Bordetella holmesii: Still Emerging and Elusive 20 Years On

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ABSTRACT Since the first description of Bordetella holmesii in 1995, almost 100 publications have contributed to the increasing knowledge of this emerging bacterium. Although first reported to induce bacteremia mainly in immunocompromised patients, it has also been isolated in healthy persons and has shown the capacity to induce pertussis-like symptoms and other clinical entities, such as meningitis, arthritis, or endocarditis. Respiratory diseases are generally less severe than those induced by Bordetella pertussis. However, B. holmesii was found to have a higher capacity of invasiveness given the various infection sites in which it was isolated. The diagnosis is difficult, particularly as it is a slow-growing organism but also because respiratory infections are systematically misdiagnosed as B. pertussis because both genomes contain the insertion sequence (IS) targeted by the pertussis diagnostic test, namely, IS481. Following this, several research groups developed discriminative Bordetella diagnostic tests and retrospectively reanalyzed nasopharyngeal swabs that were Bordetella positive in order to determine to what extent this new species was contributing to the increase in pertussis cases worldwide. Other groups have also conducted prospective studies with a similar objective. Simultaneously, microbiologists studied further this bacterium by investigating its virulence factors and similarity to other Bordetella species. Its entire genome was published in 2013.

INTRODUCTION

Bordetella holmesii was first described in 1995 by the Centers for Disease Control and Prevention (CDC). The initial 15 strains identified were assigned to the Bordetella genus following cellular fatty acid profiles, DNA relatedness studies, 16S rRNA sequencing, and guanine-plus-cytosine (G+C) content analysis. They were originally isolated from cultures of blood from patients from nine different states in the United States, one patient in Switzerland, and one in Saudi Arabia. Initially, B. holmesii was described as an agent responsible for bacteremia or other invasive diseases, such as arthritis or endocarditis, particularly in asplenic patients. Five years after its first description, a report showed that B. holmesii could also cause pertussis-like symptoms in otherwise healthy individuals. Subsequently, it was demonstrated that B. holmesii respiratory infections were systematically misdiagnosed as B. pertussis because both genomes contain the insertion sequence (IS) targeted by the pertussis diagnostic test, namely, IS481. Following this, several research groups developed discriminative Bordetella diagnostic tests and retrospectively reanalyzed nasopharyngeal swabs that were Bordetella positive in order to determine to what extent this new species was contributing to the increase in pertussis cases worldwide. Other groups have also conducted prospective studies with a similar objective. Simultaneously, microbiologists studied further this bacterium by investigating its virulence factors and similarity to other Bordetella species. Its entire genome was published in 2013.
In parallel, an increasing number of reports of *B. holmesii* infections in a variety of different sites were published (34–61). Nevertheless, *B. holmesii* still remains an underrecognized causative agent for respiratory or invasive infections, partly due to diagnostic difficulties (62). The aim of this chapter is to summarize the current knowledge on *B. holmesii*.

**MICROBIOLOGY**

*Bordetella* Genus

The genus *Bordetella* is part of the Alcaligenaceae family. It contains 12 species of Gram-negative pleomorphic aerobic bacilli: *B. pertussis*, *B. parapertussis*, and *B. bronchiseptica* (the classical species); *B. avium* and *B. hinzii* (the avian species); and *B. holmesii*, *B. trematum*, *B. petrii*, and *B. ansorpii* (added in the last 20 years and considered new species). Very recently, *B. bronchialis*, *B. flavilis*, and *B. sputigena* have been isolated from human respiratory specimens (63).

**Morphological and Biochemical Characteristics**

*B. holmesii* organisms are predominantly small coccoid and short rods, with rare longer and wider forms (Fig. 1 and 2). Each *Bordetella* species has distinct biochemical characteristics (Table 1). *B. holmesii* differs from the other species because it is nonoxidizing, nonsaccharolytic, urease negative, and not hemolytic on blood agar plates (1). Moreover, it is the only *Bordetella* species that produces brown soluble pigments after 48 h of culture (Fig. 3).

**Genome**

The genome size of *B. holmesii* is approximately 3.6 Mb, and its G+C content is 63% (33). Cellular fatty acid profiles and genome analyses have demonstrated a strong similarity between *B. holmesii* and the avian *Bordetella* species (1, 27, 31–33). However, it is also genetically closely related to the classical *Bordetella* species, which mainly infects mammals (62). Indeed, the 16S rRNA sequences of *B. pertussis* and *B. holmesii* are 99.5% similar (30), and both genomes count several copies of the IS481 gene (approximately 200 and less than 10 copies, respectively) (4, 64) (Fig. 4). Hence, *B. holmesii* may be originally an avian species that has become pathogenic for humans due to the lateral transfer of genetic material from *B. pertussis* (27) or other bacteria (33). Indeed, Diavatopoulos et al. identified in the genome of *B. holmesii* a 66-kb region highly conserved between *B. pertussis* and *B. holmesii* containing genes primordial for pathogenesis. Analysis shows that this region has likely been transferred from one bacterium to the other (27). Another group found 24 to 114 unique genes in the genome of nine sequenced *B. holmesii* isolates. One of these strains had a gene coding for a residual protein normally found in *Escherichia coli* (33). Thus, all these hypothetic transfers may have contributed to the emergence of *B. holmesii* as a human pathogen.
TABLE 1  Biochemical characteristics of *Bordetella holmesii* and comparison with other *Bordetella* spp.

<table>
<thead>
<tr>
<th>Biochemical characteristic</th>
<th><em>B. holmesii</em></th>
<th><em>B. pertussis</em></th>
<th><em>B. parapertussis</em></th>
<th><em>B. bronchiseptica</em></th>
<th><em>B. avium</em></th>
<th><em>B. hinzii</em></th>
<th><em>B. petrii</em></th>
<th><em>B. trematium</em></th>
<th><em>B. anasparii</em></th>
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</thead>
<tbody>
<tr>
<td>Oxidase</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
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<tr>
<td>Nitrate reduction</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Urease</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+/−</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Motility</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Beta-like hemolysis</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
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<tr>
<td>Production of brown soluble pigment</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Species group</td>
<td>New</td>
<td>Classical</td>
<td>Classical</td>
<td>Classical</td>
<td>Avian</td>
<td>Avian</td>
<td>New</td>
<td>New</td>
<td>New</td>
</tr>
</tbody>
</table>

Pathogenic Factors

*B. pertussis* and most other *Bordetella* species produce biologically active components that are regulated by the *bvgAS* two-component system. Gerlach et al. have extensively studied the *bvgAS* system of the new *Bordetella* species and have shown that although there are similarities, *B. holmesii*’s system significantly differs from that of *B. pertussis*. They concluded that *B. holmesii* was therefore more closely related to the avian *Bordetella*, although certain cytoplasmic signaling domains are functionally interchangeable between *B. pertussis* and *B. holmesii* (26). Regarding the classical pathogenic factors, *B. holmesii* produces a protein highly related to the filamentous hemagglutinin (FHA), an adhesin essential for colonization in other pathogenic *Bordetella* species. FHA expression is tightly regulated by the *bvgAS* locus (28). It also produces lipopolysaccharides, essential components of the outer membrane of Gram-negative bacteria, but its expression is different from that found in other *Bordetella* species. These lipopolysaccharides probably play a role in invasiveness, specifically in the higher invasive potential of *B. holmesii* (25). *B. holmesii* does not produce the pertussis toxin, one of the key pathogenic factors of *B. pertussis* (32, 65, 66). Moreover, the genome of *B. holmesii* lacks most of the other virulence factors implicated in the pathogenicity of *Bordetella* species (e.g., adenylate cyclase toxin, *Bordetella* type II and III secretion systems, pertactin, and fimbriae) (31, 32, 65). It has been found that approximately 400 genes of the *B. holmesii* genome have never been reported previously for any *Bordetella* species. Many of these genes are involved in microbial pathogenicity, e.g., are implicated in transport and detoxification of organic compounds or antibiotics, and it is possible that they have been acquired partly by lateral transfer (33). It remains unknown whether *B. holmesii* has a capsule. If this is the case, its presence could explain to some extent why asplenic patients have an increased risk for *B. holmesii* bacteremia (67).

CLINICAL FEATURES

Pertussis-Like Respiratory Infections

Clinical manifestations of a *B. holmesii* respiratory infection are similar to a pertussis-like disease. They include mild fever, associated with the classical pertussis symptoms of paroxysmal cough, inspiratory whoop, and post-tussive vomiting. The expected duration of the illness and whether it is also divided into the three typical stages of pertussis disease, namely, the catarrhal, paroxysmal, and convalescent periods, is still unknown. However, it is believed that it is similar to a *B. pertussis* infection. In a study comparing 21 cases of *B. holmesii* respiratory infection with 122 cases of *B. pertussis* infection, the authors concluded that the clinical presentation was less severe with *B. holmesii*, as patients presented two or less of the three classical pertussis symptoms (9). Conversely, Rodgers et al. reported that clinical features were similar in 48 cases of *B. holmesii* respiratory infection and 112 cases of *B. pertussis* (68). However, they found that cough duration was shorter in *B. holmesii* infection, with almost 70% of patients being cough-free 80 days after antibiotic administration (clarithromycin or azithromycin), compared to 30% of patients with *B. pertussis*. This could possibly be
explained by the lack of pertussis toxin in B. holmesii (68). Neither complications nor deaths have been reported after respiratory infections, but this may reflect a reporting or detection bias. Given the high similarity between B. holmesii isolates in respiratory and invasive disease, secondary bloodstream dissemination after a respiratory infection with secondary complications cannot be excluded.

B. pertussis infection in infants correlates with a high mortality and complication rate. The only published report of B. holmesii infection of infants younger than 6 months shows no cyanosis or apnea. However, this reassuring information is based on only a very limited (seven) number of patients (69).

**Bacteremia**

B. holmesii was first reported as an organism causing bacteremia, mainly in immunocompromised individuals. The clinical course is always nonspecific, with mild fever occasionally accompanied by headache, chills, or vomiting (37, 45). Concomitant respiratory symptoms are frequent, suggesting possible secondary blood dissemination. Laboratory assessments are noncontributive; in particular, there is no high lymphocytosis as described for B. pertussis respiratory infection. This might be explained also by the lack of pertussis toxin in B. holmesii. Although it could be questioned whether B. holmesii isolated in patients is the actual cause of infection and not due to infection by another microorganism, growing evidence proves that it is truly pathogenic. In most patients, B. holmesii was isolated from two or more cultures in blood samples, obtained at different times during the same infectious episode, and was the only microorganism isolated (37). The outcome is usually favorable when the infection is treated with antibiotics, with no fatality reported. However, the presentation can sometimes be severe with secondary infections and even require admission to intensive care (37, 70).

**Other Invasive Infections**

B. holmesii has been isolated in a variety of body sites, mostly documented in case reports. These have been summarized recently in a review (62) and include cases of pneumonia, endocarditis, pericarditis, meningitis, arthritis, diskitis, and cellulitis. The infection was usually confirmed by using different diagnostic tools, repeated sampling, and, exceptionally, tissue biopsy, suggesting causality. Interestingly, some patients complained of concomitant mild upper respiratory tract symptoms, thus raising the question of whether a primary B. holmesii respiratory infection may have further disseminated to a secondary infectious site. Unfortunately, this was investigated only once (56). Although some patients experienced infection relapse, required prolonged treatment, were admitted to the intensive care unit, or even needed a surgical procedure, such as the removal of prosthetic material, outcomes have generally been favorable at the end of the treatment, with no fatality reported (62).

In particular, three cases of pneumonia have been described; two were complicated by pleural effusion (36, 38, 56). One patient had an acute presentation with
mediastinal collection, pericarditis, coagulopathy, and pulmonary fibrosis, resulting in a severe restrictive syndrome 6 months later \((36, 38)\). \textit{B. holmesii} has been reported to trigger exacerbation of chronic obstructive pulmonary disease in a 41-year-old woman, requiring intubation and admission to critical care \((2)\). Endocarditis on both native and prosthetic valves was reported for eight patients \((1, 2, 41, 47, 48, 51, 58)\). Clinical symptoms differed among individuals, ranging from subacute endocarditis to septic shock with acute renal failure. Patients usually required valve replacement. Two additional patients had \textit{B. holmesii} pericarditis; one required more than 2 months of hospital stay \((36, 53)\). Two cases of \textit{B. holmesii} meningitis were reported, one in a 14-year-old girl with anorexia nervosa and the other in a 39-year-old woman with end-stage renal disease secondary to systemic lupus erythematosus. One patient experienced persistent convulsions that required continuous intravenous diazepam and mechanical ventilation \((71, 72)\). Septic arthritis has been reported for patients with both normal and prosthetic knees, followed by the removal of the prosthesis in an immunocompetent 54-year-old woman \((1, 46, 60)\). A case of lumbar diskitis was diagnosed by identification of \textit{B. holmesii} on cultures of both blood and L3-L4 disk biopsy \((61)\). Finally, \textit{B. holmesii} was isolated four times in cultures of blood from a 67-year-old patient receiving rituximab and presenting subsequently with three episodes of cellulitis and one episode of pneumonia. Nasal carriage of \textit{B. holmesii} was also reported later \((56)\).
**DIAGNOSIS**

Various methods can be used for the detection of *B. holmesii* in clinical specimens. The organism can be cultured if appropriate media are used, such as Bordet-Gengou or Regan-Lowe medium without cephalaxin. Its presence can be identified by PCR, whole-cell fatty acid analysis, 16S rRNA analysis, or mass spectrometry (62). In respiratory infections, specimens are collected by either swab, aspiration, or nasopharyngeal wash as for *B. pertussis*, but no study has yet evaluated which sample site yields the best results. *B. holmesii* has been isolated also from blood, tissue biopsy samples, and pleural, articular, and other fluids (62).

**Culture**

Although culture is frequently used to diagnose *B. holmesii* invasive or respiratory infection, this diagnostic tool is cumbersome, as for all other Bordetella species, because of its fastidious growth and low analytical sensitivity (12% to 60%) (7). Specific swabs are required, and rapid transfer to the laboratory is necessary to ensure optimal sensitivity (3, 73). The specimen needs then to be directly plated onto the appropriate medium. If plate inoculation cannot be done rapidly, special transport medium is also required (Regan-Lowe transport medium without cephalaxin). Interestingly, it has been demonstrated that the growth of *B. holmesii* is inhibited by cephalaxin, an antimicrobial agent widely recommended and used in various Bordetella culture media (74). Therefore, recommendations have now changed, and oxacillin or methicillin is now preferred instead of cephalaxin to grow *B. holmesii* (75). This intrinsic susceptibility explains also why most laboratories failed to identify *B. holmesii* in nasopharyngeal specimens of patients with pertussis-like symptoms before 2000 (74).

**Polymerase Chain Reaction**

In 2000, Loeffelholz et al. first reported that the most frequently used technique at that time for the diagnosis of *B. pertussis*, i.e., PCR targeting the IS481 sequence, was not species specific, as it systematically falsely diagnosed *B. holmesii* respiratory infection as *B. pertussis* (3). This was confirmed by quality control exercises carried out worldwide and showed that only a very few laboratories were able to routinely identify *B. holmesii* (76–78). Indeed, PCR is the most commonly used diagnostic tool when suspecting pertussis given its high sensitivity compared to that of culture (93% sensitivity with the IS481 target, compared to 15% for culture in a study using an expanded case definition [79]).

Diagnosing infections using PCR has also the advantages of remaining positive later in the course of the disease and of being less affected by antibiotic treatment. However, as no universal recommendations exist, PCR protocols for *B. pertussis* diagnosis differ widely among centers, with each laboratory defining its own assay procedure and detection limit (77, 80, 81). Nevertheless, most laboratories use IS481 as the target sequence to diagnose *B. pertussis* (77, 81). Since a substantial number of copies of IS481 is found in the *B. pertussis* genome, the sensitivity of PCR targeting this sequence is greater than that of those using single-copy target sequences (e.g., pertussis toxin) (11). The high sensitivity is at a cost of lower specificity, as few copies of IS481 are also present in the genome of other Bordetella species, such as *B. holmesii* and, occasionally, *B. bronchiseptica* (76, 82). Thus, laboratories aware of this potential false-positive result have decided to perform a second PCR assay on IS481-positive specimens using either a *B. pertussis*- or a *B. holmesii*-specific target, or both. However, these other targets are at least 10-fold less sensitive than the IS481 target, since they are present in fewer copies of the genome. This might lead subsequently to false-negative results (83). A number of potential target sequences have been proposed to increase the diagnosis of *B. pertussis* (ptx, IS1002, BP283, and BP485) and *B. holmesii* (recA, hIS1001, and bhoE) (10–12, 84, 85), but there is no recommendation on what is the best PCR diagnostic strategy to use at the present time.

**Loop-Mediated Isothermal Amplification Assay**

First described by a Japanese group in 2004, the loop-mediated isothermal amplification assay is a novel method that uses a DNA amplification technique and offers a rapid diagnosis of various viral and bacterial infectious diseases. It is usually less expensive and simpler to use than conventional PCR, since it is isothermal and does not require expensive thermocyclers, thus making it a promising method for microbial diagnosis, especially in countries with limited resources. Ōtsuka et al. developed the first loop-mediated isothermal amplification assay targeting the recA gene that successfully detected *B. holmesii* and discriminated it from other Bordetella species (86). Although not extensively used, this technique is of potential interest and could increase in the future.

**16S Ribosomal RNA**

The 16S rRNA sequencing technique is the most frequently used method in the case reports of invasive
B. holmesii infection (62). Of note, as the sequence obtained in B. holmesii is very similar to that of B. pertussis (>99% similarity [30]), it is recommended to perform additional sequence analysis for confirmation in a second step, such as detection of B. holmesii-specific genes by PCR, for example (27).

Spectrometry
Matrix-assisted laser desorption ionization–time-of-flight mass spectrometry (MALDI-TOF MS) is a soft ionization technique used in mass spectrometry that enables identification of most pathogens retrieved in clinical microbiology (87). Few groups have detected the presence of B. holmesii in various clinical specimens by MALDI-TOF MS (51, 54, 59–61). This promising diagnostic tool has the advantage of allowing a rapid and accurate identification of B. holmesii in any clinical specimen. However, only a limited number of laboratories have access to this new and expensive technology.

Automated Microbial Identification Devices
Automated microbial identification devices are widely used in clinical microbiology laboratories and enable the rapid and accurate identification of selected medically relevant bacteria. However, reports have highlighted that these devices failed to identify B. holmesii or systematically erred, since it was not included in their database (35, 39, 51, 54, 88). For example, Jonckheere et al. (51) and Panagopoulos et al. (88) reported several cases of systematic misidentification of the bacteria as Acinetobacter spp. by Vitek2 (bioMérieux Inc., Marcy L’Etoile, France) and API 20 NE gallery (bioMérieux Inc.), respectively.

TREATMENT
No evidence-based recommendations are available regarding the best antibiotic regimen for treating B. holmesii infection. Several groups have investigated the in vitro susceptibility of B. holmesii to various antibiotics using broth microdilution (37), the Epsilometer test (31, 38, 44, 46, 51, 53, 56, 58, 71, 72, 88), automated systems (39, 48), agar dilution (2), and disk diffusion (34, 47, 51, 89). In summary, investigations show that third-generation cephalosporins may not be optimal to treat B. holmesii (37). Ceftazidime is probably the best in this class, given its low MICs (2, 29, 51, 88, 89). There are conflicting data on cefotaxime, which is reported as both active (2, 34, 58) and inactive (37, 39, 42, 47, 51, 56, 88) against B. holmesii. Resistance to ceftriaxone, cefotaxime, and also trimethoprim-sulfamethoxazole has been reported (42, 56, 71). Concerning macrolides, some data show that erythromycin has a lower activity against B. holmesii than B. pertussis (1). As for other antimicrobials, carbapenems and fluoroquinolones were effective in vitro against B. holmesii (37, 53) and are often suggested as the most effective treatment for B. holmesii infection (37, 45). As very few data are available on this subject, further microbiological investigations are required to determine the optimal antibiotic treatment and the breakpoints to be used for antimicrobial susceptibility testing of clinical isolates (51).

Respiratory Infections
In cases of B. holmesii respiratory infection, most patients are treated as for a B. pertussis infection. This happens because the patient has been misdiagnosed as infected with B. pertussis or because physicians give empirically the same antimicrobial for any Bordetella respiratory infection.

Macrolides are usually the first-choice treatment for a B. pertussis infection (75). However, they may not be the best choice for B. holmesii (1), and this could become an issue if the distinction between the two species is not made. From both an individual and a public health point of view, it is not clearly established at present whether it is indicated to administer antibiotics to patients with B. holmesii respiratory infection. This could probably be discussed on an individual basis for a patient with (or in contact with a person with) an underlying immunocompromised status in order to prevent secondary invasive infections.

Supportive care that is traditionally used in B. pertussis infection may also be suitable for B. holmesii infections. Examples include avoidance of factors triggering cough, such as physical exercise, cold air, or nasopharyngeal suctioning, as well as maintenance of adequate hydration and nutrition with the use of intravenous fluids and nasogastric feeding if required. Assisted ventilation may be necessary for some severe cases. Other adjunctive treatments, such as bronchodilators, corticosteroids, or antitussive agents, have not been proven to be beneficial in the case of B. pertussis infection and should probably not be used either for patients with B. holmesii (90).

Bacteremia and Other Invasive Infections
Due to the delayed identification of B. holmesii, patients with B. holmesii bacteremia or other invasive infections were initially treated empirically with the antibiotics recommended according to the focus of infection. Treatments were sometimes switched later when the
microorganism and its antibiotic susceptibility were known. The different antibiotic regimens documented in published case reports have been recently summarized in a review (62). Third-generation cephalosporins, often used empirically in various invasive infections, are not the first-choice antimicrobials for *B. holmesii* (37, 42, 54, 59). Most authors suggest carbapenems and fluoroquinolones, as they are probably the most effective agents against *B. holmesii* (37, 45). Clinicians should also keep in mind that a treatment course of more than 5 to 12 weeks (34, 36, 47, 49) is sometimes required, with some patients experiencing relapse when a shorter antimicrobial course was used (34, 47, 56). Finally, it should be recalled that *B. holmesii* bacteremia has been reported for patients receiving penicillin or trimethoprim-sulfamethoxazole prophylaxis (31, 35, 44, 57).

**PREVENTION**

**Vaccination**

As shown by Zhang et al. in an animal model, neither the whole-cell nor the acellular *B. pertussis* vaccine confers protection against *B. holmesii* (17). This observation was confirmed clinically during a *B. pertussis* and *B. holmesii* outbreak in which 60% of patients with a *B. holmesii* respiratory infection had been previously boosted with pertussis vaccine, compared to 44% of the *B. pertussis* cases (68). Since it has been demonstrated that the genes coding for the antigens targeted by the *B. pertussis* acellular vaccine (pertussis toxin, FHA, pertactin, and/or fimbriae, depending on the manufacturer) are absent from the *B. holmesii* genome (32, 34) or immunogenically distinct, antigen-specific immunoglobulins induced by pertussis vaccination will not protect against a *B. holmesii* infection. At the present time, there is no intention to develop a vaccine that induces protection against *B. holmesii*, and this will probably not be necessary in the near future.

**Antibiotic Prophylaxis**

As the same *B. holmesii* strain could potentially induce both respiratory and invasive disease, postexposure antibiotic prophylaxis may be indicated for individuals particularly at risk of invasive disease, such as asplenic patients. Although macrolides are the first choice for antibioprophylaxis following *B. pertussis* contact, they do not appear to be the best choice in this setting, given their lower activity against *B. holmesii* (1). Penicillins could probably be used as an alternative.

**Management Following an Index Case**

It is not mandatory to notify a case of *B. holmesii* infection to public health bodies, whereas it is for *B. pertussis* in many countries (91). Misidentification of a case of *B. holmesii* respiratory infection as a pertussis case may result in unnecessary and costly case investigations by public health authorities, including postexposure evaluation and management of contacts of index cases (92). In a hospital setting, droplet precautions should be implemented for a confirmed case of *B. holmesii* infection with respiratory symptoms in order to reduce transmission of the disease (93).

**EPIDEMIOLOGY**

**Transmission and Reservoir**

Transmission of respiratory infection is thought to be via droplets, although this has not been extensively investigated. The attack rate among contacts after an index case is unknown. *B. holmesii* carriage may be also suspected, although it is unclear if it is transient or not (48). Incubation time and the inoculum needed for infection are also unknown. Evidence suggests that *B. holmesii* cocultures with *B. pertussis* (9), as it has been isolated during several pertussis outbreaks (15, 22, 68) and five cases of *B. holmesii* and *B. pertussis* coinfection have been reported (68). The main routes of transmission of *B. holmesii* invasive disease have still to be elucidated. *B. holmesii* strains causing respiratory disease do not seem to differ from strains causing invasive disease, and it can be postulated that secondary blood dissemination can occur following respiratory infection. A few copies of *B. holmesii* have previously been detected in two platelet concentrates, which had been missed by routine bacterial screening (94). *B. holmesii* is believed to be a strictly human pathogen with no recognized animal reservoir. However, this has never been investigated and should be challenged because *B. holmesii* is closely related to the avian *Bordetella* species (27, 30–32, 85, 95).

**Prevalence and Incidence**

Epidemiological data are lacking, and the prevalence of *B. holmesii* is unclear and probably underestimated, as *B. holmesii* has been recognized as a human pathogen only recently and is challenging to detect. Awareness of *B. holmesii* is increasing, and it seems likely that an increasing number of laboratories will be able to detect it. As reported recently in a laboratory performance exercise, the number of U.S. public health laboratories that are capable of correctly diagnosing *B. holmesii* has increased...
from 5% to 75% in 2015 (81, 96). However, previous studies have shown that elsewhere, only a very limited number of laboratories were able to distinguish B. holmesii from other Bordetella: 1/11 (9%) and 1/24 (4%) European laboratories in 2005 and 2013, respectively (76, 77) and 7% of Australian laboratories in 2013 (78).

Studies worldwide have reported that B. holmesii could be the causative agent for 0% to 29% of patients with pertussis-like symptoms (6, 9, 10, 14, 15, 19, 20, 62, 68). The highest prevalence was reported in a study conducted during the 2010 Ohio pertussis outbreak, when B. holmesii was identified in approximately one-third of the cases of Bordetella-confirmed infections and at an even higher proportion in children 11 to 18 years old (45%) (68). All these prevalence studies have been listed in a review (62).

The prevalence of B. holmesii can widely differ from one country to another, even when the countries are geographically very close (62). In addition, the organism is more frequently reported between September and March and possibly follows a seasonal pattern (9, 21). At first, B. holmesii respiratory infection was identified more frequently in healthy adolescents and young adults (9), but since then, it has been detected in all age groups (19, 97).

Impact of Systematic Misidentification of B. holmesii Respiratory Infection as B. pertussis

Misdiagnosis of B. holmesii respiratory infection as B. pertussis affects the epidemiological studies of both species. Although the circulation of B. holmesii is low or nonexistent in some areas, one study found that it was present in almost half of the Bordetella-positive patients in a certain age group (68). However, given the seemingly high variability in prevalence of B. holmesii worldwide, countries should use Bordetella species-specific tests at least temporarily to determine whether and to what extent B. holmesii contributes to the pertussis cases. The specific diagnosis of Bordetella species is important because (i) case investigation required for B. pertussis is likely unnecessary for B. holmesii (92), (ii) antibioprophylaxis for immunosuppressed or asplenic patients (or persons in contact with them) may be indicated with B. holmesii respiratory infection, and (iii) misdiagnosing a B. holmesii respiratory infection as a B. pertussis breakthrough case following pertussis vaccination modifies the evaluation of the vaccine efficacy.

CONCLUSIONS

B. holmesii is an underdiagnosed emerging organism for which only limited clinical, microbiological, and epidemiological data are available. It has a greater invasive capacity than other Bordetella species. Lateral transfer of genetic material of other bacteria has possibly contributed to the emergence of B. holmesii as a human pathogen and may enhance its pathogenicity in the future. Hence, increasing awareness and surveillance of this entity are required for both invasive and respiratory infections. Although the optimal treatment for B. holmesii is unknown, infection with the organism can be easily diagnosed by PCR, 16S rRNA analysis, or mass spectrometry. Future studies should focus on understanding the epidemiology of B. holmesii, including its relation to other Bordetella species, establish the full spectrum of its clinical presentation, and determine the best management for patients, depending on the infection site.

ACKNOWLEDGMENTS

We gratefully thank Stéphane Emonet, Patrick Linder, Karl Perron, François Barja, and David Hernandez for the figures, Martine Leplay Fontana for her help in retrieving articles, and Rosemary Sudan for editorial assistance.

REFERENCES


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