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SPECIAL REPORT

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Acute infections caused by *Tropheryma whipplei*

Jean-Christophe Lagier¹, Florence Fenollar¹ & Didier Raoult^{*1}

Tropheryma whipplei is the causative bacterium of Whipple's disease. Its first culture has led to an enlargement of the field of the caused infections. Here, we comprehensively review acute *T. whipplei* infections. In a cohort study featuring 4000 children, *T. whipplei* was significantly more common in patients with diarrhea (4%) than in those without (1.7%). A case–controlled study highlighted 58 patients suffering from pneumonia with the detection of *T. whipplei* in their bronchoalveolar fluids. Finally, a recent study detected *T. whipplei* in the blood of 36 febrile patients experiencing pulmonary symptoms in a rural area of Senegal. *T. whipplei* is definitively an agent of acute gastroenteritis, a cause of nonmalarial fever in Africa, and probably a cause of pulmonary infections.

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Tropheryma whipplei is the causative bacterium of classic Whipple's disease, a chronic and rare infectious disease involving mainly middle-aged Caucasian males [1–3]. Recent epidemiological estimations, however to interpret with caution, have suggested a prevalence of 1.1 per 1 million populations and an annual incidence from one to six per 10 million populations but with strong geographical differences [3]. The typical Whipple's disease clinical involvement associates arthritis followed by diarrhea and weight loss. Whipple's disease is diagnosed by histological analysis of a small-bowel biopsy (positive periodic acid-Schiff staining and/or *T. whipplei* immunohistochemistry) [2]. Since the first cell culture of *T. whipplei* in 2000 [4,5], the range of chronic infections or asymptomatic carriage caused by this bacterium, their diagnosis and their management has expanded dramatically [2]. The spectrum of chronic infections caused by *T. whipplei* includes endocarditis, neurological infections, uveitis, arthritis and osteoarticular infections and, less frequently, isolated adenopathies [2,6]. Moreover, as a result of this culture, the recommended treatment is no longer empirical but evidence-based, on the grounds of both *in vitro* results and clinical outcomes [7,8]. This includes a 1-year combination of doxycycline and hydroxychloroquine followed by a lifetime treatment with doxycycline [7,9–10] because of the lifelong susceptibility of Whipple's disease patients to this bacterium [9]. Some other teams proposed a treatment associating intravenous ceftriaxone followed by a 1-year trimethoprim-sulfamethoxazole regimen [3]. As trimethoprim is inefficient for *T. whipplei* [2], and as we observed relapses in most of our patients including several cases of resistance to sulfamethoxazole [7,10], we cannot recommend this antibiotic treatment. Finally, *T. whipplei* stool carriage was also comprehensively described, particularly in sewer workers in France and Germany, in homeless shelters, in healthy individuals in

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- gastroenteritis
- pneumonia • *Tropheryma whipplei*

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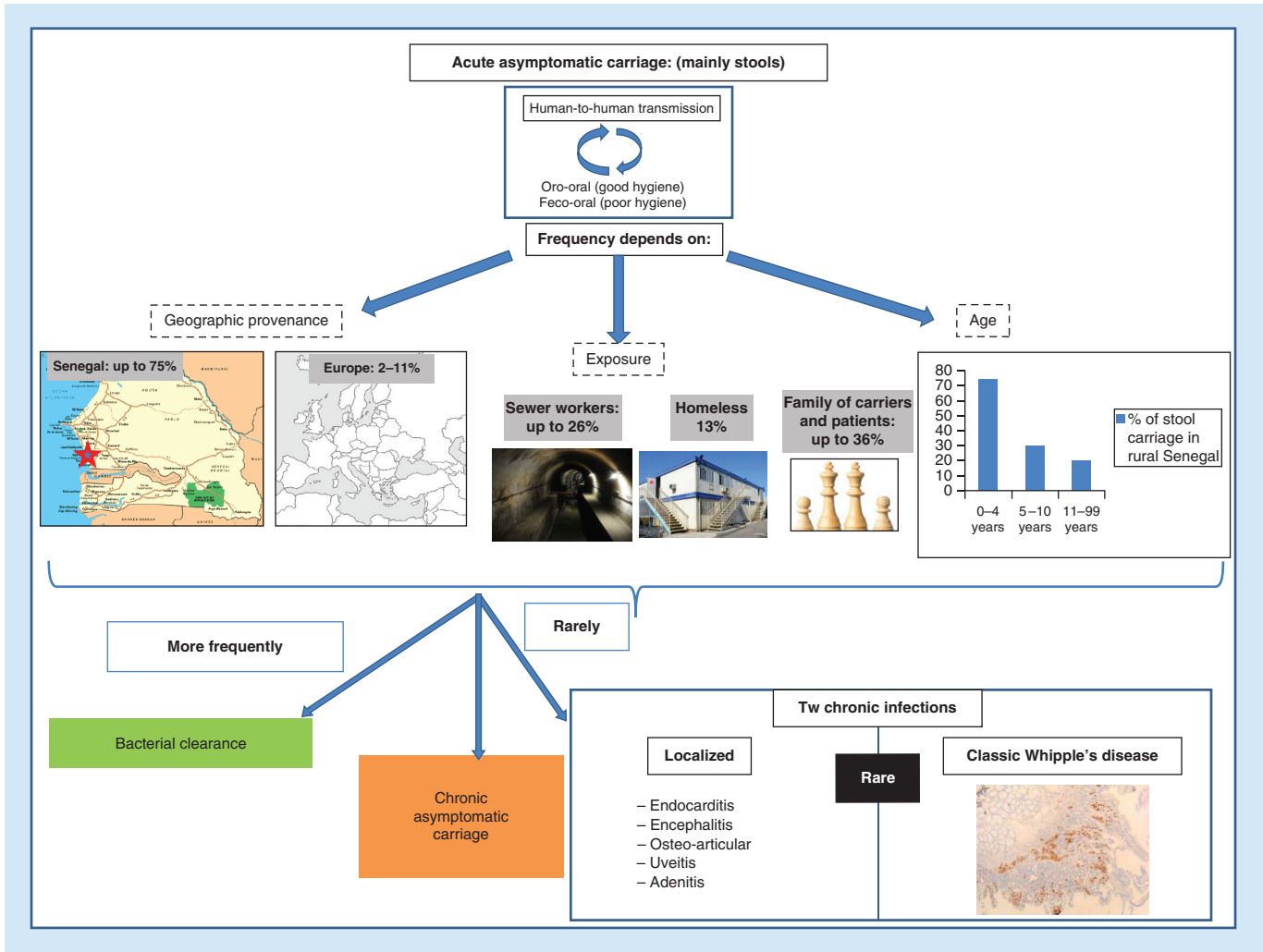


Figure 1. Natural history of *Tropheryma whippiei* carriage. This summary allows highlighting that *T. whippiei* acute asymptomatic carriage depends on geographic provenance, age and exposure. In most of the cases, we observe a bacterial clearance although in rare cases, individuals evolve to chronic asymptomatic carriage or to chronic *T. whippiei* infections.

rural Senegal and in both patients' and carriers' families [2,11-13] (Figure 1). This carriage appears to be worldwide as it has also been observed in Laos and in Ghana [14,15].

However, in addition to these chronic infections and asymptomatic carriage, acute *T. whippiei* infections may be sometimes encountered [2] (Figure 2). Recently, new data were made available on *T. whippiei* bacteremia in febrile Senegalese patients, on *T. whippiei* acute gastroenteritis as well as on *T. whippiei* pneumonia [16-18]. In this paper, we propose focusing on these acute infections, highlighting the possible natural history of this surprising bacterium. In terms of outlook, we will underline the possible avenues for future research in order to confirm these suggestions.

Tropheryma whippiei bacteremia

In the first piece of research, from November 2008 to July 2009, a prospective study was performed in two villages in rural Senegal (Dielmo and N'Diop) which have 700 inhabitants in the Sine-Saloum area [19]. Two-hundred and four febrile patients were included in this study. *T. whippiei* DNA was detected in the blood samples of 13 different patients (6.4%) without malaria. The controls were French *T. whippiei* stool carriers, and none of them had a positive *T. whippiei* blood sample. Interestingly, although all the patients were febrile, ten (77%) had a concomitant cough. This symptom as well as sleep disorders were significantly more common in patients with *T. whippiei* bacteremia than in the 191 febrile patients without *T. whippiei*

bacteremia ($p = 0.002$ and $p = 0.005$, respectively) [19]. No link with feces carriage of *T. whipplei* was observed [19].

In the second study, which included a control group with healthy people living in the same area, and which was performed in the same two villages, between June 2010 and March 2012, whole-blood finger-prick samples were analyzed from 786 febrile and 385 healthy villagers. *Tropheryma whipplei* DNA was detected in the blood samples of 36 febrile patients (4.6%) and one control (0.25%) [17]. Seasonality was observed because 100% of the cases occurred during the rainy season (June–October) but none of the cases occurred during the dry season (November–May). A comprehensive analysis demonstrated that most cases were diagnosed in August 2010, highlighting a probable *T. whipplei* outbreak. The main clinical manifestations were a headache (69%) and a cough (36%) with no significant difference between the *T. whipplei* positive and negative groups. Familial cases were observed, with 75% of the patients living in a

household that had experienced the *T. whipplei* bacteremia [17]. Finally, because of the lack of samples available, genotyping has been only established for eight patients. These partial data lead us to suspect the presence of a potential but not confirmed new epidemic clone. Despite the low number of strains that have been genotyped, the authors suspected that an epidemic clone was present. Interestingly, the local baker lived in the household where the prevalence of *T. whipplei* was the highest. Since the departure of this baker and his family, no outbreaks were observed and a concomitant decrease of *T. whipplei* prevalence was also noted [17].

In another African country, Gabon, the presence of *T. whipplei* in blood samples of febrile patients was investigated between 2014 and 2015. *T. whipplei* DNA was detected with a prevalence of 0.2% in the 410 febrile patients living in both rural and urban areas [20]. *Tropheryma whipplei* was detected only in febrile patients and not in controls. In conclusion, the real prevalence of *T. whipplei* bacteremia is currently difficult to

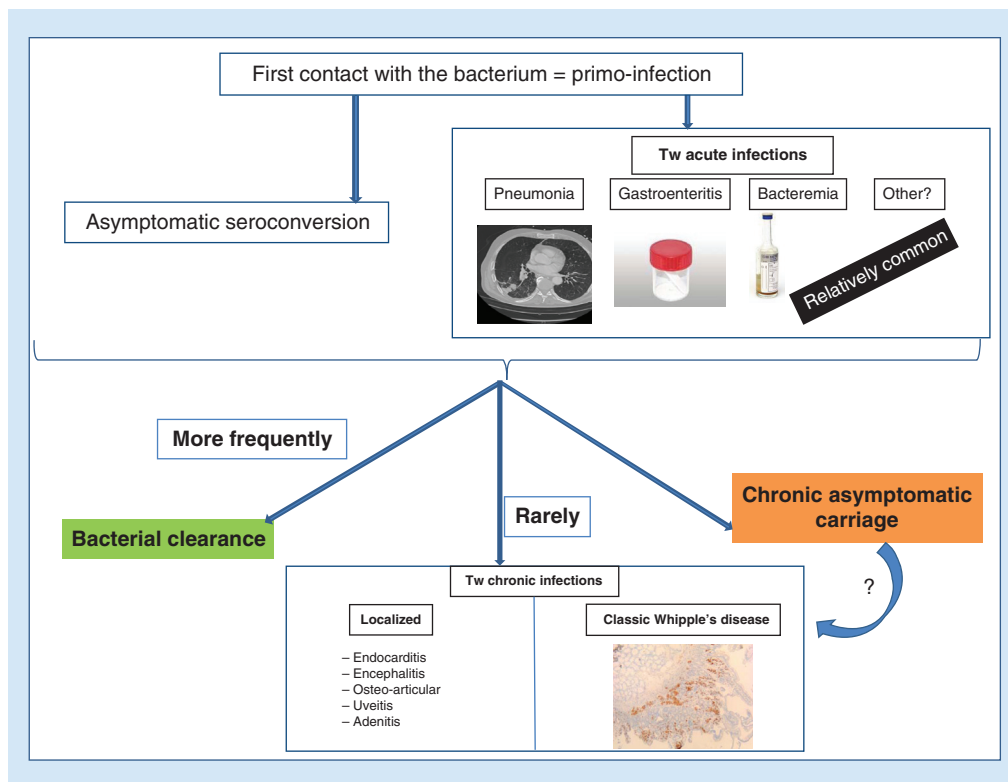


Figure 2. Natural history of *Tropheryma whipplei* infections. This summary highlights that *T. whipplei* acute infection consists more frequently of an asymptomatic seroconversion and in rare cases in *T. whipplei* acute infections. In most of the cases, we observe a bacterial clearance although in rare cases, individuals evolve to chronic asymptomatic carriage or to chronic *T. whipplei* infections.

estimate, but these recent large-scale studies confirm the role of *T. whipplei* in febrile nonmalaria episodes and indicate that it may depend on the epidemic situation.

Gastroenteritis

A variety of strong data have been accumulated over the years pointing to a link between acute diarrhea and *T. whipplei*. A first major study was conducted in France looking at the presence of *T. whipplei* DNA in stool samples of children aged between two and four. *Tropheryma whipplei* was detected in 36 of the 241 samples tested (15%) from children suffering from gastroenteritis, while none of the 47 controls tested were positive ($p = 0.008$). The rate of positive samples was comparable between 2006 and 2008 and no seasonal variation was observed [21]. Most of the patients had a high bacterial load ($>10^4/g$ of stool), comparable to that of patients suffering from Whipple's disease. A third of the children were coinfecting with another pathogen. Despite the large heterogeneity of the strains, evidence of clonal circulation was observed. Experimental model, demonstrating that orally administered *T. whipplei* may induce diarrhea in mice, has confirmed Koch's postulates that *T. whipplei* is a bacteria which causes gastroenteritis [22].

In a hospital-based case-control study performed in rural Ghana on 534 stool samples of children aged between 2 months and 15 years, *T. whipplei* DNA was detected in 27.5% of the samples. Overall, no difference between cases and controls was observed, although in the children under the age of one, *T. whipplei* was more likely to be detected in patients (23.3%) than in the controls (11.4%) suggesting a possible role in gastroenteritis in young children in rural Africa [15]. In rural Senegal, *T. whipplei* was also more significantly detected in stool samples of patients with diarrhea (25/51, 49%) compared with asymptomatic individuals (139/446, 31.2%; $p = 0.015$) and only in patients under 11 years old [11].

In a subsequent study performed between 2009 and 2013, the link between *T. whipplei* and acute diarrhea was investigated in a larger cohort of children [18]. A total of 3796 rectal swabs were collected from the emergency departments of hospitals in Marseille, France and were tested for *T. whipplei*. When stool samples were also available for children with diarrhea, tests were carried out to detect *Salmonella*, *Shigella*, *Campylobacter* and *Yersinia* species, *Escherichia coli* 0157:H7, *Aeromonas* species as well as the

presence of rotavirus, adenovirus, norovirus and astrovirus. Of the 3796 children included, 555 suffered from diarrhea. Among them, 22 (4%) were positive for *T. whipplei* and a significant difference emerged when compared with the 56 positive samples among the 3241 nondiarrheic children tested (1.7%, $p = 0.001$). *T. whipplei* was occasionally detected in association with adenovirus and rotavirus. Monomicrobial detection of *T. whipplei* was observed in eight cases, whereas monomicrobial detection of *Salmonella* spp. was only observed in four cases. The incidence of diarrhea associated with *T. whipplei* varied from year to year, from 2% in 2012 [18], 15% in 2006–2008 [21], to 16% in 2009 [18]. In this large cohort, the seasonal circulation of *T. whipplei* was mainly observed during autumn [18].

Among travelers to Senegal, 59 individuals returned stool samples both before and after travel. Of them, two patients (3.4%) who had no diarrhea were negative for *T. whipplei* before travel and positive after travel, demonstrating that stool carriage was acquired after travel in a tropical area [23]. In another study performed on 129 pilgrims in Saudi Arabia which analyzed the presence of *T. whipplei* DNA on rectal swabs before and after Hajj and during episodes of diarrhea, it was revealed that two of nine pilgrims with diarrhea during their pilgrimage were positive for *T. whipplei* [24]. Further studies exploring this issue in larger cohorts of travelers, including stays in rural area, would contribute toward a better understanding of the potential role of *T. whipplei* in traveler's diarrhea.

Lung involvement

• Pneumonia

Lung involvement is a rare but classic manifestation of Whipple's disease [1,25], with an isolated cough sometimes being the first clinical involvement revealing the disease [26]. In terms of acute pneumonia, *T. whipplei* was first detected in 2007 by Harris *et al.* from bronchoalveolar (BAL) fluid when they were investigating the microbiota of children with cystic fibrosis [27]. *Tropheryma whipplei* was detected in a control from a previously healthy child suffering from acute interstitial pneumonia [27]. A study performed on patients hospitalized with pneumonia in an intensive care unit in Marseille, France, detected *T. whipplei* DNA in six of the 210 (3%) BAL fluids tested [28]. Of these six patients, three suffered from aspiration pneumonia, two from a ventilator-associated pneumonia and one

from a community-acquired pneumonia [28]. Interestingly, for this last patient, *T. whipplei* was the only microorganism identified and half of the six patients were immunocompromised. In addition to this study, a case of *T. whipplei* pneumonia has been reported in a 24-year-old Senegalese HIV-infected patient with a CD4-positive cell count of 269/mm³ [29]. A chest CT scan revealed a right upper lobe pneumonia as well as bilateral alveolar condensation. Blood culture, *Legionella pneumophila* and *Streptococcus pneumoniae* urinary antigens were negative, and analysis of BAL fluid for *Mycobacterium tuberculosis*, *Pneumocystis jirovecii*, *Aspergillus* sp., cytomegalovirus and herpes virus was also negative. The pure *T. whipplei* culture from the BAL fluid of a 70-year-old patient suffering from pneumonia was performed for the first time in 2012, for supporting the role of this bacterium in acute respiratory infections [30]. This patient suffered from 3 weeks of nocturnal sweats with fever and dyspnea. Histological examination of the duodenal biopsy sample was negative (periodic acid-Schiff staining and immunohistochemistry) and, unfortunately, the sample was not available for histological analysis focusing on *T. whipplei* involvement.

Recently, a case-control study of 1438 BAL tested for *T. whipplei* by qPCR, included 88 patients that were positive and 88 controls matched for aged, sex and hospitalization unit [16]. Of them, 58 patients suffered from pneumonia (66%) in the *T. whipplei* group, while 72/88 (81%) in the control group had pneumonia. *Tropheryma whipplei* was significantly associated with aspiration pneumonia (18/88 cases in comparison with 6/88 controls, $p = 0.01$) and *T. whipplei* was detected as the sole pathogen in nine additional patients [16]. Overall, immunocompromised status was no different between the *T. whipplei* group and patients but, despite a low number of patients, *T. whipplei* was more likely to emerge in AIDS patients with a low CD4 level as well as in patients receiving TNF- α inhibitor treatment. Interestingly, regarding a potentially similar susceptibility, *P. jirovecii* was more frequently associated with the *T. whipplei* group compared with control group [16].

• Other lung & airways involvements associated with *Tropheryma whipplei*

Alongside acute pneumonia, several studies have reported the presence of *T. whipplei* in the airways either as probable colonization or

as another clinical involvement for which their potential implication continues to be unknown. Recently, a metagenomic study comparing both lung and oral microbiota from 64 healthy subjects revealed a high *T. whipplei* prevalence of 26% in BAL lavage samples but not in oral washes [31]. The increased presence of *T. whipplei* in BAL compared with washes was also observed in another larger study which included HIV-infected and HIV-negative individuals [32]. In addition, a higher prevalence of *T. whipplei* lung colonization in asymptomatic HIV-infected individuals was observed in comparison with a control group. Moreover, a decrease in the *T. whipplei* bacterial load was observed after initiation of antiretroviral therapy [33].

In addition, a recent study demonstrated the potential implications of this bacterium on patients with poorly controlled asthma [34]. Thirty patients were included and analysis of the sputum microbiome was performed by 16SrRNA pyrosequencing and *T. whipplei* qPCR for confirmation of the results. Overall, 12 (40%) of the patients were detected with *T. whipplei* DNA. In another metagenomic study analyzing the lung microbiome from BAL fluid samples, one of the 29 patients tested who had cortico-resistant asthma, had *T. whipplei* as a unique microorganism in his airways [35]. Additional studies are needed to prove a relationship between *T. whipplei* and asthma.

• Place of these acute infections in the natural history of *Tropheryma whipplei*

Epidemiological studies on *T. whipplei* carriage which were recently performed demonstrated human-to-human *T. whipplei* transmission [11,12,14,36]. The prevalence of this carriage depends upon geographical provenance, mode of exposure and age (Figure 1) [2,3]. Most patients fully clear the bacterium but, rarely, some patients have developed chronic carriage or a chronic *T. whipplei* infection (Figure 1). Of the chronic carriers, some appear to be protected against reinfection because they have a strong immune response, while others with a low immune response may be recolonized by another *T. whipplei* strain [37]. In addition, these 175 acute *T. whipplei* infections (Table 1 & Figure 2), correspond to another mode of primo-infection. This pointed toward strong evidence on the putative pathway of the natural history of *T. whipplei*, implying that most patients developing the relatively frequent acute *T. whipplei* infection could spontaneously clear the bacteria, although a tiny

Table 1. Clinical implication of *Tropheryma whipplei* in acute infections.

Type of involvement	Type of studies	Place of inclusion	Countries	Years of inclusion	Patients (n)	Ref.
Pneumonia						
	Cohort	Control	USA	2006	1	[27]
	Cohort	Hospitalized in intensive care units	France	2007–2008	6	[28]
	Case report	AIDS-infected outpatient	France	2013	1	[29]
	Case control	Hospitalized in university hospital	France	2013–2014	57	[16]
Gastroenteritis						
	Cohort	University hospital for children	France	2006–2008	22	[21]
	Cohort	Emergency departments of university hospitals for children	France	2009–2013	36	[18]
	Cohort	Hajj pilgrims	Saudi Arabia	2013	2	[24]
Bacteremia						
	Cohort	Febrile outpatients	Senegal	2008–2009	13	[19]
	Cohort	Febrile outpatients	Senegal	2010–2012	36	[17]
	Cohort	Febrile outpatients	Gabon	2013–2014	1	[20]
Total no. of patients					175	
Fifty-eight patients were included in this study but the AIDS-infected patients reported in [29] had been also included.						

proportion of them developed a chronic infection due to an undetermined genetic predisposition, while another tiny proportion could develop chronic asymptomatic carriage [2,37] (Figure 2).

Conclusion & future perspective

T. whipplei, the causative agent of Whipple's disease, can be involved in acute infections as gastroenteritis or pneumonia and is a cause of nonmalarial fever in Africa.

Most of the studies discussed in this paper were performed in our reference laboratory. We are confident in the results because these studies were conducted on large populations including controls, because the detection of *T. whipplei* was considered after at least two positive specific qPCR tests, and because stringent protocols, including positive and negative controls, were used [38]. Nevertheless, our results are supported by the fact that other teams have also detected *T. whipplei* using different techniques whether in gastroenteritis [15], pneumonia and lung carriage, or other airway involvements [27,33,35,39]. Interestingly, a key issue to underline remains interpretation of the results of such studies when a same pathogen is associated with both colonization and infections. Indeed, we consider that *T. whipplei* is one of the main significant examples of the absolute need to use controls in the study of epidemiological acute infectious diseases [40]. *Tropheryma whipplei* is a proof of this concept, whether on stool samples or in BAL fluids samples, or in blood samples where

this bacterium was sometimes detected in totally asymptomatic individuals [16–18].

The involvement of *T. whipplei* in acute infections is definitively based on strong evidence, at least in cases of acute gastroenteritis for which there is strong epidemiological and clinical data as well as an experimental model [18,21,22]. Further larger studies will be needed to support the hypothesis that *T. whipplei* is a causative agent of traveler's diarrhea [23,24]. Regarding pneumonia, the recent case–controlled study provides definitive clinical and epidemiological evidence [16]. Moreover, the immunocompromised status of patients with *T. whipplei* pneumonia has not yet been thoroughly elucidated and larger specific studies could be designed [16]. Further study in countries other than Senegal continues to be needed to confirm that *T. whipplei* is a causative agent of nonmalarial fever in rural Africa. Finally, future large studies will allow to better estimate the frequency of acute infections caused by *T. whipplei*.

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EXECUTIVE SUMMARY

- *Tropheryma whippelii* is the causative agent of Whipple's disease, a rare chronic infectious disease.
- The first culture of *T. whippelii*, performed in 2000, has improved knowledge of the infections caused by this bacterium.
- *Tropheryma whippelii* has also been reported as an agent of acute infections including gastroenteritis, bacteremia and acute pneumonia.
- Epidemiological and clinical data as well as experimental model have demonstrated that *T. whippelii* is an agent of acute gastroenteritis.
- *Tropheryma whippelii* DNA was detected in the blood samples of 36 febrile patients (4.6%) and only one control (0.25%) is a cause of nonmalarial fever in Africa.
- In acute pneumonia, *T. whippelii*, sometimes detected as sole pathogen, is significantly associated with aspiration pneumonia and is more likely detected in AIDS patients with a low CD4 level and in patients treated by TNF- α inhibitors.

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