORY**
Received 4 January 2024
Revised 16 February 2024
Accepted 25 February 2024

**KEYWORDS**
*Bordetella pertussis*; disease burden; underreporting; Tdap vaccination; adults

## Introduction

Pertussis is a highly contagious respiratory infection caused by the bacterium *Bordetella pertussis* and commonly characterized by severe, repeated coughing episodes.[1,2] It is a worldwide public health problem and a notifiable disease in many countries.[3,4]

Pertussis accounts for a significant level of morbidity and mortality in infants who are too young to be vaccinated worldwide, despite high levels of pediatric vaccination coverage.[3] Although widely considered a childhood illness, the age distribution of clinically significant pertussis reported in recent years has been changing in countries with high primary vaccination coverage.[3,5] Reported cases increasingly involve older children and adults, particularly where acellular pertussis (ap) vaccines have replaced whole-cell pertussis (wp) vaccines for primary vaccination.[3,5] Although case notifications and seroprevalence data provide an indication of this evolving epidemiologic pattern, the true burden of pertussis in adults is unknown due to lack of recognition and underreporting in clinical practice.[3,6] Pertussis can have severe and sometimes fatal consequences in adults, and is associated with a significant detrimental impact on quality of life, and substantial healthcare utilization and costs.[7–11]

An enduring (lifelong) approach to pertussis vaccination has been proposed to increase immunity and reduce disease burden in all age groups, while helping to decrease the risk of transmission to unvaccinated infants and other vulnerable populations.[6,12] However, universal adult vaccination recommendations have not been adopted consistently or funded even in high-income countries. Where recommendations are in place, evidence of low uptake is common.[13–16]

A previous publication examined methods to improve pertussis vaccination in at-risk groups including older adults.[17] The current publication, developed by an international panel of pertussis experts, builds on that article to provide up-to-date perspectives on the burden of pertussis in adults, identify current gaps in the evidence around adult Tdap vaccination, and lay out recommendations for future research directions.

## Methods

In July 2022, an academic panel was assembled to discuss their views on the evolving epidemiology of *B. pertussis* infection and the need for adult pertussis vaccination. The panel

**CONTACT** Peter Kardos kardos@lungenzentrum-maingau.de Group Practice and Centre, Red Cross Maingau Hospital, Office: Friedberger Anlage 31-32, Frankfurt am Main 60316, Germany.

Supplemental data for this article can be accessed on the publisher's website at https://doi.org/10.1080/21645515.2024.2324547.

consisted of 24 renowned national and international experts in pertussis and vaccination from 14 countries.

The panel discussion was organized by Sanofi, took place during seven virtual meeting sessions, and via an online discussion platform. Discussion was facilitated by open-ended questions relating to potential knowledge gaps and practical challenges in adult pertussis illness and pertussis vaccination in adults, with a goal of driving development of expert recommendations on how gaps might be addressed. This manuscript summarizes the panel's positions and recommendations, which are informed by key peer-reviewed publications, surveillance data, and health authority assessments, as well as real-world experience.

## Etiology, transmission, pathogenesis, and presentation of pertussis disease

Pertussis (whooping cough) is an ancient, contagious respiratory infection caused by the aerobic Gram-negative bacterium *Bordetella pertussis*, with other *Bordetella* species (e.g., *B. parapertussis, B. holmesii*) also causing pertussis-like symptoms.[1,2,18,19] The incubation period is typically 7–10 d (range: 4–21 d).[1]

Transmission most commonly occurs from human to human via contact with infectious airborne respiratory droplets from a cough or sneeze, and requires repeated or prolonged exposure and/or close contact.[1,20] Attack rates for nonimmune contacts in the household setting have been estimated at up to 90%,[21] and inoculation studies show that as few as 140 organisms are required to infect susceptible people.[20]

While the molecular pathogenesis of pertussis is not completely understood, the disease appears to be primarily toxin driven, as *B. pertussis* creates various biologically active and antigenic products, including filamentous hemagglutinin (FHA), pertactin (PRN), and pertussis toxin (PT).[1] These toxins are released when the bacteria attach to cilia of the respiratory system mucosa, paralyzing the cilia and causing inflammation in the respiratory tract.[1] Clearance of pulmonary secretions is subsequently impeded, leading to the classic symptoms of pertussis: paroxysms of rapid coughing, ending with a long inspiratory whoop (i.e., "whooping cough"), post-tussive apnea, and post-tussive emesis.[1,8] The molecular pathogenesis of pertussis has been investigated in infants, for whom disease is severe.[22] Adolescents and adults less often present with the classic symptoms of pertussis, because they are usually milder than in children,[17] yet there are limited data available on the pathology of mild or typical pertussis in adults.[23]

## Current understanding of the epidemiology of adult pertussis and burden of disease

### *Incidence, lack of recognition, and missed diagnosis*

Despite a general trend of increased childhood pertussis vaccination rates globally in recent years and declines in disease in this age group since the pre-vaccine era, pertussis remains a threat to public health.[3,24] It is an endemic disease, with cyclical outbreaks typically seen every few years and a higher incidence reported in the summer months.[18,25,26] The seasonality of pertussis remains unexplained.[25] Outbreaks among adolescents and adults are commonly associated with school and workplace settings, but may also occur in elderly residents of care homes.[8,27,28]

The epidemiology of pertussis among all age groups is not well known; there is a lack of global surveillance data for pertussis, as many countries have neither obligatory notification nor national reporting systems in place.[29] Data collected by global and local authorities over the past four decades highlight the growing burden of pertussis (Table S1). Even though pertussis is a notifiable disease in some countries, reported case rates are much lower than actual true incidence rates due to lack of recognition, missed diagnosis, and underreporting in clinical practice (Table S1).[6,7,30]

Failure to recognize pertussis has critical consequences, as timely diagnosis, isolation, and treatment of pertussis are needed to mitigate transmission to vulnerable populations and minimize potential disease complications.[1,31] Moreover, pertussis is a relatively long-lasting, but frequently self-limiting disease in adolescents and adults, thus there is a large gray area in terms of reporting disease. Several analyses of pertussis incidence over the past 40 y have indicated a resurgence in reported cases in high-income and many middle-income countries (Table S1), as well as a shift toward an increase in reported cases among adolescents and adults following widespread routine pediatric vaccination.[4,5,32–35]

The trend of an increase in adult pertussis is concerning, especially as a shift in peak incidence to include women of childbearing age may increase the risk of infection among newborns and unimmunized infants, who are at highest risk of significant morbidity, hospitalization, and death due to pertussis.[36–39] Data on pertussis in pregnant women are limited, but one US case surveillance study – conducted after maternal Tdap vaccination during pregnancy had been introduced – found similar reported rates of pertussis between pregnant and non-pregnant women.[40] Infection in older adults is also a concern because they may suffer serious complications and loss of independence, but could also be involved in grandparent care of vulnerable infants. Consequently, vaccination could prevent pertussis spreading to very young grandchildren.

Various factors probably contribute to the observed upward trends in pertussis incidence and affected older age groups, including increased awareness of the disease, developments in diagnostics, aging populations with waning immunity against *B. pertussis*, and pathogen adaptation perhaps caused by vaccine-driven immune selective pressure.[32–34,36,40] The relative contribution of these factors to the changing epidemiology of pertussis disease may differ between and within regions and countries.[32]

A 2019 systematic literature review of pertussis epidemiology in adults (≥40 y old) demonstrated that numbers of notified cases based on surveillance data were consistently and significantly (several hundred- or even thousand-fold) lower than seroprevalence data indicative of *B. pertussis* infection.[7] As well as being dependent on level of care-seeking, underreporting of pertussis in adults may in part be due to the atypical nature of adult disease, in which the classic symptom of whooping may often be absent. Pertussis may therefore not be considered a likely cause by healthcare professionals (HCPs) when evaluating subacute cough in older age groups, despite evidence of *B. pertussis* infection reported in approximately 20% of adults presenting with a persistent (7–31 d) cough and no evident diagnosis.[22,41]

A failure to recognize pertussis may be particularly important in adults with respiratory comorbidities, such as asthma and chronic obstructive pulmonary disease (COPD), due to similarities in clinical presentation with characteristics of these conditions (e.g., persistent cough); acute pertussis may be misinterpreted as a COPD or asthma exacerbation, leading to delayed or missed diagnosis.[11,42,43] Data from a seroprevalence study in adults 40–85 y of age with COPD indicate high circulation rates of *B. pertussis* in this subgroup (evidence of exposure to *B. pertussis* in 13.5% of patients over two years), adding to data from other studies suggesting an increased risk of *B. pertussis* infection and disease in adolescents and adults with COPD or asthma.[43–46]

## Impact of adult pertussis

### Disease presentation

A better insight into the signs and symptoms, and course of pertussis disease in adults could help HCPs differentiate it from other common causes of cough and ensure prompt diagnosis. However, these aspects of pertussis have not been well documented; symptoms can vary widely between age groups and throughout the disease course, making diagnosis based on clinical presentation challenging.[7,8,47]

Early symptoms in older, vaccinated adolescents and adults are frequently mild and similar to those of the common cold.[1] Conversely, delayed diagnosis and treatment of adult pertussis can result in clinical complications, sequelae, and an increased risk of transmission within households or semi-closed communities (e.g., nursing homes), adding to the individual and societal burden of disease. Pertussis-linked symptoms and the associated complications from delayed diagnosis and treatment are summarized in Table 1. It should be noted that the proportion of cases with more than one disease complication is typically greater among adults than adolescents (28% vs. 16% in one study).[8]

## Severe disease, hospitalizations, and mortality

A range of factors, including a patient's age and immunocompetence, and previous immunizations and *B. pertussis* infections, can influence the severity of pertussis symptoms and associated healthcare needs.[22] In one analysis, nearly half of surveyed adolescents and adults with pertussis rated the severity of their disease as ≥8 on a scale of 1 (very mild) to 10 (the most severe disease), and pertussis-related illness was reported to have disturbed a median of 14–21 nights of sleep.[8]

A recent literature review indicated that adolescents and adults with underlying conditions, such as asthma, COPD, obesity, or immunodeficiency, and/or past smokers, are potentially at increased risk of worsened symptoms and pertussis-related hospitalization.[6] Older adults frequently have chronic comorbidities such as asthma, COPD, or other respiratory diseases, so it is unsurprising that studies suggest severe pertussis sequelae (e.g., pneumonia as a secondary diagnosis) and pertussis-related hospitalizations increase with age[8,9,39] (Table 2). In addition, the length of hospital stays and the proportion of pertussis-related mortalities have also been suggested to increase with age (Table 2). It is also to be expected that complications arising from severe paroxysmal coughing, such as encephalopathy, intracranial hemorrhage, and herniated lumbar discs,[22] may be recorded as the cause of hospitalization, without mention of pertussis.

## Economic impact

Healthcare utilization and related costs associated with adult pertussis are substantial, particularly in adults ≥65 y old and/or those with underlying respiratory conditions, such as COPD

**Table 1.** Pertussis is associated with a multitude of symptoms, and complications from delayed diagnosis and treatment.

| Classic symptoms[1–7,8–10,22,48–53] | Secondary symptoms[10,53] | Reported complications from delayed diagnosis and treatment[1,7,8,22,48,54] |
|---|---|---|
| • Persistent cough* (mean duration 10–12 weeks†)<br>• Paroxysmal in 99% of cases<br>• Whoop<br>• Post-tussive emesis<br>• Feelings of suffocation<br>• Fainting from cough | • Rhinorrhea<br>• Pharyngitis<br>• Sweating attacks<br>• Fever<br>• Fatigue | • Sinusitis<br>• Otitis media<br>• Urinary incontinence<br>• Pneumonia<br>• Weight loss<br>• Rib fracture<br>• Cough syncope<br>• Conjunctival hemorrhage<br>• Stroke<br>• Encephalitis<br>• Seizures<br>• Rectal prolapse |

*Many adolescents and adults with serological evidence of recent *B. pertussis* infection do not report persistent cough.[1,7,8,22,48]
†Pertussis recovery time may be prolonged, with symptoms reportedly lasting up to 6 months.[10,53]

**Table 2.** The proportion of pertussis-related hospitalizations, fatalities, and the length of hospital stays increase with age.[7,8,34,39,46]

| Hospitalization proportion* | | Mean length of hospital stay | | Case-fatality rate† | |
|---|---|---|---|---|---|
| Age group | % | Age group | Days | Age group | % |
| Adolescents and adults | 1–3[8,39,46] | <50 years | 3[8] | 18–64 years | 11.5[34] |
| ≥75 years | 11–14[8,39,46] | >50 years | 17[8] | ≥65 years | 17.4[30‡] |

*Pertussis-related hospitalizations (particularly for patients with chronic diseases, where the chronic disease is likely to be documented as the cause of hospitalization despite pertussis symptoms being present).
†Pertussis-related fatalities are likely to be underestimated due to the acknowledged underreporting of the disease.[7]
‡Adults ≥65 y.

or asthma.[9,22,44,55] Furthermore, the household and societal economic burdens linked to adult pertussis often arise from direct and indirect healthcare costs (Table S2).

### Impact on quality of life

Pertussis can have a serious, detrimental impact on the quality of life of infected adults and increase risk of dependency for activities of daily living.[10,11] Persistent, severe cough has been identified as the main cause of lost quality of life in adults with pertussis, since it affects sleep, and induces vomiting and tiredness.[10,56] In a large UK study that analyzed EQ-5D questionnaire responses among confirmed pertussis cases following the 2011–2012 outbreak, the authors observed that pertussis impacts a range of quality-of-life dimensions (as shown in Figure 1) and concluded that the adverse impact of pertussis on quality of life was about 10-fold greater than that reported in a similar study of influenza.[10,57]

## Data gaps and evidence generation

### Epidemiology and burden: key evidence gaps

Several knowledge gaps in the epidemiology and burden of adult pertussis and their associated drivers were perceived by the panel (Table 3). A key example is the suitability of laboratory detection methods, which vary at different times in the disease course of pertussis (Figure 2).

The panel also concluded that to help create a better understanding of the burden of disease, additional evidence is needed on the broader individual and societal impacts of

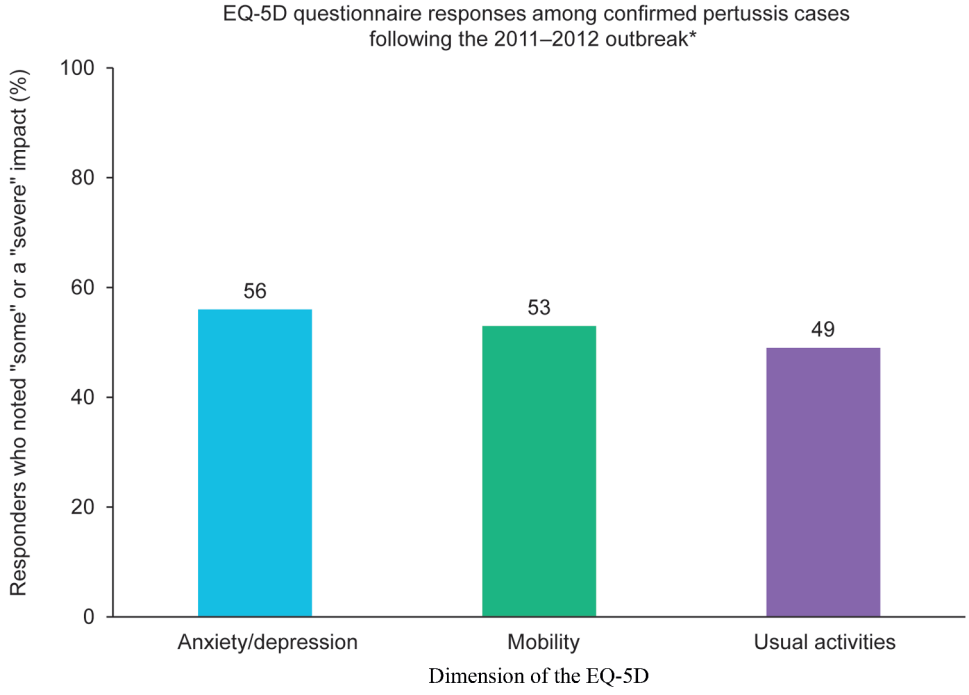


**Figure 1.** Questionnaire responses among school-age children and adults highlight the negative impact pertussis may have on quality of life.[10] *Data from a large UK study that analyzed EQ-5D (QoL questionnaire with a 5-dimension scale) responses.[10] QoL, quality of life.

**Table 3.** Knowledge gaps in the epidemiology and burden of disease identified by the panel and their associated drivers justify the importance of adult pertussis vaccination.[4,7,58]

| Identified knowledge gap | Drivers |
|---|---|
| Data on the true disease incidence and its complications in adults | • Lack of targeted, systematic testing in adults<br>○ Testing has little relevance to guide treatment, particularly for patients presenting late after the onset of coughing<br>○ Results only become available within 1–2 weeks of disease onset, before paroxysms occur, thus demotivating the utilization of tests[31]<br>• The availability and suitability of laboratory detection methods varies at different times in the disease course and in different populations (see Figure 2)<br>• Limitations of the detection techniques and cut-offs currently employed<br>• Local financial constraints on testing in different settings |
| Regional variations in disease recognition and reporting in adults | • Surveillance approaches can be insensitive and may vary widely among and within countries[4,7,59]<br>○ Variations in the case-ascertainment method (laboratory confirmed or just clinically defined)<br>○ Variations in laboratory testing methods<br>○ Variations in case definition<br>○ Variations in the age-groups reported<br>○ Presence/absence of active sentinel surveillance |
| Incidence of severe disease, hospitalizations, and deaths in older adults | • Under ascertainment of death rates or hospitalizations, or the impacts of pertussis in individuals with comorbidities[7]<br>○ Prevents comparisons of the risks of these outcomes relative to other health conditions (e.g., pneumonia or myocardial infarction) |

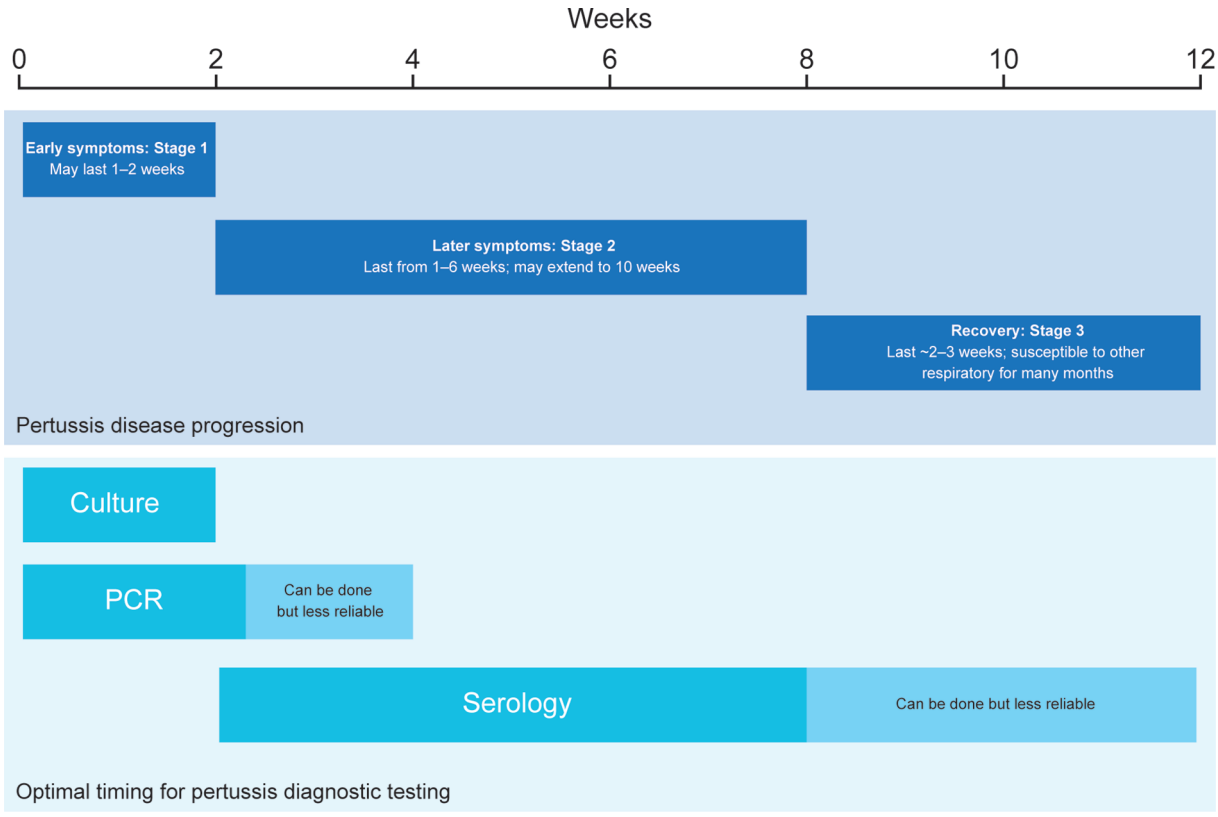


**Figure 2.** The optimal timing for pertussis diagnostic testing is dependent on the stage of disease. Adapted from https://www.cdc.gov/pertussis/about/signs-symptoms.html. PCR, polymerase chain reaction.

pertussis in the general adult population. A range of readily measurable impacts were identified by the panel as having strong potential for justifying a change in adult vaccination policy (Table S3). Overall, a detailed understanding of the burden of disease is a prerequisite for informed decisions regarding vaccination strategies.

The concept of an adverse long-term impact of other acute infections, such as RSV and SARS-CoV-2, has been established via studies in older/at-risk patients. These studies demonstrated a significant long-term worsening in health-related quality of life and frailty post infection, which was independent of potential confounders, such as age and comorbidities.[59–61] Some panel members positioned similar research as a priority for understanding the burden of adult pertussis.

Incidence of subclinical or asymptomatic adult pertussis infection is another important yet understudied topic identified by panel members. Such infections are a public health consideration, as asymptomatic carriers of *B. pertussis* do not alter their behavior to prevent disease transmission. As humans are the only source of pertussis, some asymptomatic adults could represent a highly significant reservoir of infection. Prevalent asymptomatic infection may also explain the finding of broad immunologic reactivity to hundreds of non-ap *B. pertussis* antigens seen in a recent full genome analysis of healthy ap-vaccinated adults.[62] While the formation of bacterial biofilms, which are resistant to host defenses, has been proposed as a mechanism for chronic and asymptomatic respiratory tract colonization of *Bordetella* spp. in mammals,[63] the panel noted a current absence of evidence on the role of biofilms in *B. pertussis* infection and transmission in humans.

### *Epidemiology and burden: future research directions*

Various approaches to evidence generation were proposed by the panel to address knowledge gaps in the epidemiology and burden of adult pertussis (Table S4). Panel members agreed that the highest priority was to conduct a prospective, observational global study of adults presenting with cough of unknown origin and/or respiratory symptoms (see Figure 3 and Table S4). Most panel members agreed this approach had high feasibility based on similar studies on pertussis,[64,65] and for other pathogens,[66–68] and would be high impact, in terms of providing useful data to address current gaps in understanding of the incidence and impact of adult pertussis disease. Furthermore, the panel recommended the inclusion of sensitivity analyses in future models that reflect a range of different scenarios, prior to conducting rigorous active surveillance studies to validate the models.

### *Pertussis vaccination in adults: key evidence gaps*

Panel members had differing opinions on whether the available literature accurately reflects the true benefits of Tdap vaccination in adults. Important data gaps regarding the efficacy/effectiveness of pertussis vaccination in adults remain and represent a barrier to wider implementation by policymakers. The panel emphasized that data are needed on the efficacy/effectiveness of adult vaccination in preventing pertussis-related hospitalizations, severe disease, and death, most notably in at-risk subgroups, for whom evidence of Tdap efficacy is critical. Generating robust data on these outcomes was seen as a major priority, alongside information

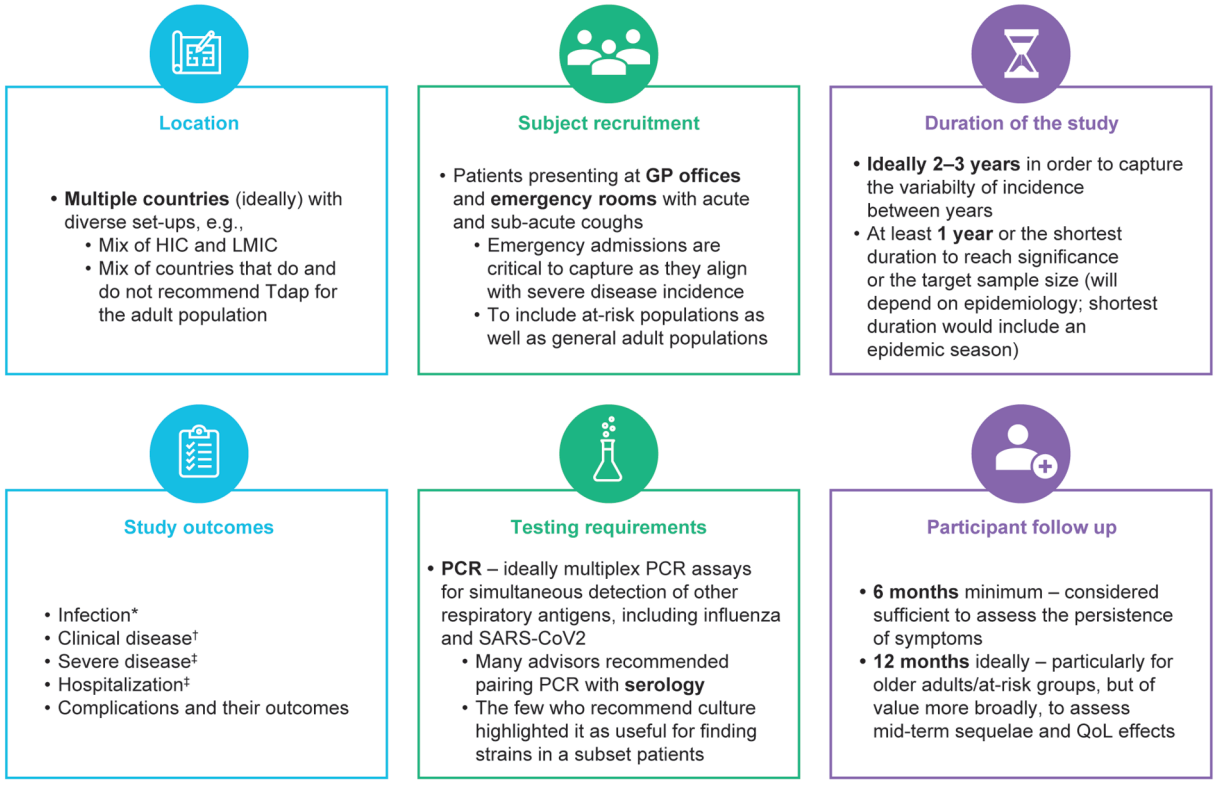


**Figure 3.** Panel recommendations for the design of a large prospective study assessing the incidence and impact of adult pertussis. *Mixed views among panel members: some felt important to include, others felt not a priority unless searching for secondary cases. †Independent of severity. ‡Both outcomes were felt to be important by several panel members, but in some cases may be difficult to adequately differentiate. GP, general practitioner; HIC, high-income country; LMIC, low-to-middle-income country; PCR, polymerase chain reaction; QoL, quality of life; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

on the safety of vaccination in older adults and those with underlying comorbidities.

The duration of protection afforded by vaccination must be evaluated, both in the general adult population and in at-risk groups. Such data are vital for designing rational, effective pertussis-containing booster vaccination programs for adults. The panel also noted that information on the immunogenicity of multiple Tdap boosters in adults is needed, including confirmation of whether immune tolerance develops over time in older adults – who are likely to have been primed with the wp vaccine – with repeat ap booster vaccinations. Older adults will typically have had asymptomatic *B. pertussis* infections during their lifetime, and the impact of immunosenescence and escape variants on Tdap booster efficacy in this population is unknown. Indeed, evidence from a recent analysis of the benefit of performing adult booster vaccinations against tetanus and diphtheria have raised questions on the rationale for combining these with pertussis boosters and the potential need for a standalone adult pertussis vaccine.[69,70]

While some research has been undertaken on the transmission dynamics of pertussis using passive surveillance,[71,72] patterns of transmission in older adults are not currently understood. The panel noted that research in this area is required to determine any indirect effects of adult Tdap vaccination on interrupting transmission and establish the most effective timing for administering adult boosters. Consideration of living arrangements and close contacts should lead to a study of household pertussis transmission and carriage.

Factors underlying the lack of uptake of adult Tdap vaccine, including among pregnant women, is another area identified by the panel as lacking in data. Implementation research is needed to understand why current adult pertussis vaccination recommendations are not more widely adhered to in routine practice,[13–16] and to provide insights on how HCP and organizational behavior can be evolved toward improved implementation practices. Further evidence generation around Tdap vaccination in underserved groups of adults, including the effects of population demography on disparities in uptake, would also help to inform the direction that needs to be taken to optimize uptake implementation strategies.

### *Pertussis vaccination in adults: future research directions*

A range of approaches to evidence generation were assessed by the panel when considering how to address the knowledge gaps around adult Tdap vaccination strategy (Table S5). These approaches included:

- **Prospective, observational cohort studies**, including studies focused on evidence generation in at-risk populations, such as COPD and asthma sufferers (either separate studies, or via subgroups in larger studies in the adult population)
- **Case – control studies** (vaccinated vs. non-vaccinated and/or non-boosted adults) in patients hospitalized with pertussis, stratified by age; ideally conducted during an outbreak

- **Prospective, parallel data collection** on pertussis disease burden and vaccination history; ideally executed in countries that have both adult Tdap recommendations and well-documented vaccination records
- **Retrospective analyses of electronic healthcare records** where databases can be linked, e.g., hospitalized patients in settings with adult Tdap recommendations and acceptable vaccine coverage
- **Seroprevalence studies** – most panel members felt such studies would have little impact on vaccination policy, where a focus on prevention of severe disease is the priority
- **Cost-effectiveness analyses** (including impact on indirect costs and quality of life) – critical for policy-making and public funding; however, robust data on Tdap efficacy/effectiveness and the true burden of adult disease are essential before undertaking such analyses
- **Contagiosity studies** – to investigate how easily pertussis is spread following index cases

On considering the potential approaches to studying Tdap efficacy/effectiveness in adults (Table S5), the panel agreed that a randomized, controlled trial evaluating the efficacy of vaccination on severe pertussis disease versus standard of care (as use of a placebo could be considered unethical) is likely to have the maximum impact on national vaccination recommendations. Agreed requirements for such a study included both a clinical diagnosis of pertussis and polymerase chain reaction (PCR) confirmation of *B. pertussis* infection, as well as the documented vaccination history of study participants. In the absence of a randomized study, real-world evidence from regions with a recommendation for adult Tdap vaccination, using a cohort or test-negative case-control study design, could also generate estimates of Tdap effectiveness and cost-effectiveness that could be used for policy decision-making.

To help address the current data gap on duration of protection from adult Tdap vaccination and determine the optimal timeframe for booster vaccinations, the panel proposed a modeling study. The typical recommendation for a 10-year booster interval for Tdap is historically based on presumed protection against tetanus, rather than on evidence demonstrating adequate protection for pertussis.

### *Future directions in pertussis vaccine research and development*

Although not completely understood, the resurgence of pertussis seen in recent decades in many high- and middle-income countries with high vaccination coverage has been widely linked to the replacement of wp vaccines with ap vaccines in the 1990s.[73–75] However, there is evidence from a recent collaborative study of Central and Eastern European countries that this might not be true.[76] Whilst both ap and wp vaccines induce durable protection from symptomatic disease, the mechanisms initiated to achieve this differ (Table 4). Indeed, several preclinical studies and exploratory analyses of blood samples from vaccinated human subjects have revealed distinct differences in *T*- and B-cell immune responses induced by ap and wp vaccines, depending on the type of vaccine used for initial priming and for subsequent booster vaccinations (see Szwejser-Zawislak *et al*. for a recent systematic review on this topic).[77]

**Table 4.** Wp and ap vaccines induce durable, but distinct immune responses.[73,78,79]

| Immunity | wp vaccine | ap vaccine |
|---|---|---|
| Confers persistent protective immunity against asymptomatic colonization of the airways or prevents transmission of *B. pertussis* to unvaccinated contacts?[73,78,79] | Yes* | No* |
| Type of Th immunity induced[78] | Th17 and Th1 (correlate with the ability to clear infection) | Th2 and Th1 (memory responses) |

*Inference made using data collected from animal models.[73,78,79]
ap, acellular pertussis; Th, t helper; wp, whole-cell pertussis.

Based on these observations, development of next-generation pertussis vaccines capable of inducing protective immunity in the respiratory tract, as well as the optimal design of life-course vaccination strategies, are now high priorities on the research agenda. The panel, however, noted important gaps in understanding that will need to be addressed to expedite these research goals, and effectively bridge the findings from animal model research to clinical trials in humans,[78–82] including:

- Mechanistic understanding of vaccine- and infection-induced immunity to pertussis in humans, including memory imprinting of cellular immune responses in the nasal mucosa against asymptomatic infection
- Identification of biomarkers that correlate with protective immunity against asymptomatic infection and transmission in humans and which can be readily evaluated in vaccine trials
- Development of a safe and reproducible model of *B. pertussis* infection in humans to facilitate ethical, compelling human challenge studies that evaluate nasopharyngeal colonization with *B. pertussis* as an endpoint.

The panel acknowledged emerging approaches to inducing potent cellular immune responses in the respiratory mucosa, with potential to improve protective local pertussis immunity in humans. These strategies include novel vaccine delivery methods, such as vaccine antigens entrapped in biodegradable microparticles,[83] and investigational vaccine candidates, including ap vaccines formulated with novel Th17/Th1-skewing adjuvants,[84] outer membrane vesicle (OMV) vaccines,[85] and live attenuated vaccines.[86] Among all candidates to date, only BPZE1, a nasally administered live attenuated pertussis vaccine, has advanced into clinical development. A recent proof-of-concept study in healthy, mostly wp-primed, adults, showed that BPZE1 could induce nasal secretory IgA responses and serum IgG responses against *B. pertussis* antigens, indicating potential for protective immunity in humans against asymptomatic infection and transmission.[87]

It was also noted how the scope of future potential pertussis vaccine technologies has been broadened by the COVID-19 pandemic. The significant pace of SARS-CoV-2 vaccine research stimulated a range of novel vaccine development

approaches – such as nucleic acid-based and recombinant viral vector-based vaccine platforms – that may also have potential for the development of next-generation pertussis vaccine candidates.[88]

## Concluding remarks

The resurgence in pertussis cases reported in many countries over the past few decades has highlighted a need to revisit adult pertussis vaccination recommendations (which are frequently absent or inconsistent), address barriers to uptake, and generate appropriate supporting evidence. In their review and appraisal of the current adult pertussis vaccination landscape, the expert panel identified differing data needs among countries that already have adult Tdap recommendations in place, and those that do not. For countries with established recommendations, generation of compelling evidence in areas such as vaccine efficacy/effectiveness and protection duration are needed to motivate HCPs to deliver adult Tdap vaccination and encourage the public to seek it. Where recommendations for adult vaccination do not exist, there is a requirement for convincing evidence of the need to protect adults from pertussis disease, based on a realistic understanding of its current epidemiology, burden, and impact in both the general population and at-risk groups, as well the value of broader immunization of the adult population in reducing transmission from carriers with asymptomatic infection to unvaccinated infants and other vulnerable populations. Addressing these critical evidence gaps and driving a deeper understanding of these factors will help highlight important areas of unmet need and justify the importance of adult pertussis vaccination to HCPs, policymakers, and payers.

## Acknowledgments

Medical writing support funded by Sanofi was provided by Caroline Minshull of Inizio Medical who captured the outline, wrote the initial draft of the manuscript based on the discussions of the authors, and incorporated comments from the authors.

## Disclosure statement

**PK** received honoraria for participating in the 2022 Zoom meetings by Sanofi; he also received honoraria for participation in advisory boards and lectures, and travel costs from the following companies: AstraZeneca, Bionorica, Chiesi, Engelhard, GSK, Janssen, Klosterfrau, Novartis, MSD, and Schwabe. His institution received honoraria for clinical trial participation from Bellus, the ERS NEuroCOUGH Initiative, and MSD. **JCS** received research support from AstraZeneca and GSK; and honoraria from AstraZeneca, GSK, Bial, Sanofi, and Medinfar, He also participated in a company-sponsored speaker's bureau for AstraZeneca and Sanofi. **UH** received consulting fees from Sanofi and GSK, and lecture fees from GSK, Infectopharm, Merck, Moderna, Pfizer, Roche, Sanofi Genzyme and Sanofi-Pasteur. He participated on the Data Monitoring Committees of a poliomyelitis vaccine (Takeda), a phase II study of an adjuvanted pandemic influenza vaccine (GSK/Watermark), the Norovirus Bivalent VLP Vaccine Program (Takeda/HilleVax), and the Cell culture influenza vaccine (Seqirus/IQVIA). He is a member of the Meta Data Safety Monitoring Board for CEPI (Coalition for Epidemic Preparedness Innovations) and of the Varicella Advisory Board, Switzerland (Merck). **CRM** is supported by an NHMRC Investigator Grant, grant no. [2016907]. She is on the WHO COVID-19 Vaccine Composition Technical Advisory Group and the WHO SAGE Working Group on Smallpox and Monkeypox. She currently receives funding from Sanofi for influenza and pertussis research. **DM** received personal fees from Dynavax, Seqirus, Sanofi, and GSK; and grants and personal fees from Pfizer. **TN** received research contracts to conduct clinical trials, with funding to the institution from Moderna, Sanofi, GSK, Iliad Biotechnologies, Dynavax, Seqirus, Janssen, and MSD; consulting fees from GSK, Seqirus, MSD, Sanofi, AstraZeneca, Moderna, BioNet, and Pfizer; and has served on data safety and monitoring boards for Seqirus, Clover, Moderna, Emergent, Serum Institute of India, SK Bioscience Korea, Emergent Biosolutions, and Novavax. **AP** received grants or contracts from Chiesi, AstraZeneca, GSK, Sanofi, and Agenzia Italiana del Farmaco (AIFA); consultancy fees from Chiesi, AstraZeneca, GSK, Novartis, Sanofi, Avillion, and Elpen Pharmaceuticals; payment or honoraria for lectures, presentations, manuscript writing or educational events from Chiesi, AstraZeneca, GSK, Menarini, Novartis, Zambon, Mundipharma, Sanofi, Edmond Pharma, Iqvia, Avillion, and Elpen Pharmaceuticals; and participated on a data safety monitoring board or advisory board for Chiesi, AstraZeneca, GSK, MSD, Novartis, Sanofi, Iqvia, Avillion, and Elpen Pharmaceuticals. **AR** received consulting fees, honoraria for lectures, presentations, speakers' bureaus or educational events, and participated in advisory boards from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK and Sanofi; and received support for travel/attending meetings from Chiesi. **KS** received a salary from the Australian Immunisation Coalition which has received funding towards some of its activities from industry sources, including GSK, Sanofi, Roche and Seqirus. He also received a consultancy fee from APACI, which derives its income from similar sources. **AS** is a consultant for AstraZeneca Pharmaceuticals, Calyptus Pharmaceuticals, Inc, Darwin Health, EmerVax, EUROIMMUN, F. Hoffman-La Roche Ltd, Fortress Biotech, Gilead Sciences, Granite bio., Gritstone Oncology, Guggenheim Securities, Moderna, Pfizer, RiverVest Venture Partners, and Turnstone Biologics. La Jolla Institute for Immunology has filed for patent protection for various aspects of T cell epitope and vaccine design work. **TT** received grants from Merck and Sanofi; personal fees from GSK Biologicals and Sanofi; and honoraria from Sanofi. **CWO** received grants/contracts and payment/honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AstraZeneca, GSK, Janssen, MedImmune, Pfizer, Sanofi, and Sanofi-Aventis; consulting fees, acting as a punctual consultant or directly as an independent expert, from AstraZeneca, GSK, Janssen, MedImmune, MSD, Pfizer, Sanofi, and Sanofi-Aventis; and acted in a leadership or fiduciary role for Coalition for Life Course Immunisation and Infovac-France. **BW** received honoraria for participation in advisory boards and lectures, and travel costs from the following companies: GSK, MSD, Sanofi, Moderna. **TW** received research funding and consultancy fees from Synairgen Research Ltd. **CHWVK** received honoraria for attending meetings sponsored by Sanofi, GSK Biologicals and MSD. **AK**, **AAR**, and **ES** have no competing interests to declare.

## Funding

This work was supported by Sanofi. However, Sanofi was not involved in the development of this manuscript. The opinions and views expressed in this manuscript are solely those of the authors and do not reflect the position of Sanofi.

## Author contributions

In July 2022, 24 international academic experts convened to discuss the challenges associated with the detection, monitoring, and vaccination of pertussis in adults. Authors listed are those who wished to develop two publications associated with the discussions. Given the nature of discussions, all authors contributed to the paper equally. It was agreed that Dr Peter Kardos would take overall responsibility and serve as lead and corresponding author; all other authors are listed alphabetically.

The second publication is titled: 'Public health management of pertussis in adults: practical challenges and future strategies,' authored by Professor C Raina MacIntyre, Dr Jaime Correia de Sousa, Professor

Ulrich Heininger, Dr Peter Kardos, Professor Andreas Konstantopoulos, Dr Donald Middleton, Professor Terry Nolan, Professor Alberto Papi, Dr Adrian Rendon, Dr Albert Rizzo, Mr Kim Sampson, Dr Alessandro Sette, Ms Elizabeth Sobczyk, Dr Tina Tan, Professor Catherine Weil-Olivier, Dr Birgit Weinberger, Professor Tom Wilkinson, and Dr Carl Heinz Wirsing von König.

## References


1. CDC. The Pink Book: Pertussis. Atlanta, GA: Centres for Disease Control and Prevention; 2021.
2. Diavatopoulos DA, Cummings CA, Schouls LM, Brinig MM, Relman DA, Mooi FR, Hultgren S. Bordetella pertussis, the causative agent of whooping cough, evolved from a distinct, human-associated lineage of B. bronchiseptica. PLoS Pathog. 2005;1(4):e45. doi:10.1371/journal.ppat.0010045.
3. WHO. Pertussis vaccines: WHO position paper – August 2015. World Health Organization; 2015 [accessed 2023 Sep 7]. https://apps.who.int/iris/rest/bitstreams/959578/retrieve.
4. WHO. WHO SAGE pertussis working group. Background Paper; 2014 [accessed 2023 Sep 29]. https://terrance.who.int/mediacentre/data/sage/SAGE_Docs_Ppt_Apr2014/8_session_pertussis/Apr2014_session8_pertussis.pdf.
5. ECDC. Surveillance atlas of infectious diseases for infectious diseases: pertussis. European Centre For Disease Prevention and Control; 2021 [accessed 2023 Aug 18]. https://atlas.ecdc.europa.eu/public/index.aspx?Dataset=27&HealthTopic=38.
6. Jenkins VA, Savic M, Kandeil W. Pertussis in high risk groups: an overview of the past quarter century. Hum Vaccines Immunother. 2020;16(11):2609–2617. doi:10.1080/21645515.2020.1738168.
7. Kandeil W, Atanasov P, Avramioti D, Fu J, Demarteau N, Li X. The burden of pertussis in older adults: what is the role of vaccination? A systematic literature review. Expert Rev Vaccines. 2019;18(5):439–455. doi:10.1080/14760584.2019.1588727.
8. De Serres G, Shadmani R, Duval B, Boulianne N, Déry P, Douville Fradet M, Rochette L, Halperin SA. Morbidity of pertussis in adolescents and adults. J Infect Dis. 2000;182(1):174–179. doi:10.1086/315648.
9. McGuiness CB, Hill J, Fonseca E, Hess G, Hitchcock W, Krishnarajah G. The disease burden of pertussis in adults 50 years old and older in the United States: a retrospective study. BMC Infect Dis. 2013;13(1):32. doi:10.1186/1471-2334-13-32.
10. van Hoek AJ, Campbell H, Andrews N, Vasconcelos M, Amirthalingam G, Miller E. The burden of disease and health care use among pertussis cases in school aged children and adults in England and Wales; a patient survey. PLoS One. 2014;9(11):e111807. doi:10.1371/journal.pone.0111807.
11. Aris E, Harrington L, Bhavsar A, Simeone JC, Ramond A, Papi A, Vogelmeier CF, Meszaros K, Lambrelli D, Mukherjee P. Burden of pertussis in COPD: a retrospective database study in England. COPD. 2021;18(2):157–169. doi:10.1080/15412555.2021.1899155.
12. Hewlett EL, Edwards KM. Pertussis — not just for kids. N Engl J Med. 2005;352(12):1215–1222. doi:10.1056/NEJMcp041025.
13. Walker JL, Rentsch CT, McDonald HI, Bak J, Minassian C, Amirthalingam G, Edelstein M, Thomas S. Social determinants of pertussis and influenza vaccine uptake in pregnancy: a national cohort study in England using electronic health records. BMJ Open. 2021;11(6):e046545. doi:10.1136/bmjopen-2020-046545.
14. Pelullo CP, Della Polla G, Napolitano F, Di Giuseppe G, Angelillo IF. Healthcare workers' knowledge, attitudes, and practices about vaccinations: a cross-sectional study in Italy. Nato Adv Sci Inst Se. 2020;8(2):148. doi:10.3390/vaccines8020148.
15. Kolobova I, Nyaku MK, Karakusevic A, Bridge D, Fotheringham I, O'Brien M. Vaccine uptake and barriers to vaccination among at-risk adult populations in the US. Hum Vaccin Immunother. 2022;18(5):2055422. doi:10.1080/21645515.2022.2055422.
16. Rieck T, Steffen A, Feig MAS. Impfquoten bei Erwachsenen in Deutschland – Aktuelles aus der KV-Impfsurveillance. Das Robert Koch-Institut; 2022 [accessed 2023 Sep 7]. https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2022/Ausgaben/49_22.pdf?__blob=publicationFile.
17. Choi JH, Correia de Sousa J, Fletcher M, Gabutti G, Harrington L, Holden M, Kim H, Michel JP, Mukherjee P, Nolan T, et al. Improving vaccination rates in older adults and at-risk groups: focus on pertussis. Aging Clin Exp Res. 2022;34(1):1–8. doi:10.1007/s40520-021-02018-3.
18. Guiso N, König C. Surveillance of pertussis: methods and implementation. Expert Rev Anti-infect Ther. 2016;14:657–667. doi:10.1080/14787210.2016.1190272.
19. van der Zee A, Schellekens JFP, Mooi FR. Laboratory diagnosis of pertussis. Clin Microbiol Rev. 2015;28(4):1005–1026. doi:10.1128/cmr.00031-15.
20. Lutwick L, Preis J. Chapter 27 - Pertussis. In: Ergönül Ö, Can F, Madoff L, Akova M, editors. Emerging infectious diseases. Amsterdam: Academic Press; 2014. p. 359–371.
21. WHO. Pertussis vaccines: WHO position paper – January 2010. World Health Organization; 2010 [accessed 2023 Sep 7]. https://www.who.int/publications/i/item/WER8540.
22. Kilgore PE, Salim AM, Zervos MJ, Schmitt H-J. Pertussis: microbiology, disease, treatment, and prevention. Clin Microbiol Rev. 2016;29(3):449–486. doi:10.1128/cmr.00083-15.
23. Mattoo S, Cherry JD. Molecular pathogenesis, epidemiology, and clinical manifestations of respiratory infections due to bordetella pertussis and other bordetella subspecies. Clin Microbiol Rev. 2005;18(2):326–382. doi:10.1128/cmr.18.2.326-382.2005.
24. WHO. World health statistics 2022: monitoring health for the SDGs, sustainable development goals. World Health Organization; 2022 [accessed 2023 Sep 7]. https://cdn.who.int/media/docs/default-source/immunization/vpd_surveillance/vpd-surveillance-standards-publication/who-surveillancevaccinepreventable-16-pertussis-r2.pdf.
25. Bhatti MM, Rucinski SL, Schwab JJ, Cole NC, Gebrehiwot SA, Patel R. Eight-year review of bordetella pertussis testing reveals seasonal pattern in the United States. J Pediatric Infect Dis Soc. 2015;6(1):91–93. doi:10.1093/jpids/piv079.
26. ECDC. Pertussis - annual epidemiological report for 2018. European Centre for Disease Prevention and Control; 2020 [accessed 2023 Sep 7]. https://www.ecdc.europa.eu/en/publications-data/pertussis-annual-epidemiological-report-2018.
27. Addiss DG, Davis JP, Meade BD, Burstyn DG, Meissner M, Zastrow JA, Berg JL, Drinka P, Phillips R. A pertussis outbreak in a Wisconsin nursing home. J Infect Dis. 1991;164(4):704–710. doi:10.1093/infdis/164.4.704.
28. Schellekens J, von König CH, Gardner P. Pertussis sources of infection and routes of transmission in the vaccination era. Pediatr Infect Dis J. 2005;24(5 Suppl):S19–S24. doi:10.1097/01.inf.0000160909.24879.e6.
29. Stone H, Moa A, MacIntyre CR, Chughtai AA. Using open source data to estimate the global epidemiology of pertussis. Global Biosecur. 2020;1(4). doi:10.31646/gbio.65.
30. Deville JG, Cherry JD, Christenson PD, Pineda E, Leach CT, Kuhls TL, Viker S. Frequency of unrecognized Bordetella pertussis infections in adults. Clin Infect Dis. 1995;21(3):639–642. doi:10.1093/clinids/21.3.639.
31. CDC. Pertussis treatment recommendations. Centers for Disease Control and Prevention; 2023 [accessed 2023 Sep 22]. https://www.cdc.gov/pertussis/clinical/treatment.html.
32. Mooi FR, van Loo IH, van Gent M, He Q, Bart MJ, Heuvelman KJ, de Greeff SC, Diavatopoulos D, Teunis P, Nagelkerke N, et al. Bordetella pertussis strains with increased toxin production associated with pertussis resurgence. Emerg Infect Dis. 2009;15(8):1206–1213. doi:10.3201/eid1508.081511.
33. Macina D, Evans KE. Bordetella pertussis in school-age children, adolescents, and adults: a systematic review of epidemiology, burden, and mortality in Asia. Infect Dis Ther. 2021;10(3):1115–1140. doi:10.1007/s40121-021-00439-1.
34. Macina D, Evans KE. Bordetella pertussis in school-age children, adolescents and adults: a systematic review of epidemiology and

mortality in Europe. Infect Dis Ther. 2021;10(4):2071–2118. doi:10.1007/s40121-021-00520-9.
35. CDC. Pertussis 2020 case definition. Centers for Disease Control and Prevention; 2023 [accessed 2023 Sep 25]. https://ndc.services.cdc.gov/case-definitions/pertussis-2020.
36. Seppälä E, Kristoffersen A, Bøås H, Vestrheim D, Greve-Isdahl M, De Blasio B, Steens A. Pertussis epidemiology including direct and indirect effects of the childhood pertussis booster vaccinations, Norway, 1998–2019. Vaccine. 2022;40:3142–3149. doi:10.1016/j.vaccine.2022.04.038.
37. Bagordo F, Grassi T, Savio M, Rota MC, Baldovin T, Vicentini C, Napolitano F, Trombetta CM, Gabutti G. Assessment of pertussis underreporting in Italy. J Clin Med. 2023;12(5):1732. doi:10.3390/jcm12051732.
38. WHO. Laboratory manual for the diagnosis of whooping cough caused by bordetella pertussis/bordetella parapertussis: update 2014. World Health Organization; 2014 [accessed 2023 Sep 7]. https://apps.who.int/iris/handle/10665/127891.
39. Clarke MF, Rasiah K, Copland J, Watson M, Koehler AP, Dowling K, Marshall HS. The pertussis epidemic: informing strategies for prevention of severe disease. Epidemiol Infect. 2013;141(3):463–471. doi:10.1017/s095026881200091x.
40. Skoff TH, Faulkner AE, Liang JL, Barnes M, Kudish K, Thomas E, Kenyon C, Hoffman M, Pradhan E, Liko J, et al. Pertussis infections among pregnant women in the United States, 2012-2017. Clin Infect Dis. 2021;73(11):3836–3841. doi:10.1093/cid/ciaa1112.
41. Gilberg S, Njamkepo E, Du Châtelet IP, Partouche H, Gueirard P, Ghasarossian C, Schlumberger M, Guiso N. Evidence of bordetella pertussis infection in adults presenting with persistent cough in a French area with very high whole-cell vaccine coverage. J Infect Dis. 2002;186(3):415–418. doi:10.1086/341511.
42. Bhavsar A, Aris E, Harrington L, Simeone JC, Ramond A, Lambrelli D, Papi A, Boulet LP, Meszaros K, Jamet N, et al. Burden of pertussis in individuals with a diagnosis of asthma: a retrospective database study in England. J Asthma Allergy. 2022;15:35–51. doi:10.2147/jaa.S335960.
43. Wilkinson TMA, Van den Steen P, Cheuvart B, Baudson N, Dodet M, Turriani E, Harrington L, Meyer N, Rondini S, Taddei L, et al. Seroprevalence of bordetella pertussis infection in patients with chronic obstructive pulmonary disease in England: analysis of the AERIS cohort. COPD. 2021;18(3):341–348. doi:10.1080/15412555.2021.1920904.
44. Buck PO, Meyers JL, Gordon LD, Parikh R, Kurosky SK, Davis KL. Economic burden of diagnosed pertussis among individuals with asthma or chronic obstructive pulmonary disease in the USA: an analysis of administrative claims. Epidemiol Infect. 2017;145(10):2109–2121. doi:10.1017/s0950268817000887.
45. Kwon JH, Wi CI, Seol HY, Park M, King K, Ryu E, Sohn S, Liu H, Juhn YJ. Risk, mechanisms and implications of asthma-associated infectious and inflammatory multimorbidities (AIMs) among individuals with asthma: a systematic review and a case study. Allergy Asthma Immunol Res. 2021;13(5):697–718. doi:10.4168/aair.2021.13.5.697.
46. Liu BC, McIntyre P, Kaldor JM, Quinn HE, Ridda I, Banks E. Pertussis in older adults: prospective study of risk factors and morbidity. Clin Infect Dis. 2012;55(11):1450–1456. doi:10.1093/cid/cis627.
47. Teepe J, Broekhuizen BD, Ieven M, Loens K, Huygen K, Kretzschmar M, de Melker H, Butler CC, Little P, Stuart B, et al. Prevalence, diagnosis, and disease course of pertussis in adults with acute cough: a prospective, observational study in primary care. Br J Gen Pract. 2015;65(639):e662–e667. doi:10.3399/bjgp15X686917.
48. Postels-Multani S, Schmitt HJ, Wirsing von König CH, Bock HL, Bogaerts H. Symptoms and complications of pertussis in adults. Infection. 1995;23(3):139–142. doi:10.1007/bf01793853.
49. de Greeff SC, de Melker HE, van Gageldonk PG, Schellekens JF, van der Klis FR, Mollema L, Mooi FR, Berbers GA. Seroprevalence of pertussis in the Netherlands: evidence for increased circulation of bordetella pertussis. PLoS One. 2010;5(12):e14183. doi:10.1371/journal.pone.0014183.
50. Bolotin S, Deeks SL, Marchand-Austin A, Rilkoff H, Dang V, Walton R, Hashim A, Farrell D, Crowcroft NS, Hozbor DF. Correlation of real time PCR cycle threshold cut-off with bordetella pertussis clinical severity. PLoS One. 2015;10(7):e0133209. doi:10.1371/journal.pone.0133209.
51. Bocka JJ. Pertussis clinical presentation. Medscape; 2023 [accessed 2023 Sep 26]. https://emedicine.medscape.com/article/967268-clinical.
52. Jones TC, Gasser M, Erb P, Oechslin H. Cough and fear of sleep: early clinical signs of bordetella pertussis in an adult. Braz J Infect Dis. 2004;8(4):324–327. doi:10.1590/s1413-86702004000400009.
53. Lee LH, Pichichero ME. Costs of illness due to Bordetella pertussis in families. Arch Fam Med. 2000;9(10):989–96. doi:10.1001/archfami.9.10.989.
54. Danuta MS, Buxton JA, Hestrin M, Keyes RD, Lynch K, Halperin SA. Carotid artery dissection as a possible severe complication of pertussis in an adult: clinical case report and review. Clin Infect Dis. 2003;36(1):1–4. doi:10.1086/344776.
55. Leong RNF, Wood JG, Liu B, McIntyre PB, Newall AT. High healthcare resource utilisation due to pertussis in Australian adults aged 65 years and over. Vaccine. 2020;38(19):3553–3559. doi:10.1016/j.vaccine.2020.03.021.
56. Koh MT, Liu CS, Chiu CH, Boonsawat W, Watanaveeradej V, Abdullah N, Zhang X, Devadiga R, Chen J. Under-recognized pertussis in adults from Asian countries: a cross-sectional seroprevalence study in Malaysia, Taiwan and Thailand. Epidemiol Infect. 2016;144(6):1192–200. doi:10.1017/s0950268815002393.
57. van Hoek AJ, Underwood A, Jit M, Miller E, Edmunds WJ. The impact of pandemic influenza H1N1 on health-related quality of life: a prospective population-based study. PLoS One. 2011;6(3):e17030. doi:10.1371/journal.pone.0017030.
58. Fernández-Cano MI, Armadans Gil L, Martínez Gómez X, Campins Martí M. Incidence of whooping cough in Spain (1997–2010): an underreported disease. Eur J Pediatr. 2014;173(6):721–726. doi:10.1007/s00431-013-2228-8.
59. Juhn YJ, Wi CI, Takahashi PY, Ryu E, King KS, Hickman JA, Yao JD, Binnicker MJ, Natoli TL, Evans TK, et al. Incidence of respiratory syncytial virus infection in older adults before and during the COVID-19 pandemic. JAMA Netw Open. 2023;6(1):e2250634. doi:10.1001/jamanetworkopen.2022.50634.
60. McCarthy A, Galvin R, Dockery F, McLoughlin K, O'Connor M, Corey G, Whiston A, Carey L, Steed F, Tierney A, et al. Multidisciplinary inpatient rehabilitation for older adults with COVID-19: a systematic review and meta-analysis of clinical and process outcomes. BMC Geriatr. 2023;23(1):391. doi:10.1186/s12877-023-04098-4.
61. Covino M, Russo A, Salini S, De Matteis G, Simeoni B, Pirone F, Massaro C, Recupero C, Landi F, Gasbarrini A, et al. Long-term effects of hospitalization for COVID-19 on frailty and quality of life in older adults ≥80 years. J Clin Med. 2022;11(19):5787. doi:10.3390/jcm11195787.
62. da Silva Antunes R, Garrigan E, Quiambao LG, Dhanda SK, Marrama D, Westernberg L, Wang E, Abawi A, Sutherland A, Armstrong SK, et al. T cell reactivity to bordetella pertussis is highly diverse regardless of childhood vaccination. Cell Host Microbe. 2023;31(8):1404–16.e4. doi:10.1016/j.chom.2023.06.015.
63. Cattelan N, Dubey P, Arnal L, Yantorno OM, Deora R, Carbonetti N. Bordetella biofilms: a lifestyle leading to persistent infections. Pathog Dis. 2016;74(1):ftv108. doi:10.1093/femspd/ftv108.
64. Moore A, Harnden A, Grant CC, Patel S, Irwin RS, Altman KW, Azoulay E, Barker AF, Bolser DC, Birring SS, et al. Clinically diagnosing pertussis-associated cough in adults and children: CHEST guideline and expert panel report. CHEST. 2019;155(1):147–154. doi:10.1016/j.chest.2018.09.027.
65. Wright SW, Edwards KM, Decker MD, Zeldin MH. Pertussis infection in adults with persistent cough. JAMA. 1995;273(13):1044–1046. doi:10.1001/jama.1995.03520370086042.

66. Huang QS, Baker M, McArthur C, Roberts S, Williamson D, Grant C, Trenholme A, Wong C, Taylor S, LeComte L, et al. Implementing hospital-based surveillance for severe acute respiratory infections caused by influenza and other respiratory pathogens in New Zealand. Western Pac Surveill Response J. 2014;5(2):23–30. doi:10.5365/wpsar.2014.5.1.004.
67. Rigoine de Fougerolles T, Puig-Barbera J, Kassianos G, Vanhems P, Schelling J, Crepey P, de Lejarazu RO, Ansaldi F, Fruhwein M, Galli C, et al. A comparison of coronavirus disease 2019 and seasonal influenza surveillance in five European countries: France, Germany, Italy, Spain and the United Kingdom. Influenza Other Respir Viruses. 2022;16(3):417–428. doi:10.1111/irv.12941.
68. Vega T, Lozano JE, Meerhoff T, Snacken R, Beauté J, Jorgensen P, Ortiz de Lejarazu R, Domegan L, Mossong J, Nielsen J, et al. Influenza surveillance in Europe: comparing intensity levels calculated using the moving epidemic method. Influenza Other Respir Viruses. 2015;9(5):234–246. doi:10.1111/irv.12330.
69. Slifka AM, Park B, Gao L, Slifka MK. Incidence of tetanus and diphtheria in relation to adult vaccination schedules. Clin Infect Dis. 2021;72(2):285–292. doi:10.1093/cid/ciaa017.
70. Heininger U. Diphtheria, tetanus, and pertussis: unequal vaccine siblings with distinct characteristics. Clin Infect Dis. 2020;74(3):562–563. doi:10.1093/cid/ciaa643.
71. Rohani P, Zhong X, King A. Contact network structure explains the changing epidemiology of pertussis. Science (New York, NY). 2010;330:982–985. doi:10.1126/science.1194134.
72. Saeidpour A, Bansal S, Rohani P, Perkins A. Dissecting recurrent waves of pertussis across the boroughs of London. PLoS Comput Biol. 2022;18(4):e1009898. doi:10.1371/journal.pcbi.1009898.
73. Holubová J, Staněk O, Brázdilová L, Mašín J, Bumba L, Gorringe AR, Alexander F, Šebo P. Acellular pertussis vaccine inhibits Bordetella pertussis clearance from the nasal mucosa of mice. Vaccines (Basel). 2020;8(4):695. doi:10.3390/vaccines8040695.
74. Barkoff AM, Mertsola J, Pierard D, Dalby T, Hoegh SV, Guillot S, Stefanelli P, van Gent M, Berbers G, Vestrheim D, et al. Pertactin-deficient bordetella pertussis isolates: evidence of increased circulation in Europe, 1998 to 2015. Euro Surveill. 2019;24(7). doi:10.2807/1560-7917.Es.2019.24.7.1700832.
75. Bart MJ, Harris SR, Advani A, Arakawa Y, Bottero D, Bouchez V, Cassiday PK, Chiang CS, Dalby T, Fry NK, et al. Global population structure and evolution of bordetella pertussis and their relationship with vaccination. mBio. 2014;5(2):e01074. doi:10.1128/mBio.01074-14.
76. Heininger U, André P, Chlibek R, Kristufkova Z, Kutsar K, Mangarov A, Mészner Z, Nitsch-Osuch A, Petrović V, Prymula R, et al. Comparative epidemiologic characteristics of pertussis in 10 Central and Eastern European countries, 2000–2013. PLoS One. 2016;11(6):e0155949. doi:10.1371/journal.pone.0155949.
77. Szwejser-Zawislak E, Wilk MM, Piszczek P, Krawczyk J, Wilczyńska D, Hozbor D. Evaluation of whole-cell and acellular pertussis vaccines in the context of long-term herd immunity. Vaccines (Basel). 2022;11(1):1. doi:10.3390/vaccines11010001.
78. Warfel JM, Zimmerman LI, Merkel TJ. Acellular pertussis vaccines protect against disease but fail to prevent infection and transmission in a nonhuman primate model. Proc Natl Acad Sci USA. 2014;111(2):787–792. doi:10.1073/pnas.1314688110.
79. Chasaide CN, Mills KHG. Next-generation pertussis vaccines based on the induction of protective T cells in the respiratory tract. Vaccines (Basel). 2020;8(4):621. doi:10.3390/vaccines8040621.
80. Wilk MM, Borkner L, Misiak A, Curham L, Allen AC, Mills KHG. Immunization with whole cell but not acellular pertussis vaccines primes CD4 T(RM) cells that sustain protective immunity against nasal colonization with Bordetella pertussis. Emerg Microbes Infect. 2019;8(1):169–185. doi:10.1080/22221751.2018.1564630.
81. Kapil P, Wang Y, Zimmerman L, Gaykema M, Merkel TJ. Repeated bordetella pertussis infections are required to reprogram acellular pertussis vaccine–primed host responses in the baboon model. J Infect Dis. 2023;229:376–383. doi:10.1093/infdis/jiad332.
82. Diavatopoulos DA, Mills KHG, Kester KE, Kampmann B, Silerova M, Heininger U, van Dongen JJM, van der Most RG, Huijnen MA, Siena E, et al. PERISCOPE: road towards effective control of pertussis. Lancet Infect Dis. 2019;19(5):179–186. doi:10.1016/S1473-3099(18)30646-7.
83. de Graaf H, Ibrahim M, Hill AR, Gbesemete D, Vaughan AT, Gorringe A, Preston A, Buisman AM, Faust SN, Kester KE, et al. Controlled human infection with Bordetella pertussis induces asymptomatic, immunizing colonization. Clin Infect Dis. 2020;71(2):403–411. doi:10.1093/cid/ciz840.
84. Conway MA, Madrigal-Estebas L, McClean S, Brayden DJ, Mills KH. Protection against bordetella pertussis infection following parenteral or oral immunization with antigens entrapped in biodegradable particles: effect of formulation and route of immunization on induction of Th1 and Th2 cells. Vaccine. 2001;19(15–16):1940–1950. doi:10.1016/s0264-410x(00)00433-3.
85. Yount KS, Hall JM, Caution K, Shamseldin MM, Guo M, Marion K, Fullen AR, Huang Y, Maynard JA, Quataert SA, et al. Systemic priming and intranasal booster with a BcfA-adjuvanted acellular pertussis vaccine generates CD4+ IL-17+ nasal tissue resident T cells and reduces B. pertussis nasal colonization. Front Immunol. 2023:14. doi:10.3389/fimmu.2023.1181876.
86. Carriquiriborde F, Martin Aispuro P, Ambrosis N, Zurita E, Bottero D, Gaillard ME, Castuma C, Rudi E, Lodeiro A, Hozbor DF. Pertussis vaccine candidate based on outer membrane vesicles derived from biofilm culture. Front Immunol. 2021;12:730434. doi:10.3389/fimmu.2021.730434.
87. Solans L, Debrie AS, Borkner L, Aguiló N, Thiriard A, Coutte L, Uranga S, Trottein F, Martín C, Mills KHG, et al. IL-17-dependent SIgA-mediated protection against nasal bordetella pertussis infection by live attenuated BPZE1 vaccine. Mucosal Immunol. 2018;11(6):1753–1762. doi:10.1038/s41385-018-0073-9.
88. Keech C, Miller VE, Rizzardi B, Hoyle C, Pryor MJ, Ferrand J, Solovay K, Thalen M, Noviello S, Goldstein P, et al. Immunogenicity and safety of BPZE1, an intranasal live attenuated pertussis vaccine, versus tetanus-diphtheria-acellular pertussis vaccine: a randomised, double-blind, phase 2b trial. Lancet. 2023;401(10379):843–855. doi:10.1016/S0140-6736(22)02644-7.