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Update on Epidemiology, Diagnosis, and Treatment of Pertussis

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Abstract

Pertussis, commonly known as whooping cough, is one of the most common vaccine-preventable infections. In adolescents and adults, infection may result in a protracted cough and is occasionally associated with substantial morbidity. In children and particularly infants, morbidity is more often substantial and the disease may be fatal. Two types of vaccines against pertussis exist: whole-cell vaccines (wP), developed in the 1940s, containing the entire inactivated *Bordetella pertussis* organism, and acellular vaccines (aP) constituting of 1–5 purified bacterial proteins. The aPs were developed in the 1970s in order to diminish the adverse effects that could occur in the wP vaccinations. In many industrialized countries, aP replaced the wP formulations; however, wPs are still used for primary vaccination doses in developing countries. The massive use of both types of vaccines significantly reduced the morbidity and mortality associated with the disease; nevertheless, pertussis is still an important public health problem. In fact, pertussis incidence has increased in many countries, with large sustained epidemics occurring most notably in developed countries that only use acellular vaccine for all the doses included in the calendar. This chapter focuses on some recent developments in the areas of epidemiology, diagnosis, and treatment of pertussis.

Keywords: pertussis diagnosis, epidemiology, treatment

1. Introduction

Whooping cough or pertussis is a respiratory disease that though preventable by vaccination remains an important health problem not only for infants but also for adolescents and adults [1, 2]. By definition, the etiologic agent responsible for this disease is the Gram-negative bacterium named *Bordetella pertussis*. However, pertussis-like symptoms can be caused by several other *Bordetella* species, including *B. parapertussis*, *B. bronchiseptica*, and *B. holmesii* [3–8]. The

disease usually starts with cold-like symptoms and irritating cough that gradually becomes paroxysmal. Paroxysms are characterized by repeated violent coughs; each series of paroxysm has many coughs without intervening inhalation and can be followed by the characteristic inspiratory whoop. Complications are frequent: about half of the babies younger than 1-year old who get pertussis need care in the hospital. Of those babies with pertussis who are treated in the hospital, about 1 out of 4 (25%) get pneumonia, 1 out of 100 (1%) will have convulsions, 1 out of 300 (0.3%) will have encephalopathy, and 1 out of 100 (1%) will die.

The best control strategy to prevent pertussis is vaccination. Currently, two types of vaccines against pertussis are in use: the whole-cell vaccines (wP) composed of whole, inactivated bacteria, and the acellular vaccines (aP) consist of purified *B. pertussis* immunogens. With the massive use of the first developed vaccine against the disease, the wP, in the 1950s, the incidence and mortality associated with pertussis fell to very low levels. Reports on safety concerns in the 1970s, however, cast doubt on the wP vaccines' value since they were associated not only with side effects at the injection site but also with serious systemic reactions [9, 10]. These drawbacks contributed to reducing pertussis vaccine acceptance in different countries [10, 11]. The widespread apprehension about wP prompted the development of acellular vaccines containing purified antigenic protein components of *B. pertussis* (two, three, or five immunogens) [12, 13]. Though finally there is no evidence to suggest that wP vaccines cause severe adverse reactions such as brain damage or severe neurological disorder, the aP vaccines are more accepted, especially in industrialized countries where they have gradually superseded the wP formulations. Currently, most of the countries of the EU and the USA use only aP vaccines. The aP formulations restored people's confidence in pertussis-containing vaccines, and infection appeared controlled for several years. Notwithstanding, during the last two decades, the epidemiology of pertussis has changed [14, 15] with several major outbreaks occurring, the incidence of which not only indicated a waning immunity but also demonstrated that the wP vaccines gave children a more lasting immunity than aP [16–18]. Furthermore, the risk of pertussis was increased in schoolchildren, and adolescents vaccinated exclusively with aP compared to those receiving only one wP dose [18, 19]. This difference could result from the weaker immune response induced by aP vaccines characterized mainly by Th2 profiles [20]. In 2015, the Strategic Advisory Group of Experts on immunization expressed concerns regarding the resurgence of pertussis in some industrialized countries despite high aP-vaccine coverage [21]. The switch from wP to aP for primary infant immunization was proposed as at least partially responsible for that resurgence. The World Health Organization (WHO), therefore, recommended considering the switch only if, in the national immunization schedules, large numbers of doses including several boosters could be assured. Countries currently using aP vaccines may continue using them but should consider the need for additional booster doses and strategies to prevent early childhood mortality upon pertussis resurgence.

Besides these recommendations and in order to control the disease in countries that use cellular, acellular, or even mixed vaccine schedules, it is important not only to achieve coverage levels above 95% but also to avoid delays in the application of vaccines [22]. By means of a mathematical model, it was reported that strategies that avoid delays in vaccination have a relevant impact on infant incidences' reduction. It was estimated that the elimination of

delays in the primary doses reduces infant incidences by approximately 20% [22]. In the same way, the simultaneous reduction of delays and increased coverage lead to a significant improvement in disease control [22] for those regions where the administration of vaccines was previously deferred for long periods of time.

2. Epidemiology

The maximal risk of pertussis infection and severe morbidity takes place before infants are old enough to have received the primary series of vaccination. [23–25]. In recent years, waning immunity seems to be the main cause for pertussis in adults and adolescents [26–28], and for this reason, these persons constitute a significant reservoir of infection. Evidence from studies of infant pertussis cases indicates that household contacts and carriers are frequently the source of infection, with parents identified as the cause for more than 50% of cases [29]. There has also been a case report documenting nosocomial infection in young infants acquired from health-care workers [30, 31].

Despite a long-standing vaccination program, pertussis remains highly prevalent in many countries [15]. Pertussis is the least well controlled of all vaccine-preventable diseases, and epidemics occur every 3–5 years. During the last decades, multiple epidemics of pertussis took place in many countries including those with high vaccination coverage [14, 15]. In the United States, where aP is used for all vaccination doses since 1996, in 2010–2012, the incidence rate in infants with less than 1 year duplicated those in 2002 (125 vs. 60 per 100,000 inhabitants), and incidence rates were very high not only in infants but also in 7–10-year-old children and adolescents (13–14 years) <http://www.cdc.gov/pertussis/outbreaks/trends.html>. In 2014, 32,971 cases of pertussis were reported to the Centers for Disease Control and Prevention (CDC). This represents a 15% increase compared to the 28,639 cases reported during 2013. During 2015, a decrease in the number of pertussis cases was reported: 20,762 cases in 2015 compared to 32,971 cases reported during 2014. As in previous years, in 2015, the incidence rate of pertussis in infants exceeded that of all the other age groups. However, the incidence rates in adolescents aged 13–16 years were also high.

Another industrialized country experiencing a notable outbreak is the UK, where, in 2012, 14 infant deaths were reported (Public Health England; cf. <https://www.gov.uk/government/publications/whooping-cough-pertussis-statistics>, accessed October 2017).

In Australia, the highest annual incidence of notifications (173 cases per 100,000 population) was reported in 2011, with 38,732 notified cases. In the epidemic period 2008–2011, an increase in the reporting of pertussis in children between 3 and 9 years of age was detected. On the other hand, notifications in adolescents and adults decreased compared to previous epidemic periods. In this country, there have been a number of changes introduced to the vaccination schedule over time in an attempt to improve control of pertussis. In this way, acellular pertussis vaccine replaced wP for booster doses in 1997 and for all doses from 1999. In 2003, the aP booster dose at 18 months of age was removed, shifting the first booster dose to 4 years of age.

Outbreaks were also detected in countries where wP vaccines were used. For example, in Argentina, where wP is used for primary series of three doses at 2, 4, and 6 months of age followed by two boosters at 18 months and 6 years old, the number of pertussis reported cases has increased steadily since 2002. In fact, in 2011, reported cases were four times higher than those detected in 2006 (4.1 vs. 16 per 100,000 inhabitants) [32] and 76 deaths were reported in children under 1 year (www.snvs.msal.gov.ar, [32]). Because of this epidemiological situation during 2009, the Ministry of Health recommended vaccination with aP for children at age 11 and for health-care workers in contact with infants under 12 months of age. In 2011, the Argentinean Ministry of Health recommended aP vaccination for household contacts of very-low-birth-weight infants (<1500 g); in 2012, they also offered immunization to all pregnant women after 20 weeks of gestation. Finally, in 2013, the national calendar included the maternal immunization against pertussis during a single pregnancy for each woman, while, in 2016, the recommendation was extended for all pregnancies.

Brazil, other country that uses wP for primary series, reported cases of pertussis from 2007 to 2014 [33]. The annual distribution of confirmed cases demonstrated a significant increase in incidence rate since 2012. Of the 80,068 suspected cases, 32% were confirmed by various criteria. The majority of confirmed cases occurred in infants who were less than 2 months (34.5%) and in infants aged 3–6 months (22.4%). Only 8% of the total confirmed cases was reported in adults >21 years. From the total confirmed cases, 47.2% met only clinical criteria, and 36.6% were confirmed in a laboratory. The overall case fatality rate was 2.1%, reaching 4.7% among infants aged 0–2 months. Of the confirmed cases, 23.1% occurred in subjects who received at least three doses of the pertussis vaccine [33].

These epidemic situations detected in different countries have moved the scientific community and health professionals to seek an understanding of this alarming new situation to identify the causes [34–36], and review and implement new strategies for the control of pertussis [37].

Though several factors apparently contribute to this pertussis-case increase, a consensus exists in identifying, as part of the causes of the epidemic, several factors related to the vaccines currently in use and the vaccination—for example, suboptimal coverage of the three primary doses, noncompliance with vaccination schedule timing (delayed vaccination) [22, 38], the waning of vaccination-conferred immunity [39–41], and the circulation of a resistant bacterial population resulting from the selection pressure exerted by mass vaccination [36]. Probably, the relative contributions of each factor may differ between countries.

To assess the trends of the disease in real time, a reliable and specific pertussis diagnosis is required. Laboratory diagnosis is also important to distinguish between the several etiologic agents of pertussis-like diseases, which involve both viruses and bacteria (i.e., adenovirus, parainfluenza viruses, respiratory syncytial virus, *Mycoplasma pneumoniae*, and *Chlamydomphila pneumoniae*) [42].

3. Clinical case definition

The clinical case definition used is based on CDC/WHO clinical criteria (www.cdc.gov/ncphi/disss/nndss/casedef/pertussis_current.htm, www.who.int/entity/immunization_monitoring/

diseases/pertussis_surveillance/en/index.html) that refers to a person with a cough illness lasting at least 2 weeks with one of the following symptoms/signs: coughing paroxysms, inspiratory whoop, or post-tussive vomiting. In patients younger than 6 months of age, cyanosis and apneas could also be present, and, for this reason, these symptoms are also included for pertussis clinical diagnosis. The different countries have considered adaptations in clinical criteria including age stratification and cough duration [43].

4. Diagnosis

Although classical pertussis can be diagnosed reliably based on clinical symptoms, infections in infants, older vaccinated children, adolescents, and adults often follow an atypical course. In these cases, the diagnosis of pertussis requires laboratory methods for confirmation. The laboratory criteria for diagnosis are mainly based on isolation of *B. pertussis* from clinical specimen and/or through PCR for *B. pertussis* or serology.

4.1. Culture

The isolation of the etiological agent is the gold standard for pertussis diagnosis. To perform the bacterial isolation, a clinical sample from the nasopharynx should be obtained by aspiration or swabs. Aspirates give better yields than nasopharyngeal swabs though this last could be used, but swabs should be composed of Dacron or nylon if both culture and PCR are to be performed. While cotton swabs are not recommended since they contain substances that could inhibit *B. pertussis* growth, calcium alginate swabs are appropriate only for culture because they inhibit PCRs [44]. Successful recovery of the causative agent depends on a number of factors, including collection and transport conditions of the sample, the stage of disease in which the sample is collected, and the use of antibiotics. *B. pertussis* should be cultivated in Regan Lowe medium and/or Bordet Gengou agar supplemented with defibrinated blood in concentration of 7–15% (**Figure 1**). Addition of the antibiotic cephalixin has been recommended to inhibit growth of contaminating bacteria. However, since cephalixin has been suggested to also inhibit growth of *B. holmesii* [45], plates with and without cephalixin should be used. Incubation periods of up to 10–14 days are recommended for optimal sensitivity. Though *B. pertussis* growth may be retarded, *B. bronchiseptica* usually grows faster (1–3 days), and *B. parapertussis* shows an intermediate growth rate. Growth should be checked daily to prevent overgrowth by contaminating microorganisms.

After growth, *Bordetella* can be detected by Gram staining and identified by biochemical reactions, agglutination with specific sera or PCR. *Bordetella* species can be distinguished biochemically by oxidase, urease, motility, and nitrate reduction.

4.2. PCR assays

Molecular diagnosis methods based on PCR are 2–6 times more sensitive than culture. The sensitivity of the PCR decreases with the time of evolution of the pathology as occurs with the microbiological tests. After the 4th week of cough, the amount of bacterial DNA diminishes,

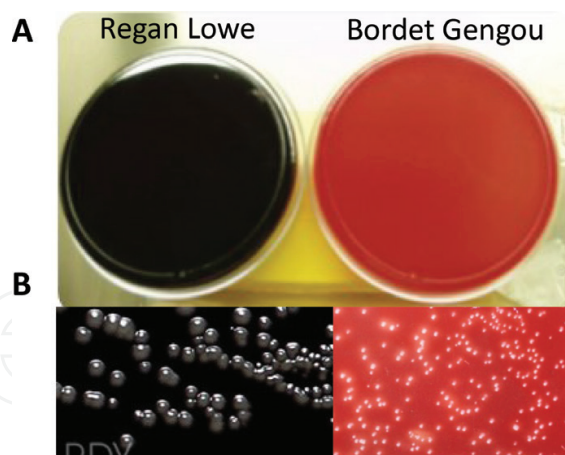


Figure 1. A—Regan low and Bordet Gengou culture media supplemented with 10% v/v sheep blood. B—Growth of *B. pertussis* in Regan Lowe and Bordet Gengou media.

and PCR has optimal sensitivity during the first 3 weeks of cough. As mentioned earlier, the sample of choice is nasopharyngeal aspirate or nasopharyngeal swab.

Extraction and purification of DNA is necessary to limit the action of inhibitors present in samples. There are home methods for the extraction of DNA, which are gradually being replaced by commercial methods. The latter are based on the use of ion exchange resins or magnetic separation using silica particles [46]. Neither of these methods is validated for the extraction of DNA from respiratory samples [46]. There are studies demonstrating that, in general, the different methods are suitable for the extraction of DNA from these samples. The PCR assays have evolved from conventional assays to real-time PCR and from singleplex to multiplex PCR. Conventional PCR employs two different sets of primers that are visualized on agarose gels. The most commonly used target sequences for *B. pertussis* DNA detection are the insertion sequence 481 (*IS481*) and the pertussis toxin promoter region. To detect *B. parapertussis*, primers that hybridize to the insertion sequence *IS1001* are used. *IS* elements are generally present in multiple copies in genomes, offering excellent targets for highly sensitive PCR detection. *IS481* and *IS1001* occur in *B. pertussis* and *B. parapertussis* isolates obtained from humans at copy numbers of 253 and 22, respectively [47, 48]. *IS481* is also present in *B. holmesii* isolates and in some isolates of *B. bronchiseptica*. These target sequences are also used in real-time PCR assays [49]. In fact, for simultaneous detection of *B. pertussis*, *B. parapertussis*, and *B. holmesii*, a combination of multiplex and singleplex real-time PCR assays targeting *IS* elements and pertussis toxin sequence has been developed [49].

It is recommended that PCR (conventional or real-time PCR) be used together with the culture. Cultivation of the etiological agent should be performed, especially when an outbreak is suspected.

4.3. Serodiagnosis

Validation and harmonization of serologic methods are still necessary before they can be widely applied as diagnostic tools. Many of the problems associated with serodiagnosis, such

as the interference of previous vaccinations or previous infections, cross-reactivity with other *Bordetella* species or perhaps other bacteria, and the variable response to *B. pertussis* antigens should still be overcome. However, in some countries, pertussis serology is currently used for diagnostic purposes [50], in particular, during outbreaks [51].

Bordetella pertussis-specific antibodies can be detected by enzyme-linked immunosorbent assays (ELISAs) or multiplex immunoassays. Assays use purified or mixed antigens, and only pertussis toxin (PTx) is specific for *B. pertussis*. Cross-reactivity with other microbial antigens from other *Bordetella* species could be detected when antibodies against filamentous hemagglutinin (anti-FHA), pertactin (anti-PRN), fimbriae (anti-FIM), and adenylate cyclase (anti-ACT) are measured and, for this reason, the measurement of these antibodies is not recommended for the diagnosis of pertussis. The evaluation of the titers of such antibodies may be used in specific studies [52]. For pertussis diagnosis, only IgG anti-PTx antibody titer evaluation is recommended. IgA and IgM assays lack adequate sensitivity and specificity.

Dual-sample serology based on $\geq 100\%$ increase in antibody concentration or on $\geq 50\%$ decrease in antibody concentration is a sensitive and specific method for serological diagnosis [53]. In clinical practice, diagnosis is mostly based on single-sample serology using a single or a more continuous cutoff. The optimal timing for specimen collection is 2–8 weeks following cough onset. For ELISA assays, it is recommended to use a standard serum from WHO [54]. Due to high levels of vaccine-induced IgG-Ptx, single-serum diagnosis is not reliable for 1–3 years after vaccination with Ptx-containing vaccines. If the IgG-Ptx level is below the chosen cutoff, the diagnosis of pertussis can be neither confirmed nor denied, and a second serum obtained at least 2 weeks later and 4–6 weeks after the onset of disease should be investigated. Increases of threefold in paired sera or any increase to a value above the cutoff or absolute values in single sera can then be considered to confirm the diagnosis of pertussis.

4.4. Recommendations for diagnosis testing with suspected pertussis

In neonates and young infants, PCR and/or culture should be performed on nasopharyngeal samples as soon as possible post-onset of symptoms. These methodologies are also recommended in vaccinated children, adolescents, and adults with less than 2 weeks of coughing. For patients older than 11 years with coughing of less than 3 weeks, PCR and IgG-anti-PTx measurement should be performed. The measurement of IgG-anti-PTx is only meaningful for older children/adults, including parents and other household members.

In outbreak situations, PCR and culture should be performed from nasopharyngeal samples and IgG-anti-PTx should be measured in serum samples.

It is important to note here that the microbiological diagnosis for pertussis is more useful during the first 2 weeks of coughing and before starting the antibiotic treatment. PCR assays may effectively be used for pertussis diagnosis from 2–4 weeks of cough. On the other hand, the serological tests are most useful in 2–8 weeks after the onset of cough.

5. Treatment

Early antimicrobial treatment is recommended to reduce transmission and for disease control by protecting close contacts [55]. An antimicrobial can be administered as prophylaxis for close contacts of a person with pertussis if the person has no contraindication to its use.

Individuals with pertussis are infectious from the beginning of the catarrhal period through the first week after the onset of paroxysms and until day 5 after the start of effective antimicrobial treatment.

The macrolide erythromycin has been the antimicrobial of choice for treatment or post-exposure prophylaxis of pertussis [56]. It is usually administered in 4 divided daily doses for 14 days. Unfortunately, erythromycin is accompanied by uncomfortable to distressing side effects that result in poor adherence to the treatment regimen. Two other macrolide agents (azithromycin and clarithromycin) have been shown to be effective against *B. pertussis*. Azithromycin and clarithromycin are more resistant to gastric acid, achieve higher tissue concentrations, and have a longer half-life than erythromycin, allowing less frequent administration (1–2 doses per day) and shorter treatment regimens (5–7 days) [57]. Azithromycin is the preferred antimicrobial for use in infants younger than 1 month of age. The antibiotic doses recommended for infants aged <6 months comprise a regimen of 10 mg/kg per day for 5 days. For patients aged >6 months, 10 mg/kg on day 1, followed by 5 mg/kg per day during the next 4 days is recommended. For adults, 500 mg on day 1 is recommended, followed by 250 mg per day on the following 4 days. The regimen recommended for clarithromycin for infants and children aged >1 month is 15 mg/kg per day in two divided doses each day for 7 days. For adults, 1 g per day in two divided doses for 7 days is recommended. Clarithromycin is not prescribed in infants aged <1 month. Trimethoprim-sulfamethoxazole (TMP-SMZ) in a regimen of two doses a day for 14 days is used as an alternative to a macrolide antibiotic in patients aged >2 months who have contraindication to or cannot tolerate macrolide agents, or who are infected with a macrolide-resistant strain of *B. pertussis*. Resistance of *B. pertussis* to macrolides is rare, and antimicrobial susceptibility testing is not routinely recommended. Testing is appropriate in some circumstances and is recommended when treatment failure is suspected. TMP-SMZ should not be used to treat infants younger than 2 months of age [55].

Because data on the clinical effectiveness of antibiotic treatment against *B. parapertussis* are limited, treatment decisions should be based on clinical judgment [58].

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