

## The Return of Pertussis: Who is Responsible? What Can Be Done?

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### Abstract

The Israel Ministry of Health's epidemiology department reported a record number of 1564 new pertussis cases in 2004. This brings the incidence rate to 23 per 100,000 population, indicating a marked increase in the prevalence of pertussis, from 1–3/100,000 in 1998, 9 in 2001, to 14 in 2003. The rate of atypical pertussis presentations in vaccinated patients, the decline in pertussis immunity post-vaccination, and the decreased awareness of potential infections in the adult population make the diagnosis of pertussis difficult and contribute to the rising incidence. In this article we review the current literature in order to increase awareness of the occurrence of pertussis in children as well as adults, discuss the laboratory diagnostic methods being used, and report the currently recommended means of treating the disease.

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Pertussis is an infectious disease affecting the upper respiratory tract; it is usually caused by the bacterium *Bordetella pertussis*, and sometimes by the bacterium *Bordetella parapertussis*. Although pertussis affects all age groups, it is most often diagnosed during childhood. Ever since the development of a whole-cell vaccine (wP) against pertussis in the 1940s, the prevalence of the disease has diminished [1]. Despite this modification in the disease's course however, it is still quite prevalent around the world. In recent years, not only has a resurgence of new cases been observed in countries that practice vaccination but the disease has assumed different characteristics. For example, it has become less aggressive, presents with a wide range of symptoms, and is more difficult to diagnose. Unfortunately, infants are the most afflicted and they also have the highest rates for complications and death, but older children, adolescents and adults also constitute a significant number of pertussis cases, and the disease poses a considerable risk to infants too young to be vaccinated [1]. These factors, which are compounded by the difficulty of identifying pertussis by laboratory tests, contribute to the overall complexity of diagnosing the disease. Nevertheless, considerable progress has been made in many aspects of the battle against pertussis over the past decade. For example, polymerase chain reaction has revolutionized the diagnosis of infectious diseases caused by organisms that are difficult to grow in cultures. Different PCR diagnostic techniques are available, which differ regarding the level of the primers used. Because of its high sensitivity and specificity, PCR has become

the method of choice for detecting pertussis in many laboratories [2,3]. The acellular pertussis vaccines (aP) have dramatically altered prophylaxis of this disease [4]. To date, a fifth preschool or school-age booster dose is incorporated into the vaccine schedule in several countries (United States, Canada, France, Germany) [5], and it is hoped that Israel too will adopt this policy

### History of pertussis

The earliest reports of pertussis infections were documented during the middle of the 17th century. Guillaume de Baillou, an epidemiologist, published the first detailed description of the disease. The term pertussis ("intense cough" in Latin, and commonly known today as whooping cough) was established in 1669 by Sydenham. The cause of the disease (*Bordetella pertussis*) was not determined until 1906, by Bordet and Gengou [6]. About 30 years later, another species, *Bordetella parapertussis*, was isolated and found to be responsible for as many as 5% of pertussis cases. Only in 1947 was a massive vaccination program launched in the USA, following the development of an effective standardization method [1].

### Vaccination history

- *Cellular vaccine (wP)*: Mass vaccination against pertussis, initiated in the U.S. in the mid-1940s, led to a sharp decline in the disease's morbidity and mortality. The classic vaccine was prepared from whole, killed pertussis bacteria, and later on was combined with a vaccine against tetanus and diphtheria, which gave rise to the commonly administered DTP triple vaccine [7]. Mild local and systemic adverse events as well as more serious events (including high fever, persistent crying for at least 3 hours, hypotonic hyporesponsive episodes, and seizures) may occur after vaccination. In 1974, concerns regarding the possible side effects of the vaccine were voiced, which influenced the Japanese government to recommend that vaccination be discontinued. At the beginning of 1975, the Japanese government decided to revaccinate, but starting as late as age 2. The direct result of this policy was the outbreak of an epidemic of pertussis throughout Japan. This epidemic stimulated the development of an acellular vaccine against pertussis, approved for administration in

PCR = polymerase chain reaction

wP = whole cell vaccine

DTP = diphtheria, tetanus, pertussis

Japan in 1981, in children over 2 years old, in a combined vaccine referred to as DTaP.

- **Acellular:** aP contains various numbers of *B. pertussis* antigens and has been extensively evaluated in the past decade and a half. During this same period, many of these aPs have been approved and implemented in numerous countries. Acellular vaccines with at least three antigenic components showed higher efficacy than one- and two-component vaccines [4,8,9]. A few research groups have studied the efficacy of these vaccines compared to the DTP whole-cell vaccine, which showed fewer side effects and even better efficacy than the cellular vaccine in preventing infection [8,9]. Furthermore, it has been shown that unlike the cellular variant, aP does not cause a disturbance in the functioning of antibodies or the immune memory when used in combination with other whole-cell vaccines [10]. The cost-benefit ratio of switching from wP to aP vaccines has been evaluated and appears to be favorable [11]. Thus, aPs have proven to be advantageous in all aspects investigated, compared with the previous wP vaccine. In a study to evaluate whether pertussis vaccination causes encephalitis or encephalopathy, Moore et al. [12] screened more than 12,000 children with neurologic disorders admitted to Canadian pediatric centers between 1993 and 2002. In this cohort, only seven cases of encephalopathy occurred within 7 days of pertussis vaccination, and a more likely cause (herpes simplex, influenza A, para-influenza, gastrointestinal infection, hypoglycemia) was identified in each instance. Thus, despite more than 6.5 million doses of pertussis vaccination administered during this period, no cases of encephalopathy were attributed to the vaccination.

## Epidemiology

Pertussis is one of the major causes of vaccine-preventable deaths. Although widespread vaccination against *B. pertussis* initially resulted in a decline in incidence of the disease, there has been a dramatic rise over the last decade in both the vaccinated and unvaccinated [12]. This increase is seen especially in those < 6 months and > 15 years old [13]. As recommended in most countries, infants receive vaccinations against *B. pertussis* at age 2, 4 and 6 months, and then a booster at age 16–18 months. Adults who do not receive any vaccine booster become the main reservoir for *Bordetella pertussis*, given that the effects of the vaccination wane after 5–10 years, thus rendering the vaccinated host vulnerable to infection [15,16]. In the United States alone, there were 11,647 cases reported in 2003, the highest number reported since 1967. Indeed, in many countries there have been increasing reports of pertussis among vaccinated individuals whose clinical presentation is more protracted or atypical [13,17]. In 1999, there were an estimated 48.5 million pertussis cases in children worldwide. Deaths from pertussis were estimated at 390,000 [18], with infants accounting for more than 90% of the death cases. Pertussis is considered an endemic disease, characterized

by an epidemic every 2–5 years. This rate of exacerbations has not changed, even after the introduction of mass vaccination – a fact that indicates the efficacy of the vaccine in preventing the disease but not the transmission of the causative agent (*B. pertussis*) within the population [19]. The disease has no known animal or environmental reservoir; humans are the only natural host and are the assumed reservoir [20]. Pertussis infections occur throughout the year, though some reports claim that the incidence increases during the summer and spring seasons [21].

## Pertussis in the USA

The epidemiology of pertussis changed profoundly in the middle of the 20th century because of the introduction of the cellular vaccine to the market. During the pre-vaccination era, the morbidity in the U.S. was estimated at 872 cases per 100,000 population, whereas the main morbidity age group was children under the age of 5 [5]. After the vaccine was introduced to the public, the morbidity rate dropped initially to a low level of about 1000 reported cases per year across the U.S. (a rate of 0.47 cases per 100,000 population). More recently, the affected populations changed and the age groups most frequently affected were children in their first year of life, adults, and children over 10 years old [5,22,23]. The average annual incidence rates reported in the years 1997 to 2000 were highest among infants < 1 year old (55.5 cases per 100,000 population) and lower in children aged 1–4 years (5.5), children aged 5–9 years (3.6), persons aged 10–19 years (5.5), and persons aged ≥ 20 years (0.8) [1]. According to the U.S. Centers for Disease Control, in 2000 a total of 17 people with symptoms of pertussis died, and most of them were infants [24].

Currently, the recommended immunization schedule is to take a five-dose series of DTaP vaccine at 2, 4, 6 and 15–18 months, and an additional preschool booster dose [25].

## Pertussis in Europe

Pertussis has re-emerged in low mortality countries in the past because of low coverage after a vaccine scare in the 1980s (in the United Kingdom), and the use of vaccines with poor efficacy (Sweden) [26]. The estimated incidence of pertussis in the late 1990s was 330/100,000 in the UK [27] and 508/100,000 in France [28]. In countries such as Germany and Italy, where vaccination rates against pertussis are low, pertussis is still quite common and the distribution of cases among the population is similar to that in the pre-vaccination era [7]. Currently, preschool or school-age children receive a fifth booster dose, which is incorporated into the vaccine schedule of France and Germany [5]. Today, the vaccine recommended all over Europe is the DTaP.

## Pertussis in Israel

Vaccination of the population in Israel, launched in 1957, included the DTP triple vaccine at 2, 4, 6 and 12 months of age. Vaccine coverage was reported as 94–99% for the four doses of vaccine among Israeli children during 2004 (data obtained from the Israel Ministry of Health). In contrast to other countries, a fifth late dose of immunization is not performed in children

aP = acellular vaccine

prior to their beginning school. The impact of this decision on the spread of pertussis in Israel is currently unknown. In Israel, similar to other countries, pertussis infections are sporadic, with cycles of the disease's outbreak occurring approximately every 3 years. Ever since the vaccine was initiated in Israel, an initial steep decline in morbidity was reported and data published by the health ministry indicate the occurrence of 100–150 cases per year, about 2.5 cases/100,000. However, this was followed by a steep increase in the incidence of pertussis, advancing from 1–3/100,000 in 1998 to 9 in 2001, 14 in 2003 and 23 in 2004. In 2004, a total of 1564 new cases were reported [29]. This rise probably resulted from the combination of the outbreak occurrence and a rise in the number of reports. Undoubtedly, these numbers underestimate the actual number of infections within the population. Reasons for this underestimation include the lack of reports as well as the failure to correctly diagnose the disease both in clinics and in laboratories [30,31].

### Why is pertussis on the rise?

The reasons for this rise most likely stem from a combination of factors:

*Waning immunity of the vaccine.* This leads to a rise in the percentage of low immunization levels in the adult population. The duration of immunity provided by the vaccination is approximately 12–15 years. The wP vaccine lasts 6–8 years after the last vaccination (one booster at 16–18 months), whereas the aP vaccine's efficacy starts declining 4–6 years after the last immunization [15]. This factor is compounded by the absence of cellular immunity to pertussis in vaccinated individuals who never actually got sick. The gradual decrease of protection explains the change in the transmission [5,32].

*Incorrect diagnosis of an atypical presentation in adults.* Pertussis is underestimated in adults and adolescents because of its wide range of clinical symptoms [32]. Pertussis has mild or atypical forms and could be overlooked because clinicians may not consider pertussis to be the cause of a cough, especially in older children and adults [26]. The infected adult becomes a source of infection for non-vaccinated infants and children with low immunization levels. It is important to note that due to mass vaccination against pertussis, the clinical presentation of the disease has been modified and most pertussis cases among adults or vaccinated children are atypical, being presented as a disease associated with coughing and an upper respiratory tract infection. The cough is usually non-paroxysmal and often identified as a bronchial infection or even as a worsening case of asthma [31]. Therefore, pertussis should be suspected in any child or adult whose primary complaint is a cough, especially if the disease is not accompanied by fever, sore throat or any abnormal findings in the lungs [7].

*Underdiagnosis.* This also occurs because of the low sensitivity of the traditional diagnostic method of both culture and serology (as low as 20–40%). The far better sensitivity offered by PCR

can improve disease control on the one hand, and increase the reported incidence of the disease on the other. In light of these facts and the problematic laboratory diagnosis of the disease, the World Health Organization published a clinical definition of pertussis appropriate for patients in countries with a low level of vaccination, which includes disease with at least 21 days of relapsing cough and laboratory findings of pertussis, or a connection to a proven case of pertussis. Clearly, this definition does not include laboratory findings of pertussis with a shorter coughing period. The CDC has its own definition, which is more appropriate in countries practicing vaccination and consists of two different approaches of diagnosing pertussis:

- A positive *clinical diagnosis*, which is defined as a disease associated with coughing that lasts more than 14 days, with episodes of paroxysmal cough, inspiratory “whoop” or vomiting at the end of the cough with no other apparent reason.
- A positive *laboratory diagnosis*, defined as culture growth of *B. pertussis* or a positive PCR test of *B. pertussis* obtained via a pharyngeal specimen from the patient.

In accordance with these definitions, a “proven” case of pertussis is a case with a positive laboratory diagnosis or a case that fits the clinical diagnosis and is positive in laboratory tests or has an epidemiologic connection to a proven case of pertussis, having been confirmed by laboratory testing. A “possible” case of pertussis fits the clinical definition but is neither positive in laboratory tests nor linked epidemiologically to another patient with a proven case of pertussis, as confirmed by the laboratory [33]. Since traditionally the diagnosis of classical pertussis is based on clinical criteria, the increasing numbers of atypical presentations among children, adolescents and adults pose new diagnostic challenges. The importance of enhancing diagnostic capabilities, particularly in the case of such atypical presentations, cannot be overstated since missed early diagnoses may increase the reservoir for transmission. It should be emphasized that late diagnosis will not change transmission in spite of antibiotic treatment.

*Transmitting low antibody levels from mothers to neonates.* We rely on herd immunity and passive immunity to protect young infants before they can be protected directly by vaccination [26]. Diminishing maternal immunity increases the risk of infection among the youngest age groups, who have not yet received at least two doses of the vaccine [5].

### Clinical presentation of pertussis in different age groups

Whereas children under 10 years old are by far the most affected group, both the number and proportion of cases involving older people have increased over the last decade, triggering renewed interest in the pathogenesis of pertussis [20]. Pertussis is highly prevalent among non-vaccinated children and in previously vac-

CDC = Centers for Disease Control

inated children with fading immunity. The incubation period can last from days to weeks. In both groups the disease typically lasts several weeks and has three stages: a) catarrhal (rhinorrhea and a mild cough); b) paroxysmal (with increasing severity of coughing and repetitive coughing spells, followed by an inspiratory whoop or post-tussive vomiting, or both); and c) convalescence (decreasing severity and frequency of coughing spells. It can last for weeks to months and can include exacerbated paroxysmal coughing evoked by unrelated upper airway infections) [5]. Symptoms often occur in the absence of fever. The white blood cell count is often elevated, consisting mainly of lymphocytes. Very young infants may present with apnea and cyanosis in the absence of cough. Additionally, pertussis is one of the causes of sudden infant death syndrome. In most lethal cases of pertussis (mostly in children) the disease is complicated by pneumonia.

In adults, the disease is common but is diagnosed only rarely because awareness of its symptoms is poor. In countries that practice vaccination, the symptoms in adolescents and adults are less typical than in unvaccinated children. The symptoms are often similar to infection of the upper respiratory tract and bronchitis. Pertussis should be considered in the diagnosis of acute and chronic cough in adults [28]. However, the disease can be associated with a persistent cough for a mean duration of 36–48 days, mostly paroxysmal, which severely disturbs sleep. Here the paroxysmal nature of the cough fits the characteristics of classical pertussis in 30% of cases. Accompanying symptoms include choking, vomiting, sweating attacks, or syncope. Complications may include rib fracture, hernia, incontinence, back pain or infections such as sinusitis, otitis, and pneumonia [33]. Most of the infections in childhood originate in an adult whose disease has not been identified [34].

With regard to systemic complications, infants are most susceptible to serious complications, including seizures due to brain ischemia, encephalopathy (in about 1% of the patients), secondary infections such as bacterial pneumonia and otitis media, as well as apnea and pulmonary hypertension [6,21]. The mortality rate in infected neonates reaches 0.6%. During the year 2000 in the U.S. there were 17 cases of death caused by pertussis infection [24]. Encephalopathy is the most severe systemic complication associated with pertussis; it occurs principally in children but in some cases is also detected in adults.

### Laboratory diagnosis of pertussis

Two laboratory tests are used to detect *B. pertussis* in the respiratory secretions of patients suspected of having pertussis: bacterial culture and polymerase chain reaction. The secretions are obtained by nasopharyngeal wash or swab.

#### Culture

A positive culture of nasopharyngeal secretions is made on selective Regan-Lowe medium and is considered the main standard for the diagnosis of pertussis. The organism can be recovered from patients only during the first 3–4 weeks of illness. The sensitivity of the culture is limited by the fastidious nature of *B. pertussis*. For example, the yield is lower from patients who have been ill a

long time, when specimens are obtained after antibiotic therapy, and in previously immunized children. Nonetheless, when carried out appropriately, culture is recommended in patients who present symptoms of the disease within 3 weeks of the onset of the cough. Although antibiotic resistance is rare, isolation allows the antibiotic's sensitivity to be characterized.

#### PCR

Due to its ability to detect fewer than 10 organisms, which do not need to be viable to be detected, the PCR test has much greater sensitivity as compared to culture. PCR assays directed to different targets of the bacteria can identify and distinguish among several *Bordetella* strains. Although the period during which the organism can be identified is longer with PCR than for culture, false positive PCR results have been a problem. PCR targets two specific *Bordetella pertussis* sequences, since pertussis toxin and the rapid insertion sequence IS481 may identify false positive results as due to *B. parapertussis* and *B. tularensis* [37]. The sensitivity of the PCR is as high as 97% and the specificity is 93%, a superior sensitivity compared with the low sensitive cultures (58% sensitivity) and a better sensitivity than serology [36]. PCR is regarded as the most useful test in the diagnosis of pertussis, and both the CDC and the Israel Ministry of Health established it as an important confirmatory test [33]

#### Serology

The serum antibodies to specific components of *B. pertussis* are measured by means of enzyme-linked immunosorbent assay. Since the diagnosis of pertussis is often not considered during the period when organisms can still be cultured, the demonstration of increased antibody titers between the acute phase of illness obtained within the first week of onset of symptoms, and the convalescent phase, collected 4–6 weeks later, may be necessary. Alternatively, a single serum high antibody titer obtained at least 3 weeks after the onset of the illness may confirm the diagnosis. The main advantage of the serology tests is that it is easy to perform in the community and is therefore the most common test used to diagnose pertussis. The disadvantages of the test are the lack of early diagnosis in small infants and the low specificity (false positive during vaccination coverage). The newer test based on specific antigens like pertussis-toxin or FHA (filamentous hemagglutinin antigen) shows better specificity and sensitivity.

The CDC recommends that combinations of diagnostic tests be used to diagnose pertussis. When a cough has been present for less than 3 weeks, the use of culture and PCR is appropriate for diagnosis; when the cough has been present for 3–4 weeks, PCR and serologic tests can both be used; and after 4 weeks of coughing, serologic tests alone are most likely to provide an accurate diagnosis [5]. Today, more and more primary care clinicians send nasopharyngeal sampling for PCR testing for the detection of *B. pertussis*. The cost of two serology tests, for immunoglobulin M and A against *B. pertussis*, is similar to the cost of the PCR test.

## Treatment and prevention

### Vaccination

The ideal strategy for pertussis vaccination includes universal vaccinations against pertussis at regular intervals throughout life. Recommendations made by the International Consensus Group for adolescent and adult pertussis include primary vaccination of infants as early as possible with the highest possible coverage as well as a preschool/school booster.

When a booster dose is administered at age 4–6 years, it is expected that the immunity will be extended into adolescence. After a fifth booster dose was introduced for 4–6 year old children, the disease burden in U.S. preschool and schoolchildren decreased [37]. The preschool booster dose, however, is not yet included in the vaccination schedules in Israel.

The key factor responsible for the continuing endemicity of *B. pertussis* infection in countries with high rates of vaccination is the waning immunity, whether vaccine-induced or naturally acquired. Although the precise time frame remains unresolved, immunity provided by wP vaccines appears to persist for at least 3–5 years and then to progressively decline 6–10 years after vaccination. The limited data on acellular pertussis (aP) vaccines suggest that in most cases protective immunity persists for 6 years after the primary vaccination with three or four doses [38]. In a recent study evaluating combined tetanus, diphtheria, and 5-component pertussis vaccine for use in adolescents and adults, Pichichero et al. [38] found that it elicited robust immune responses and exhibited an overall safety profile similar to that of a licensed tetanus and diphtheria vaccine.

In response to the ongoing problem of pertussis, an international collaboration of multidisciplinary experts, the Global Pertussis Initiative, was established in 2001 to examine the rationale for vaccination beyond childhood. Immunization strategies assessed by the Global Pertussis Initiative include: a) universal adult immunization; b) selective immunization of new mothers, family, and close contacts of newborns; c) selective immunization of healthcare and child-care workers; d) universal adolescent immunization; and e) dealing with strategies for reinforcing and/or improving current infant and toddler immunization strategies [37]. Other recommendations include analyzing local situations regarding the epidemiologic data, duration of pertussis vaccination, availability of licensed vaccines, and the economic conditions [39].

### Treatment and chemoprophylaxis

Antimicrobial agents, which have been used extensively for treatment and prophylaxis, have had varying effects in reducing pertussis symptoms and clearing *B. pertussis* from the respiratory system. A recent review suggests that administering antibiotics to treat whooping cough is effective in eliminating *B. pertussis* from patients with the disease, consequently rendering them non-infectious, but this does not alter the subsequent clinical course of the illness [40].

There are several different effective regimens [Table 1]. The best regimen for microbiologic clearance, with fewer side effects, is 3 days of azithromycin (10 mg/kg as a single dose) or

**Table 1.** Choice of antibiotic agents for the treatment of pertussis [5,40]

Drug	Dosage	Side effects	Contraindications
Erythromycin	Children: 40–50 mg/kg/day Adults: 1–2 g/day in four divided doses for 7 or 14 days	Gastrointestinal irritation, abdominal cramps, nausea, vomiting; hepatic toxicity (rare). Hypertrophic pyloric stenosis has been reported in infants	Known sensitivity to any macrolide antibiotic. Should be used with caution in infants because of association with hypertrophic pyloric stenosis
Azithromycin	10 mg/kg (maximum 500 mg) as a single dose on day 1; 5 mg/kg (maximum 250 mg) thereafter for 4 additional days. Alternative: 10 mg/kg (maximum 500 mg) as a single dose for 3 days	Allergic reaction and hepatic toxicity (rare)	Known sensitivity to any macrolide antibiotic
Clarithromycin	15–20 mg/kg/day (maximum, 1 g/day); two divided doses daily for 7 days	Allergic reaction and hepatic toxicity (rare)	Known sensitivity to any macrolide antibiotic
Trimethoprim-sulfamethoxazole	Trimethoprim 8 mg/kg/day (maximum 320 mg/day) sulfamethoxazole 40 mg/kg/day (maximum 1600 mg/day); two divided doses daily for 7 days	Rash, kernicterus in newborns	Known allergy to sulfonamides or trimethoprim. Should not be given to pregnant women shortly before delivery, to breastfeeding mothers, or infants < 2 months old because of the risk of kernicterus

7 days of clarithromycin (7.5 mg/kg/dose twice daily). There is insufficient evidence to determine the benefit of prophylactic treatment of pertussis contacts [40]. The CDC guidelines suggest that chemoprophylaxis be administered to any person who has had close contact with persons suffering from pertussis [33]. A recent systemic review studying the benefits of contact prophylaxis found insufficient evidence to determine the benefit of treating contacts of people suffering from pertussis. Nevertheless, the authors of the review recommend contact prophylaxis for families who have an infant under 6 months old, because of the high risk of morbidity and mortality in infants who are incompletely immunized [40]. The recommended antibiotics and dosages for contact prophylaxis are the same as those recommended in the treatment of whooping cough [40].

### Other interventions

Infants and other patients with severe pertussis may require hospitalization for supportive care; for very severe cases, intensive care facilities may be required. Corticosteroids and albuterol (a B2-adrenergic stimulant) may be effective in reducing paroxysms of coughing but further evaluation is required before their use

can be recommended. The therapeutic use of pertussis-specific immunoglobulin is currently under investigation [33]. Inpatients with confirmed pertussis should be placed in a private room, or if known not to have any other respiratory infection, in a room with other patients with pertussis until after the first 5 days of a full course of antimicrobial treatment or 21 days after the onset of coughing if unable to take antimicrobial treatment for pertussis.

## Summary

Pertussis is an old disease that is still with us, having re-emerged in recent years. The increase in the incidence of pertussis has occurred apart from the change in reporting, and is primarily caused by under-diagnosis due to an atypical form of the disease and suboptimal diagnostic tests, combined with the change in the immunization profile of the population. In the future, using a booster dose in preschool and schoolchildren and vaccinating targeted populations such as adolescents, adults, healthcare workers and pregnant women will become common, with the use of more tolerable antibiotics for short-term treatment and chemoprophylaxis with fewer side effects and better compliance, which may have an impact on controlling the resurgence of the disease.

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