Seroprevalence of Bartonella quintana Infection: A Systematic Review

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Abstract

Introduction: Bartonella quintana is an anaerobic bacillus whose main target is the erythrocyte. This bacterium transmitted by the body louse notably infected the soldiers of the First World War from where the name of this disease: fever of the trenches. The 90s marked the return of this bacterial infection. B. quintana infection in the homeless was reported in the literature with a high incidence in these populations worldwide. This upsurge of cases justified this study for a better understanding of B. quintana infections. Methods: We conducted a systematic review to evaluate the seroprevalence of B. quintana infection by using Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to collect scientific papers from PubMed and Google Scholar based on combining keywords. Results: The review included 45 articles published from April 1996 to March 2020 with 84 subpopulations of 21 countries from 4 continents; among them, 61 subpopulations had a positive rate from 0.2% to 65%. These subpopulations were divided into four main groups: homeless people, healthy people, blood donors, and symptoms/diseases. Homeless people were the main target of this infection, and three factors related to susceptibility were homeless period, age, and alcoholism. 6/11, 12/20, and 32/41 subpopulations of healthy people, blood donors, symptoms/diseases, respectively, had a positive percentage. However, factors of exposure in these three groups were not mentioned. Other reservoirs, vectors, and transmitted routes were identified to partially explain the worldwide spread of the infection, and it is important to have more further investigations to identify potential risk factors. This will help to limit contamination and prevent effectively. Conclusions: This serological overview indicated the importance of B. quintana infection that has emerged in multiple regions, touched worldwide populations.

Keywords: Bartonella quintana, infection, seroprevalence

INTRODUCTION

Bartonella quintana is a fastidious Gram-negative bacterium and the pathogen of trench fever, a disease that has the transmission from human to human through the body louse (Pediculus humanus corporis). Trench fever caused epidemics worldwide and affected several million people during two World Wars, but the incidence decreased significantly after the end of each World War. After the incubation period from 15 to 25 days, the most frequent symptoms are acute high fever, dizziness, headache, bone pain, and a relapsing febrile every 4–6 days, thus it was called “quintana fever.” Although trench fever often caused a prolonged disability, the death was rare. Other manifestations of B. quintana infection were reported, such as chronic bacteremia, endocarditis, bacillary angiomatosis, and lymphadenopathy. Human is the natural reservoir host, in which the bacterium persists durably in erythrocytes, erythroblasts with the percentage of infected cells being very low. Since the 1990s, B. quintana was recognized as a major re-emerging agent in urban homeless people due to poor living conditions and alcoholism. These factors promote high exposure to B. quintana by ectoparasites that are the vector of transmission. Recently, there have been some scientific reports of B. quintana infection with a high rate of exposure from various subpopulations.

There are many different tests for diagnosing B. quintana infection based on clinical characteristics, but to assess the incidence in the community for epidemiological studies, we conducted a systematic review to evaluate the seroprevalence of B. quintana infection by using Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to collect scientific papers from PubMed and Google Scholar based on combining keywords.

RESULTS:

The review included 45 articles published from April 1996 to March 2020 with 84 subpopulations of 21 countries from 4 continents; among them, 61 subpopulations had a positive rate from 0.2% to 65%. These subpopulations were divided into four main groups: homeless people, healthy people, blood donors, and symptoms/diseases. Homeless people were the main target of this infection, and three factors related to susceptibility were homeless period, age, and alcoholism. 6/11, 12/20, and 32/41 subpopulations of healthy people, blood donors, symptoms/diseases, respectively, had a positive percentage. However, factors of exposure in these three groups were not mentioned. Other reservoirs, vectors, and transmitted routes were identified to partially explain the worldwide spread of the infection, and it is important to have more further investigations to identify potential risk factors. This will help to limit contamination and prevent effectively.

CONCLUSIONS:

This serological overview indicated the importance of B. quintana infection that has emerged in multiple regions, touched worldwide populations.

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How to cite this article: Mai BH. Seroprevalence of Bartonella quintana infection: A systematic review. J Global Infect Dis 2022;14:50-6.
serologic test using immunoglobulin G (IgG) and IgM titers is the most widely used method.\[6\] We conducted this systematic review of seroprevalence to evaluate the rate of *B. quintana* infection over the past 25 years.

**METHODS**

**Search strategy and selection criteria**

The seroprevalence review was conducted according to guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The databases were searched and collected before March 2020 on PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and Google Scholar (http://scholar.google.com/). The most recent article was published in March 2020. The keywords used for searching the databases were followed:

#1: “antibodies” OR “serology” OR “seroprevalence” OR “seroreactivity” OR “epidemiology” OR “prevalence”.

#2: “*Bartonella* spp.” OR “*Bartonella quintana*” OR “trench fever”.

Searched by: #1 AND #2.

Only articles published in English were referred and references from selected articles were also screened to avoid missing data.

After evaluating the abstracts, the full texts were assessed for having the correct selection in this review. Exclusion criteria were as follows: (1) some studies used the same samples, and only one study was considered, and (2) not mentioned *B. quintana*.

To evaluate the percentage of *B. quintana* infection in population, we used both IgG and IgM titers. Depending on the manufacturer, serum threshold detected is different between articles.

**Data collection**

The data were collected from each article: year of publishing, countries, sample size, positive percentage, IgG titer, IgM titer, and *P*-value if compared with group control.

**Data analysis**

As a result of the heterogeneity of subpopulations and the nature of studies, we could not have a meta-analysis, hence described the main outcomes such as prevalence and related factors. Hence the main outcomes of this review were the prevalence and related factors of the bacterial infection.

**RESULTS**

A total of 705 articles were selected through database searching and six additional articles were found through the references.

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**Figure 1:** Flow diagram of the search strategy
After screening the titles and abstracts, 70 papers were analyzed full text; among them, 24 papers were excluded and 46 articles were qualified for this systematic review [Figure 1]. A total of 21 countries of 4 continents had the serological surveys, in detail: Africa has one article for each country (Algeria, Burundi, Congo, and Tunisia), Asia is the same (Japan, Thailand, Jordan, and Korea), America has 9 articles (5 in the US, 2 in Brazil, 1 in Peru, and 1 in Colombia), and Europe has 29 articles (10 in France, 6 in Sweden, 4 in Poland, 2 in Greece, 3 in Spain, and 1 for each country: Austria, Croatia, Denmark, and the UK). These studies were published from April 1996 to Mars 2020 and conducted on 84 subpopulations, and among them, 61 subpopulations had a positive proportion, equal 72.6% [Table 1]. We divided these subpopulations into four main groups: healthy people, blood donors, homeless people, and symptoms/diseases. In healthy people, 6/11 subpopulations had an infection with the rate from 1.4% to 25% and the highest was hunters [Figure 2]. Blood donors indicated 12/20 studies from 10 countries having positive sera between 0.2% and 50.5% [Figure 3]. In the homeless group with 12 subpopulations, only intravenous drug users were negative, but the number of participants in this study was only six. The rest had a positive rate from 1.8% to 65%, remarkably homeless patients cutaneous parasitic, homeless blood culture positive, Japanese homeless people had the positive rate over 50% [Figure 4]. In the symptoms/diseases group, 32/41 subpopulations had a positive prevalence between 0.5% and 64.5%, the highest in patients regional lymphadenopathy [Figure 5].

**Discussion**

In the 1st years of the 90s, several studies on some patient cases reported that *B. quintana* caused bacillary angiomatosis, endocarditis, and chronic lymphadenopathy, but in 1993, an outbreak of bacteremia occurred in 10 homeless alcoholics. Three years later, several serosurveys on a large number of indigent population in France and the US suggested a significant proportion of *B. quintana* infection. [11-14]

The return of the common disease in World War required an easy-to-apply approach to diagnose the disease. The isolation of *B. quintana* has been a difficult challenge; the detection of antibodies remains the most practical test for diagnosis of *Bartonella* infection in the case of inaccessible tissue. [15] While IgG reflects the evidence of past infection at an undetermined time, IgM shows the recent or current infection, hence all articles used IgG and only 11 articles added IgM. 60/84 subpopulations detected IgG for diagnostic threshold and 11/31 subpopulations had IgM positive with some cases, only having two subpopulations with two patients positive with IgM without IgG. Apparently, IgM assisted IgG in diagnosing infection related to epidemiological research of *B. quintana*.

As the large scale of geographic human subpopulations were exposed to *B. quintana* around the world, the majority of homeless subpopulations had a positive percentage higher in comparison with group controls that was elucidated by the proof of the body louse being the suitable vector for transmission and highly prevalent in this group. [17,17] For homeless people, independent factors that influenced to significant serological levels were the length of homeless period with more than 1 year and the age of homeless people above 40 years, alcohol abuse. [14] In other groups, only one investigation showed that *B. quintana* antibodies in villagers having a factor of “louse infected” were significantly higher in peasants and ectoparasitic infestation had a meaningful correlation with highest altitude village and women. [19] four studies had the comparison between two subpopulations but no difference of seroprevalence. [9,20-22] Not mentioned to homeless people, we noticed that 12/20 subpopulations of blood donor group, 6/11 subpopulations of healthy group, and 32/41 subpopulations of symptoms/diseases group with a total of 50/72 subpopulations surveyed from four continents had positive proportion; remarkably, 28 subpopulations had an exposure rate at least 10%. These positive subpopulations had no evidence of having risk factors such as unsanitary living conditions, contact with infected lice; thus this infection could be a result of some non-identified under-estimated factors. Fleas could also be involved in this disease because they are responsible for zoonoses on the one hand and *B. quintana* has already been detected in cat fleas from different sites in France and monkey fleas in Gabon on the other hand. [24] Fleas could be a potential vector of *B. quintana* alongside the recognized role of human body. Human is not the only reservoir of this Gram-negative bacterium, various studies showed animals were others reservoirs and this bacterium can cause diseases, such as bacteremia in a domestic cat, in wild Japanese macaques, in rhesus macaques, endocarditis in dogs. [26] Following a serological study, the positive percentage with *B. quintana* was 36.4% in healthy rhesus macaque. An experimental study showed a similar mechanism of transmission in human that *B. quintana* located in the gastrointestinal tract of cat fleas and released into feces. [29] Rhesus macaques are susceptible to *B. quintana* and *Polypltychoides obtusus* lice acted as the vector.
Table 1: *Bartonella quintana* seroprevalence among different subpopulations by chronological order of publication

| Year | References | Countries | Subpopulations | n  | IgG (%) | IgM (%) | Percentage | P       |
|------|------------|-----------|----------------|----|---------|---------|------------|---------|
| 1996 | [14]       | US        | Patients       | 192| 20.3    | NA      | 20.3       | <0.001  |
|      |            |           | Blood donors   | 199| 2       | NA      | 2.0        |         |
| 1996 | [13]       | US        | Intravenous drug users | 630| 10     | NA      | 10         |         |
| 1996 | [12]       | France    | Homeless people | 221| 1.8    | 0       | 1.8        | <0.05   |
|      |            |           | Blood donors   | 250| 0       | 0       | 0          |         |
|      |            |           | Hospitalized homeless patients | 43| 16.3 | 2.3 | 16.3 | <0.01 |
|      |            |           | Hospitalized patients | 57| 0      | 0      | 0          |         |
| 1996 | [30]       | France    | Patients suspected cat scratch disease | 64| 9.4    | NA      | 9.4        |         |
| 1998 | [31]       | Sweden    | *Chlamydia pneumoniae* IgG positive patients | 61| 0      | NA      | 0          |         |
| 1998 | [32]       | Burundi   | Sutama patients | 102| 12.7 | NA      | 12.7       | NA      |
|      |            |           | Febrile refugees | 232| 8.2   | NA      | 8.2        |         |
| 1999 | [4]        | France    | Homeless patients | 71| 29.6 | NA      | 29.6       | <0.001  |
|      |            |           | Patients       | 31| 0      | NA      | 0          |         |
|      |            |           | Blood donors   | 250| 0      | NA      | 0          |         |
| 1999 | [33]       | Sweden    | Patients       | 109| 2.8    | NA      | 2.8        | NA      |
|      |            |           | Blood donors   | 100| 0      | NA      | 0          |         |
| 1999 | [16]       | UK        | Probable cat scratch disease | 565| 13.1 | 1.4 | 13.8 | NA |
|      |            |           | Possible cat scratch disease | 48| 8.3 | 2.1 | 10.4 | NA |
|      |            |           | Bacillary angiomatosis/peliosis | 37| 5.4 | NA | 5.4 | NA |
|      |            |           | Blood culture-negative endocarditis | 66| 15.2 | 7.6 | 16.7 | NA |
|      |            |           | Ophthalmic involvement | 17| 17.6 | NA | 17.6 | NA |
|      |            |           | “Not appropriate” patients | 143| 2.8 | NA | 2.8 | NA |
|      |            |           | “No details” patients | 124| 9.7 | 1.6 | 10.5 | NA |
|      |            |           | Blood donors   | 200| 1.5 | 0 | 1.5 | NA |
|      |            |           | Healthy adult contact | 36| 0 | 0 | 0 | NA |
|      |            |           | Toxoplasmosis | 16| 0 | 0 | 0 | NA |
|      |            |           | Mumps virus | 13| 0 | 7.7 | 7.7 | NA |
|      |            |           | *Streptococcus pyogenes* serology | 8| 0 | 0 | 0 | NA |
|      |            |           | EBV | 11| 0 | 9.1 | 9.1 | NA |
|      |            |           | Chlamydia spp. | 5| 0 | 0 | 0 | NA |
| 1999 | [17]       | Peru      | Inhabitants | 194| 12.4 | NA | 12.4 | <0.05 |
|      |            |           | Peasants | 84| 0 | NA | 0 | NA |
| 2001 | [34]       | US        | Intravenous drug users | 204| 2.0 | NA | 2.0 | NA |
| 2001 | [19]       | France    | Homeless patients cutaneous parasitic | 57| 54.4 | 5.3 | 54.4 | <0.001 |
|      |            |           | Blood donors | 53| 1.9 | 0 | 1.9 | NA |
| 2001 | [22]       | Sweden    | Elite orienteers | 1136| 1.4 | NA | 1.4 | >0.05 |
|      |            |           | Blood donors | 322| 0.3 | NA | 0.3 | NA |
| 2002 | [3]        | France    | Homeless blood culture positive | 40| 65.0 | NA | 65.0 | <0.05 |
|      |            |           | Homeless blood culture negative | 82| 19.5 | NA | 19.5 | NA |
| 2002 | [35]       | Korea     | Patients regional lymphadenopathy | 31| 64.5 | NA | 64.5 | NA |
| 2002 | [36]       | US        | Patients | 200| 9.5 | NA | 9.5 | NA |
| 2003 | [20]       | France    | Patients pericardial effusion | 204| 0.5 | NA | 0.5 | >0.05 |
|      |            |           | Blood donors | 260| 0.0 | NA | 0.0 | NA |
| 2003 | [37]       | Sweden    | Autopsy of heroin addicts | 59| 3.4 | NA | 3.4 | NA |
|      |            |           | Forensic autopsy | 44| 0.0 | NA | 0.0 | NA |
| 2003 | [10]       | Greece    | Blood donors | 500| 15.0 | NA | 15.0 | NA |
| 2003 | [38]       | Poland    | *Bartonella* patients | 265| 1.5 | 0.4 | 1.9 | NA |
| 2004 | [39]       | Denmark   | Elite orienteers | 43| 0.0 | 0 | 0 | NA |
|      |            |           | Blood donors | 159| 0.0 | 0 | 0 | NA |
|      |            |           | Elite indoor sportsmen | 63| 0.0 | 0 | 0 | NA |
| 2004 | [40]       | Jordan    | Children patients | 482| 4.1 | NA | 4.1 | NA |
| 2005 | [8]        | Brazil    | Healthy individuals | 437| 12.8 | NA | 12.8 | NA |
| 2005 | [41]       | Algeria   | Suspected endocarditis | 61| 11.5 | NA | 11.5 | NA |
| 2005 | [42]       | France    | Blood culture-negative endocarditis | 346| 15.3 | NA | 15.3 | NA |

Contd...
of transmission among this primate. From feces of infected lice, *B. quintana* penetrates into human body through altered skin. However, other evidence revealed that cat bites or insect bites can transmit *B. quintana* to human, as known that cat is pet closing to human and insects present worldwide. Thus, various reservoirs, vectors, and transmitted ways were detected to help understand more about *B. quintana* infection, but there are still many issues that have not been clarified yet to explain how *B. quintana* exposure on over the world.

Conclusions

In the last 25 years, 46 serological investigations with 84 subpopulations on over the world indicated the re-emergence of *B. quintana* infection. Other reservoirs, vectors, and

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**Table 1: Contd...**

| Year | References | Countries     | Subpopulations                              | n   | IgG (%) | IgM (%) | Percentage | P     |
|------|------------|---------------|---------------------------------------------|-----|---------|---------|------------|-------|
| 2005 | [7]        | France        | Homeless people                             | 930 | 7.5     | NA      | 7.5        | <0.001|
|      |            |               | Blood donors                                | 467 | 0.6     | NA      | 0.6        |       |
| 2005 | [43]       | Tunisia       | Blood culture-negative endocarditis         | 40  | 30.0    | NA      | 30.0       |       |
| 2005 | [44]       | Sweden        | Blood donors                                | 498 | 0.2     | NA      | 0.2        |       |
| 2005 | [45]       | Greece        | HIV patients                                | 253 | 5.9     | 0       | 5.9        |       |
| 2006 | [18]       | Japan         | Homeless people                             | 151 | 57.0    | 0       | 57.0       | <0.05 |
|      |            |               | Blood donors                                | 200 | 50.5    | 0       | 50.5       |       |
| 2007 | [46]       | Poland        | Homeless alcoholic                          | 29  | 6.9     | 3.4     | 6.9        | NA    |
|      |            |               | Homeless intravenous drug users             | 6   | 0.0     | 0       | 0.0        |       |
|      |            |               | Blood donors                                | 50  | 0.0     | 0       | 0.0        |       |
| 2008 | [47]       | Sweden        | Homeless people                             | 48  | 4.2     | NA      | 4.2        | NA    |
|      |            |               | Blood donors                                | 61  | 1.6     | NA      | 1.6        |       |
| 2008 | [48]       | France        | Uveitis                                     | 1321| 0.5     | NA      | 0.5        | NA    |
|      |            |               | Blood donors                                | 260 | 0.0     | NA      | 0.0        |       |
| 2008 | [49]       | Spain         | HIV patients                                | 340 | 12.9    | NA      | 12.9       |       |
| 2011 | [50]       | Thailand      | Febrile patients                            | 423 | 3.3     | NA      | 3.3        | NA    |
|      |            |               | Nonfebrile patients                         | 98  | 3.1     | NA      | 3.1        |       |
| 2011 | [51]       | Congo         | Patients                                    | 155 | 0.6     | NA      | 0.6        |       |
| 2012 | [52]       | Croatia       | Lymphadenopathy patients                    | 268 | 8.6     | NA      | 8.6        |       |
| 2013 | [53]       | Poland        | Patients suggesting *Bartonella* spp. infection | 663 | 0.0     | 0       | 0.0        |       |
| 2014 | [54]       | France        | Blood donors                                | 472 | 0.0     | NA      | 0.0        |       |
| 2015 | [55]       | Brazil        | Blood donors                                | 500 | 32.0    | NA      | 32.0       |       |
| 2016 | [56]       | US            | Adults                                      | 197 | 0.0     | NA      | 0.0        |       |
| 2016 | [9]        | Austria       | Hunters                                     | 100 | 25.0    | NA      | 25.0       | >0.05 |
|      |            |               | Blood donors                                | 100 | 27.0    | NA      | 27.0       |       |
| 2017 | [57]       | Colombia      | Homeless people                             | 153 | 12.4    | NA      | 12.4       |       |
| 2017 | [58]       | Spain         | Veterinarians                               | 89  | 11.2    | NA      | 11.2       |       |
| 2019 | [21]       | Poland        | Musculoskeletal patients                    | 40  | 0.0     | 0       | 0          | >0.05 |
|      |            |               | Blood donors                                | 65  | 4.6     | 1.5     | 4.6        |       |
| 2020 | [59]       | Spain         | Sanitary workers                            | 97  | 16.5    | NA      | 16.5       |       |

NA: Not applicable

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**Figure 3:** Seroprevalence diagram of blood donors

**Figure 4:** Seroprevalence diagram of homeless people
transmission were mentioned to more understanding of this disease but not enough to explain the worldwide spread. This study showed a serological overview of a common infection that has become a considerable problem of global public health.

**Research quality and ethics statement**

The authors of this manuscript declare that this scientific work complies with reporting quality, formatting and reproducibility guidelines set forth by the EQUATOR Network (http://www.equator-network.org/).

**Acknowledgment**

We would like to thank Pr. Michel Drancourt and Dr. Gerard Aboudharam (Aix-Marseille University, France) for advices and corrections.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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