Review paper

Pertussis as a constantly occurring threat to public health

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Abstract

Bordetella pertussis causes the highly contagious respiratory disease known as whooping cough, which is a global public health problem. However, *B. pertussis* continues to be a threat in countries with low vaccination coverage, and it re-emerges in countries with high coverage. Infection can cause a variety of respiratory symptoms, many of which are particularly severe in newborn infants. The bacteria express a wide range of virulence factors that act in association to promote bacterial colonisation, dissemination, persistence, resistance to host immunity, and transmission. These variables have both systemic and local effects on host tissues, resulting in a distinct disease characteristic specific to *B. pertussis*. This paper reviews the epidemiology, disease pattern, virulence factors, complications, problems of diagnosis, treatment, and prevention of *B. pertussis*.

Introduction

Whooping cough, also referred to as pertussis, is a highly transmissible respiratory infectious disease. It spreads easily through aerosol droplets, making it a significant public health concern [1, 2]. Newborns and infants are especially vulnerable to severe cases of pertussis. However, infection may also result in severe complications in adults, including pneumonia [3].

Despite strong vaccination policies, pertussis eradication has not occurred [1, 2]. Alarmingly, there has been a concerning rise in pertussis cases, potentially due to missed vaccination boosters among adolescents and adults, and consequently, the lack of herd immunity. Additionally, low immunisation status in certain regions and genetic variation of strains may contribute to the rise in cases [2]. Maintaining high vaccination coverage is essential to reduce transmission of pertussis [3].

Methods

The PubMed and Google Scholar databases were used to find relevant articles about pertussis published between 2005 and 2024. The strategy involved using a combination of words, such as pertussis, whooping cough, *Bordetella pertussis*, epidemiology, pathogenesis, symptoms, diagnosis, treatment, drug resistance, and vaccination. Books and official governmental public health websites about health issues in Europe, Poland, and England were also taken into consideration. After screening and assessing the retrieved abstracts and other information on the Internet mentioned above, we decided that 40 articles met our selection criteria, and they were considered in writing this review.

Epidemiology of pertussis

Pertussis remains endemic not only in the European Union/European Economic Area (EU/EEA) but also globally, with cases peaking every three to five years. The European Centre for Disease Prevention and Control (ECDC) observed an abrupt rise in pertussis cases since mid-2023, and this trend lasted into 2024 [4]. In 2023, there were 25,000 reported cases in the EU/EEA, and alarmingly, over 32,000 were reported between January and March 2024 alone. Infants are the most affected group, and most deaths have also occurred among them [5]. The table below (Table 1) presents reported pertussis cases and deaths in Poland and neighbouring countries from 2020 to 2022 [6].

In Croatia, for example, between 1 January 2023 and 15 March 2024 there were 6261 reported cases, mostly among patients aged 10 to 19 years. However, Czechia reported 3101 cases between 1 January and 17 March 2024, mostly among teenagers between 15 and 19 years old [4].

In Poland, epidemiological reports from 2021 showed a decline in pertussis cases by over 75% compared to 2020, mostly attributed to COVID-19-related interventions including mask wearing and commu-

Table 1. Pertussis cases and deaths in Poland and neighbouring countries in 2020–2022 [6]

Countries	2020		2021		2022	
	Reported cases	Deaths	Reported cases	Deaths	Reported cases	Deaths
Poland	753	1	182	0	371	1
Germany	3212	0	776	0	1191	0
Czechia	696	0	51	2	96	0
Slovakia	700	0	92	0	109	0
EU/EEA	12,121	5	1578	3	2623	1

Table 2. Virulence factors of *B. pertussis* [1, 12, 13]

Selected virulence factors of B. pertussis	Function, and role in immunity
Pertactin (PRN)	Resists neutrophil-mediated clearance; contributes to adherence of *B. pertussis* to ciliated respiratory epithelium in rabbits; changes in prn types resulted in less efficacious whole-cell vaccine; PRN2 and PRN3 are the most common circulating prn strain types; PRN1 antigen is present in many acellular vaccines; PRN antigenic variation in vaccines is implicated in escape from immunity to *B. pertussis* [1].
Pertussis toxin (PT)	Protein toxin; pro-inflammatory adjuvant and anti-inflammatory agent inhibits both macrophage and neutrophil migration and phagocytosis [12].
Tracheal cytotoxin (TCT)	Leads to damage of the ciliated cells by inducing their lysis and overproduction of mucus. TCT also stimulates IL-1 secretion [13].
Dermonecrotic Toxin (DNT)	Positively regulated by BvgAS system; no clear role in pathogenesis; vasoconstriction in primates; induces cell necrosis *in vitro*; *B. bronchiseptica* DNT impairs osteoplastic cell differentiation in pigs [1].
Type III secretion system (T3SS)	Translocates effector proteins into host cells, induces cell necrosis *in vitro*, subverts innate and adaptive immune responses during infection of lungs; Beta A. cytotoxicity *in vitro* (mechanism not well understood); BopN, turns off host inflammatory reaction [1].

nity distancing [3]. Recently, an increase in reported cases has been observed. The sanitary-epidemiological station in Garwolin reported 1435 cases in Mazovia Province between 1 January and 31 July 2024, whereas there were only 84 cases in 2023 [7]. Moreover, the National Institute of Public Health of the National Institute of Hygiene – National Research Institute in Warsaw declared that in Poland between 1 January 2024 and 15 October 2024 there were 20,677 cases, with an incidence rate of 54.85 per 100,000 people. During the same time period in 2023, there were only 631 cases, with an incidence rate of 1.67 per 100,000 people. These data show an almost 33-fold increase in cases between 2023 and 2024 in Poland [8]. The presented data suggest that pertussis is becoming a serious threat to public health.

There is an increase in pertussis cases not only in the EU/EEA, but also in other countries. In China, for example, in June 2023 there were 1512 cases, but in 2024 there were 15,275, 91,272, and 97,669 cases in January, April, and May, respectively [9]. The situation in England is also alarming. The UK Health Security Agency reported only 300 cases in the period from January to August in 2023, whereas in the same period in 2024 there were 13,248 cases, which gives an approximately 44-fold rise. Importantly, most of the 2024 cases were confirmed in patients aged 15 years and over (7555; 57.03%) [10].

The nature of pertussis

The *Bordetella* genus includes 16 species of Gram-negative coccobacilli or rod-shaped bacteria, such as *B. pertussis*, *B. parapertussis*, or *B. bronchiseptica* [1, 2]. Through evolution, *B. pertussis* has adapted with a variety of virulence factors, making it a highly infectious pathogen. The virulence regulatory system of *B. pertussis* comprises over 200 genes, all of which are regulated in an organised pattern by the bicomponent BvgAS system [11]. Selected factors are presented in Table 2 [1, 12, 13].

The course of whooping cough

Typically, pertussis starts with a one-to-two-week period of a catarrhal stage with fever, rhinitis, mild cough, and other nonspecific symptoms. The next

stage, lasting one to three months, is the paroxysmal one with cough followed by the characteristic whooping sound and vomiting. The further period, called convalescence, lasts one to 2 weeks, and the cough is becoming milder [2].

The progression of pertussis varies with the patient's age. In infants and young children, it tends to be more severe. In newborns and infants, pertussis often progresses rapidly and violently. Initially, it may appear as a mild respiratory infection, presenting with fever, runny nose, and cough. This is followed by characteristic coughing episodes, culminating in "whooping" – loud, wheezing gasps for breath. These episodes can lead to vomiting, apnoea, and even life-threatening cyanosis [1, 2].

In older children and teenagers, the course of pertussis is typically milder, often resembling a severe cold accompanied by a persistent, uncontrollable cough. However, even in this group, coughing can last for weeks, which can be physically draining [2].

In adults, pertussis tends to be even milder, often mistaken for other respiratory infections. Symptoms primarily include a prolonged cough that can persist for months. While the disease can be dangerous for the elderly or those with weakened immune systems, such severe cases are less common [1, 2].

Complications

Complications from pertussis primarily affect young children, though they also pose a significant health issue in adults. Comorbidities, obesity, smoking, heart and renal illnesses, asthma, diabetes, or chronic obstructive pulmonary disease (COPD) are risk factors for severe disease in adults.

Overall, approximately 11% of patients may develop complications, which are more inclined to occur in those with underlying illnesses (13.4%) than in people without them (9.5%). As a result of these complications, pneumonia is the most frequent outcome (21% of all complications), alongside difficulties in maintaining proper breathing (22%), and the need for hospitalisation (36%). Severe pertussis can exhaust the patient, lead to sleep disturbances, and result in weight loss. In patients over the age of 65 years, there is also a risk of intracranial haemorrhage [14, 15].

Challenges in diagnostics

In the diagnosis of *B. pertussis*, culture, molecular, and serological methods are utilised. The specimen may comprise a nasopharyngeal aspirate (NPA) or a swab (NPS). NPAs are more commonly collected from newborns and infants because they yield an approximately 15% higher isolation rate compared to NPSs. In contrast, NPSs are preferred for adolescents and adults due to the difficulties in obtaining NPAs in these age groups [16].

Culture methods are used in the diagnosis of whooping cough in patients of all age groups who have been coughing for less than 21 days. *B. pertussis* has demanding growth requirements. While less demanding species such as *B. parapertussis* and *B. bronchiseptica* may be cultured on basic media, *B. pertussis* grows on Bordet-Gengou (BG) agar. Regan-Lowe (RL) agar, which contains charcoal and horse blood, can also be used and is recommended as a transport medium for *B. pertussis*. Adding cephalexin to the media makes them selective for *Bordetella* species [17]. Since these bacteria are obligate aerobes, cultures should be conducted in an aerobic atmosphere for 7 days at 35–37°C. Plates showing no bacterial growth after incubation for seven days may be considered negative and rejected. *B. pertussis* grows slower on BG agar, but isolation efficiency on RL and BG plates after 7 days of incubation is comparable, with the main advantage of BG being the ability to visualise haemolysis [18]. Typical colonies are small and shiny, resembling mercury droplets. For confirmation, these colonies can be examined using the MALDI-TOF MS method [19]. Culture methods are significant in the epidemiology of whooping cough as they allow for more precise genetic characterisation.

Molecular diagnostic methods are feasible for patients with a cough lasting less than 4 weeks (< 28 days), but the sensitivities of the test are inversely correlated with the time between illness onset and specimen collection. Thus, it is advised to collect the specimen as early as possible following the onset of symptoms, optimally < 21 days after the onset of cough. For a PCR test to be reliable, the NPS or NPA must be properly collected. It is advised to use swabs made of nylon, viscose, or polyester, while cotton or calcium alginate swabs are not recommended [20]. Due to the highest sensitivity in the early stages of infection, PCR-based diagnosis of whooping cough is particularly useful in young children and infants, while adults often seek medical care only after some time [16].

Serological methods are recommended for routine whooping cough diagnosis in children over 2 years of age, adolescents, and adults who have had a cough for longer than two weeks. An ELISA test is used to detect anti-pertussis toxin (PT) IgA, IgM, and IgG antibodies in the patient's serum. To diagnose the disease, a fourfold increase in antibody titters between two serum samples obtained three to five weeks apart must be demonstrated. It is recommended to assess the dynamics of IgG antibody levels. In cases of ambiguous results or difficulties in obtaining a subsequent serum sample, IgA antibodies should be measured [16–18, 21].

The diagnosis of whooping cough can be challenging. A significant challenge is the increasingly frequent isolation of new, similar species that have not yet been well studied. Additionally, many newer, more accurate diagnostic methods are not yet used in routine whooping cough diagnosis but are only available in reference laboratories, which prolongs the waiting time for test

results. In treating *B. pertussis* infections, timing is crucial due to the need for appropriate treatment tailored to the specific phase of the disease. The phase of infection also determines the choice of appropriate diagnostic method that will allow for an accurate diagnosis. Given the nonspecific symptoms of whooping cough in its early phase, the diagnosis may be incorrectly chosen, prolonging the wait for results or even leading to a negative result. Serological diagnostics are also problematic due to widespread vaccination against whooping cough and the need to collect several samples over time. The diagnostic approach should also be adapted to the patient's age. Additionally, much depends on the cooperation between doctors and laboratory personnel; greater collaboration between them could allow for a more accurate choice of diagnostic method. It is also necessary to seek new diagnostic solutions that allow for faster, cheaper, more universal, and less phase- or age-dependent identification of *B. pertussis* infection [16, 18, 22].

Treatment options and current trends, and statistics of the resistance to antimicrobial agents

The primary method of treating pertussis is antibiotic therapy. If administered early, in the initial stage of the disease, it can alleviate its course. However, due to the nonspecific symptoms present at this stage of infection, pertussis is often diagnosed too late, resulting in delayed antibiotic administration. Antibiotic therapy in later stages of the disease does not affect its course, but it shortens the infectious period to as little as 5 days, allowing the patient to remain in isolation for a shorter time [23]. In the antibiotic treatment of pertussis, macrolides are primarily used – erythromycin, azithromycin, and clarithromycin. For patients, particularly those intolerant to macrolides, trimethoprim-sulfamethoxazole can also be administered [23].

Resistance to antibiotics in *B. pertussis* strains is rare. Decreased susceptibility of pertussis bacteria to macrolides was first documented in the USA in the 1990s. Since then, antibiotic-resistant macrolide strains have been widely reported worldwide. The highest proportion of *B. pertussis*-resistant strains had been observed in China, where in some cities, resistance reached as high as 90%, and across the country from 2017 to 2019, 85.2% of pertussis bacteria were resistant to macrolides. In other countries, the percentage of resistant strains did not exceed 20%. In Europe, most bacteria remained sensitive to macrolide antibiotics; in countries such as the Czech Republic, Finland, and the UK, no resistant strains were detected, while in France, 2.4% of *B. pertussis* strains showed resistance between 2003 and 2012. According to research, macrolide resistance in *B. pertussis* strains is linked to mutations in their genome, such as the A2047G mutation.

The relatively low number of *B. pertussis* strains showing decreased antibiotic sensitivity worldwide is probably due to the widespread use of vaccines against pertussis bacteria. However, considering the decline in vaccination rates in recent years and the resulting increase in infections, the population of resistant strains is expected to grow. It is essential to search for new antibiotics that will exhibit activity against *B. pertussis*. A potential drug could be the fourth-generation macrolide, solithromycin, which has shown better efficacy against pertussis bacteria than azithromycin or co-trimoxazole [23, 24].

In the treatment of pertussis, cough suppressants should not be used, because they are ineffective. To alleviate symptoms, expectorants and mucolytic agents can be used to help clear mucus from the lower respiratory tract. The patient should be adequately hydrated and nourished. It is important to avoid substances that irritate the respiratory tract, such as cigarettes, smoke, or dust. In some cases, oxygen therapy may be necessary. In severe cases, hospitalisation may be required. The highest mortality rate occurs in patients under the age of one year. Newborns have a high probability of cardiorespiratory complications and sudden cardiac arrest, so it is recommended that small, not fully vaccinated children be treated in hospitals. This also applies to patients with comorbidities [13].

Vaccination, public health response, and future directions

There are currently two highly efficient vaccines in use worldwide: the Diphtheria, Tetanus, and whole-cell Pertussis (DTwP), along with the Diphtheria, Tetanus, and acellular Pertussis (DTaP) vaccines [25]. The desired immune response to *B. pertussis* should include both cellular and humoral responses. Previous investigations have revealed that acellular pertussis vaccines induce a Th2 immune response, while both natural infection as well as whole-cell immunisation induce a Th1/Th17 response [26]. As a result, the immunity induced by vaccination with DTwP lasts longer than that induced by the DTaP. In addition, acellular vaccines have proven to elicit a weaker immune response than whole-cell vaccines [27].

Natural or acquired through vaccination, immunity against pertussis decreases over time. Studies to date indicate that natural infection may elicit protection for between 7 and 20 years, while available vaccines provide protection for 4 to 12 years [28]. To prevent the disease, booster vaccinations are required to preserve sufficient antibody levels. Periodic boosters are recommended after 10 years from the initial vaccination because there is a significant decline in immunity after that time, which is faster in people who have been vaccinated than in individuals who have immunity from natural disease [29, 30].

Attaining a sufficient level of immunisation across different age groups of the population is essential to controlling the disease. As a result, various vaccination programs have been established and/or implemented in a number of European nations. These efforts include immunising infants, preschoolers, adults, adolescents, and caregivers, as well as pregnant women. Those who are frail or suffer from chronic degenerative diseases, because they are more susceptible to developing post-infectious complications, should also receive booster doses of the vaccine [31].

It is important in the context of disease prevention to locate areas where vaccination coverage is low, determine the cause of this situation, and then implement a vaccination strategy. Estimating vaccination coverage nationally or at the state level can result in omitting local areas with low vaccination coverage [32].

The vaccination promotion process involves healthcare workers and funders. Pharmacies, which are involved in dispensing vaccines, play an essential role in access to vaccines, and in some countries, there are regulations allowing vaccinations in this setting. There are many factors that prevent high vaccination rates among adults, such as insufficient knowledge about the vaccination and its duration of protection and incorrect knowledge about pertussis as a disease not affecting adults. All these reasons can lead to a lack of recommendations among healthcare professionals or refusal of vaccination among patients. Therefore, recommendations from healthcare professionals are needed to increase vaccination rates among adults. Vaccination should be one of the components of patient care. In addition, greater promotion of vaccination is needed through education about the disease not only in scientific articles but also in the media. It is important to create international guidelines for vaccination of adults [33].

The spike in reported cases of infection in countries with high vaccination rates, such as the US, has forced scientists to investigate the problem and its cause. In response, studies have shown that current aP vaccines provide effective protection against disease but not against infection and transmission of the pathogen. Additionally, polymorphisms have been detected in genes that encode vaccine proteins (PTx and PRN), as well as in the promoter of the pertussis toxin (ptxP). An increase in *B. pertussis* isolates lacking certain vaccination antigens has been seen, giving these bacterial strains a selective advantage in populations immunised with aP vaccines [34, 35]. Despite the proven safety profile of aP vaccines and their efficacy, a new intranasally administered vaccine, BPZE1, which is in the clinical trial stage and has the potential to reduce *B. pertussis* transmission, is currently under investigation [36].

However, this does not affect the fact that the use of currently available pertussis vaccines provides the most efficient protection against illness.

Summary

Pertussis is a highly contagious respiratory infection that occurs worldwide and poses a serious risk to young children and adults. Current vaccination policies, although effective, have not eliminated pertussis. This is due to missed booster doses, low vaccination status in some regions, and genetic variability of strains. In addition, the incidence of infection is increasing in countries with high immunisation rates. Despite the effectiveness of currently available vaccines, the problem is the decreasing immune response over time and the need for booster doses. Promotion of vaccinations is significant in the context of prevention, which includes recommendations by medical specialists, education about vaccinations and their safety, and the creation of universal international guidelines in this area.

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Conflict of interest

The authors declare no conflict of interest.

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