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Systematic Review of Pertussis: Trends, Challenges, and Advances in Care and Prevention

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Abstract

Pertussis, or whooping cough, persists as a significant public health issue despite widespread vaccination. This review examines the disease's epidemiology, clinical challenges, diagnostic advancements, treatment, and prevention. Increasing incidence among adolescents and adults highlights the impact of waning immunity and gaps in vaccine coverage. Early diagnosis remains difficult due to nonspecific symptoms, though tools like PCR have improved detection.

Macrolide antibiotics are the mainstay of treatment, but delayed diagnosis reduces their effectiveness. The emergence of antibiotic-resistant *Bordetella pertussis* strains is concerning. Preventive measures, such as maternal immunization and booster doses, have shown effectiveness but require optimization. Acellular vaccines, while safer than whole-cell vaccines, exhibit waning immunity, prompting research into next-generation vaccines.

This review underscores the need for improved vaccination strategies, public health initiatives to combat vaccine hesitancy, and enhanced global surveillance. Addressing these challenges is vital to reducing pertussis's burden and improving outcomes, providing critical insights for policy and future research.

Keywords

Bordetella pertussis, Pertussis, Pertussis Diagnosis, Pertussis Epidemiology, Pertussis Prevention, Pertussis Treatment, pertussis vaccination

Introduction

Pertussis, caused by *Bordetella pertussis*, is a highly contagious respiratory disease that has persisted as a significant public health challenge despite the availability of effective vaccines. The disease disproportionately affects infants, who are at the highest risk of severe complications and mortality, but it has also seen a resurgence among adolescents and adults. This increase in pertussis cases in vaccinated populations has raised critical concerns about waning immunity and the limitations of current acellular pertussis (aP) vaccines.

Historically, whole-cell pertussis (wP) vaccines played a pivotal role in reducing disease burden. However, due to their higher reactogenicity, many countries transitioned to aP vaccines, which, while safer, have shown reduced durability of protection. Coupled with suboptimal vaccine coverage and increasing vaccine hesitancy, these factors have contributed to an alarming global trend of pertussis resurgence. Furthermore, the emergence of antibiotic-resistant *B. pertussis* strains and diagnostic delays due to nonspecific initial symptoms complicate disease management and control.

This systematic review aims to provide a comprehensive analysis of the current evidence on pertussis, examining its epidemiology, clinical presentation, diagnostic challenges, treatment approaches, and prevention strategies. By identifying gaps in knowledge and highlighting areas for innovation, the review seeks to inform public health policies and guide future research efforts in mitigating the burden of pertussis globally.

Methods

We conducted a systematic review following PRISMA guidelines. A comprehensive search of electronic databases, including PubMed, Scopus, and Web of Science, was performed to identify relevant studies published between 1984 and 2024. Inclusion criteria encompassed studies focusing on human populations, while non-English articles, case reports, and editorials were excluded.

Keywords

Pertussis, Whooping Cough, Vaccination, Pertussis Diagnosis, Pertussis Treatment, Pertussis Prevention, Pertussis Epidemiology, Bordetella pertussis.

Results

Epidemiology

Pertussis has experienced a concerning resurgence globally, despite extensive vaccination campaigns. (1) Historically, the introduction of whole-cell pertussis (wP) vaccines in the mid-20th century significantly reduced disease incidence and mortality. (2) However, the subsequent switch to acellular pertussis (aP) vaccines in many countries during the 1990s, due to concerns over the reactogenicity of wP vaccines, has coincided with rising pertussis cases.

While aP vaccines are associated with fewer side effects, their reduced immunogenicity and faster waning immunity have contributed to the resurgence. (3,4)

Current epidemiological trends show increased incidence among adolescents and adults, populations previously considered low-risk due to vaccine-induced immunity. (5) Waning immunity after childhood vaccination has left these groups susceptible, enabling the disease's spread to vulnerable populations, particularly unvaccinated infants. (6) Studies reveal that immunity from aP vaccines diminishes significantly within 4 to 6 years post-vaccination, necessitating booster doses to sustain protection. (4)

Geographic variations in pertussis incidence underscore the influence of vaccine coverage and public health strategies. High-income countries with robust vaccination programs report periodic outbreaks, suggesting the need for improved booster strategies and surveillance. (7) In contrast, low- and middle-income countries face challenges such as incomplete vaccine coverage and limited access to healthcare, exacerbating the disease's impact. (8)

Compounding these challenges is the emergence of antigenic variation and potential antibiotic resistance in *Bordetella pertussis*. Pathogen adaptation, including changes in pertactin expression—a key vaccine antigen—may reduce vaccine efficacy. Surveillance data indicate an increasing prevalence of pertactin-deficient strains, particularly in regions with widespread aP vaccine use. (9) These adaptations necessitate ongoing monitoring and evaluation of vaccine performance.

Global efforts to combat pertussis include strategies such as maternal immunization to protect newborns and targeted booster programs for adolescents and adults. (10) However, vaccine hesitancy and misinformation remain significant barriers, threatening to undermine progress. Addressing these issues through public health campaigns and community engagement is critical to enhancing vaccine uptake and maintaining herd immunity.

Clinical Presentation and Diagnosis

Pertussis exhibits a wide spectrum of clinical presentations, ranging from mild respiratory symptoms to severe complications, particularly in infants. (11) The disease is classically divided into three stages: catarrhal, paroxysmal, and convalescent. The catarrhal stage, lasting one to two weeks, is characterized by nonspecific symptoms such as nasal congestion, sneezing, mild cough, and low-grade fever. These early symptoms often mimic other respiratory infections, complicating timely diagnosis. (12)

The paroxysmal stage follows, lasting two to six weeks or longer, and is marked by the hallmark paroxysms of coughing. These episodes are often followed by an inspiratory "whoop" sound and may result in post-tussive vomiting or exhaustion. (13) Infants, in particular, may present atypically, with apnea or cyanosis as the primary symptom rather than the classic cough. (14) This variability in presentation poses a significant challenge to clinicians, leading to frequent delays in diagnosis. (15)

During the convalescent stage, which can persist for weeks to months, coughing gradually subsides but may recur with subsequent respiratory infections. (12) Recognizing pertussis in adolescents and adults is particularly challenging as symptoms are often milder and may be attributed to other conditions, allowing for undetected transmission to vulnerable populations, including infants. (16,17)

Severe complications are more common in infants under six months of age, who are at the highest risk of morbidity and mortality. These complications include pneumonia, seizures, encephalopathy, and in some cases, death. Apnea, a cessation of breathing, is a particularly alarming manifestation in young infants and often prompts emergency medical attention. Infants may also suffer from hypoxia due to prolonged coughing spells, which can have long-term developmental consequences. Secondary bacterial infections and malnutrition resulting from feeding difficulties during illness further exacerbate outcomes in this vulnerable group. (11,18)

Diagnostic tools have advanced significantly, yet challenges remain. Culture of *Bordetella pertussis* from nasopharyngeal specimens remains the gold standard but is limited by its low sensitivity, particularly in later stages of the disease or after antibiotic initiation. (19) Polymerase chain reaction (PCR) has emerged as a valuable tool due to its high sensitivity and rapid turnaround time. PCR can detect *B. pertussis* DNA even in cases where cultures are negative, making it particularly useful during outbreaks or for individuals presenting in later stages of the disease. (20,21)

Serological testing can aid in diagnosis by detecting pertussis-specific antibodies. However, its utility is often restricted to research settings due to the lack of standardized assays and its inability to differentiate recent from past infections. (22) Direct fluorescent antibody testing, once commonly used, has largely been replaced by PCR due to its lower sensitivity and specificity. (23)

Timely and accurate diagnosis of pertussis is critical to initiating appropriate treatment and implementing measures to prevent further transmission. This is particularly important in healthcare settings and among close contacts of infected individuals. Clinicians must maintain a high index of suspicion for pertussis, especially in patients with prolonged cough or known exposure, to improve diagnostic accuracy and reduce disease burden.

Treatment and Antibiotic Resistance

Effective management of pertussis involves early diagnosis and timely initiation of antibiotic therapy. When administered during the catarrhal stage, antibiotics can shorten the duration of symptoms, prevent progression to the more severe paroxysmal stage, and significantly reduce infectiousness. (24) However, once the disease progresses to the paroxysmal stage—characterized by intense coughing fits and post-tussive vomiting—the effectiveness of antibiotics diminishes. At this stage, the bacterial load has typically declined, and symptoms are driven by toxin-mediated effects rather than active bacterial replication. (25,26) While antibiotics can still help reduce transmission to close contacts, they do not significantly alter the clinical course of the disease in these patients. (27)

Macrolide antibiotics are the first-line treatment for pertussis due to their proven efficacy and favorable safety profiles. These antibiotics, which include azithromycin, clarithromycin, and erythromycin, work by inhibiting bacterial protein synthesis, leading to the eradication of *B. pertussis* and curtailing its spread to others. (28,29) Among macrolides, azithromycin is often preferred. Administered once daily, it is effective and well-tolerated. A typical course involves a five-day regimen, with higher doses on the first day followed by lower maintenance doses. It is the macrolide of choice for infants under one month of age due to its lower risk of pyloric stenosis compared to erythromycin. Clarithromycin is another effective option with good tolerability in older children and adults, its drawback being longer therapy and more frequent

administration – twice a day for seven days. Another alternative is erythromycin, although it is rarely used due to its more frequent side effects, such as nausea, vomiting, and abdominal cramps. It requires a four-times-daily dosing schedule over 14 days, which can reduce patient adherence. In cases where macrolides are contraindicated - such as in patients with macrolide hypersensitivity or certain drug interactions - trimethoprim-sulfamethoxazole serves as an alternative. (30) It inhibits bacterial folate synthesis and has demonstrated efficacy in eradicating *B. pertussis*. It is typically prescribed for a 14-day course and is not recommended for use in infants under two months of age due to the risk of kernicterus.

Supportive care is essential, particularly for infants and young children who may experience severe complications such as apnea, pneumonia, or seizures. Hospitalization may be required for these patients, with interventions including oxygen therapy, fluid management, and, in some cases, mechanical ventilation. (11)

A growing concern in the management of pertussis is the emergence of antibiotic-resistant strains of *Bordetella pertussis*. Resistance to macrolides, particularly erythromycin, has been reported in several countries. Mutations in the 23S rRNA gene, which confer resistance to macrolides, have been identified as a key mechanism. (31) Although the prevalence of resistant strains remains relatively low, their emergence underscores the importance of surveillance and judicious antibiotic use. (32)

In addition to resistance, delays in diagnosis pose a significant challenge to effective treatment. Patients often present with nonspecific symptoms early in the disease course, leading to misdiagnosis or delayed initiation of antibiotics. This highlights the need for heightened clinical awareness and improved diagnostic tools to facilitate timely recognition and management of pertussis.

Research into adjunctive therapies, such as anti-toxin treatments, is ongoing and may offer new avenues for mitigating disease severity in the future. Public health strategies to address antibiotic resistance include promoting appropriate antibiotic prescribing practices and investing in the development of novel antimicrobial agents. By combining effective treatment protocols with robust surveillance and prevention efforts, the global burden of pertussis can be significantly reduced.

Vaccination and Waning Immunity

Vaccination remains the cornerstone of pertussis prevention, with two primary vaccine types historically utilized: whole-cell pertussis (wP) and acellular pertussis (aP) vaccines. While wP vaccines demonstrated high efficacy in reducing disease incidence, their reactogenicity led many countries to transition to aP vaccines in the 1990s. Acellular vaccines, composed of purified antigens, significantly reduce adverse effects but provide shorter-lasting immunity compared to wP vaccines. (33–35)

A major challenge with aP vaccines is their waning immunity, which becomes apparent 4 to 6 years after the final dose in the primary vaccination series. (4) This decline leaves adolescents and adults susceptible to infection, thereby facilitating the transmission of *Bordetella pertussis* to vulnerable populations, including unvaccinated infants. (36) To address this issue, many countries have introduced booster doses for adolescents and adults, as well as maternal immunization programs to protect newborns. Maternal vaccination during pregnancy has been

shown to be highly effective in preventing severe pertussis in infants during their first few months of life. (37–39)

Despite these efforts, periodic outbreaks continue to occur, even in highly vaccinated populations. Research into next-generation vaccines aims to overcome the limitations of current aP vaccines by improving durability of protection and broadening immune responses. Novel approaches, including live attenuated vaccines and outer membrane vesicle-based formulations, are under investigation. (40)

Public health campaigns to address vaccine hesitancy are critical to ensuring high coverage rates. Misinformation about vaccine safety remains a significant barrier, necessitating community engagement and education to build public trust. Strengthening these efforts, alongside advancements in vaccine technology, is essential to achieving long-term control of pertussis.

Beyond vaccination, additional prevention strategies are critical. These include improving diagnostic tools to facilitate early detection and implementing contact tracing during outbreaks to limit disease spread. School-based vaccination programs, mandatory immunization policies for entry into certain institutions, and targeted booster campaigns for high-risk groups, such as healthcare workers and caregivers, can further bolster protection. Non-pharmaceutical interventions, like promoting respiratory hygiene, handwashing, and the use of masks in high-risk settings, also play a role in reducing transmission. Together, these strategies complement vaccination efforts to provide a comprehensive approach to pertussis prevention.

Discussion

This review emphasizes the challenges of controlling pertussis in the modern era. Vaccine hesitancy, driven by misinformation and cultural mistrust, undermines immunization efforts globally. Incomplete vaccine coverage, especially in resource-poor areas, further contributes to disease persistence. Adding to this complexity is the pathogen's ability to adapt, potentially reducing vaccine efficacy and complicating diagnosis. Addressing these issues requires a multifaceted approach. Public health campaigns must combat misinformation and promote the benefits of vaccination. Improved vaccine formulations are needed to counter waning immunity and emerging pathogen variants. Strengthening diagnostic capabilities is equally important, enabling timely detection and containment of outbreaks. Continuous surveillance and research are critical to understanding the changing epidemiology of pertussis, allowing for evidence-based interventions. Together, these efforts can help overcome the significant barriers to pertussis control and prevention

Conclusion

Pertussis remains a significant global health challenge despite advances in vaccination and disease control. Achieving effective prevention requires a multifaceted approach, including improving vaccine coverage, addressing public mistrust, and developing formulations that offer longer-lasting immunity. Public health education is crucial for countering misinformation and encouraging widespread immunization. Enhanced diagnostic systems and ongoing surveillance are essential for early detection and response to outbreaks. Continued research into pathogen evolution and vaccine efficacy will guide adaptive strategies. Through coordinated global efforts, these measures can mitigate the burden of pertussis, paving the way for more effective control and eventual eradication.

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