## 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).[1] 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.<sup>[1,2]</sup> 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."[3] Although trench fever often caused a prolonged disability, the death was rare.<sup>[4]</sup> Other manifestations of B. quintana infection were reported, such as chronic bacteremia, endocarditis, bacillary angiomatosis, and lymphadenopathy.<sup>[2,5]</sup> Human is the natural reservoir host, in which the bacterium persists durably in erythrocytes,

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erythroblasts with the percentage of infected cells being very low.<sup>[6]</sup> 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.<sup>[3,7]</sup> Recently, there have been some scientific reports of *B. quintana* infection with a high rate of exposure from various subpopulations.<sup>[8-10]</sup>

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,

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serologic test using immunoglobulin G (IgG) and IgM titers is the most widely used method.<sup>[2]</sup> 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 Mars 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.

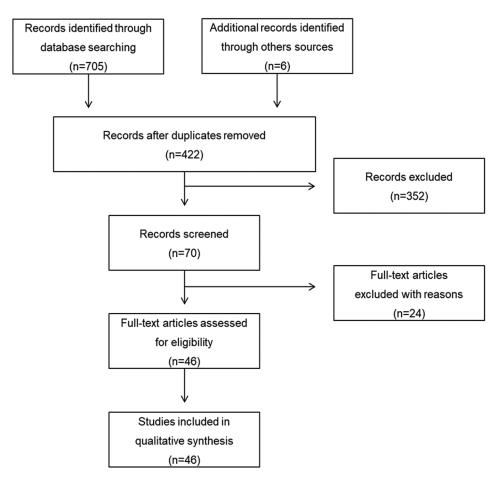


Figure 1: Flow diagram of the search strategy

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 1<sup>st</sup> 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.<sup>[11]</sup> 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.<sup>[12-14]</sup>

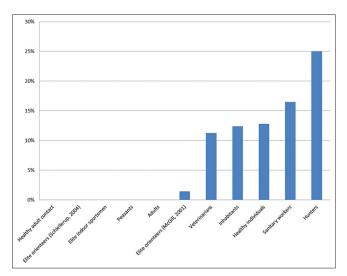


Figure 2: Seroprevalence diagram of healthy people

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.<sup>[15]</sup> While IgG reflects the evidence of past infection at an undetermined time, IgM shows the recent or current infection,<sup>[16]</sup> 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.<sup>[7,17]</sup> For homeless people, independent factors that influenced to significant serological levels were the length of homeless period with more than 1 year<sup>[18]</sup> or 3 years and the age of homeless people above 40 years,<sup>[19]</sup> alcohol abuse.<sup>[14]</sup> 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;<sup>[19]</sup> four studies had the comparison between two subpopulations but no difference of seroprevalence.<sup>[9,20-22]</sup> 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 totoal 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<sup>[23]</sup> and monkey fleas in Gabon on the other hand.<sup>[24]</sup> 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,<sup>[25]</sup> in wild Japanese macaques,<sup>[26]</sup> in rhesus macaques,<sup>[27]</sup> endocarditis in dogs.<sup>[28]</sup> Following a serological study, the positive percentage with B. quintana was 36.4% in healthy rhesus macaque.<sup>[27]</sup> 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.<sup>[29]</sup> Rhesus macaques are susceptible to B. quintana and Polyptychoides obtusus lice acted as the vector

Mai.: Seroprevalence		

Year	References	Countries	Subpopulations	п	lgG (%)	lgM (%)	Percentage	Р
996	[14]	US	Patients	192	20.3	NA	20.3	< 0.00
			Blood donors	199	2	NA	2.0	
996	[13]	US	Intravenous drug users	630	10	NA	10	
996	[12]	France	Homeless people	221	1.8	0	1.8	< 0.05
			Blood donors	250	0.0	0	0.0	
		Hospitalized homeless patients	43	16.3	2.3	16.3	< 0.01	
			Hospitalized patients	57	0	0	0	
996	[30]	France	Patients suspected cat scratch disease	64	9.4	NA	9.4	
998	[31]	Sweden	Chlamydophila pneumoniae IgG positive patients	61	0	NA	0	
998	[32]	Burundi	Sutama patients	102	12.7	NA	12.7	NA
			Febrile refugees	232	8.2	NA	8.2	
999	[4]	France	Homeless patients	71	29.6	NA	29.6	< 0.00
			Patients	31	0.0	NA	0.0	
			Blood donors	250	0.0	NA	0.0	
999	[33]	Sweden	Patients	109	2.8	NA	2.8	NA
			Blood donors	100	0.0	NA	0.0	
999	99 [16] UK	UK	Probable cat scratch disease	565	13.1	1.4	13.8	NA
			Possible cat scratch disease	48	8.3	2.1	10.4	
			Bacillary angiomatosis/peliosis	37	5.4	NA	5.4	
			Blood culture-negative endocarditis	66	15.2	7.6	16.7	
		Ophthalmic involvement	17	17.6	NA	17.6		
		"Not appropriate" patients	143	2.8	NA	2.8		
		"No details" patients	124	9.7	1.6	10.5		
		Blood donors	200	1.5	0	1.5		
			Healthy adult contact	36	0	0	0	
			Toxoplasmosis	16	0	0	0	
			Mumps virus	13	0	7.7	7.7	
			Streptococcus pyogenes serology	8	0	0	0	
			EBV	11	0	9.1	9.1	
			Chlamydia spp.	5	0	0	0	
999	[17]	Peru	Inhabitants	194	12.4	NA	12.4	< 0.05
			Peasants	84	0	NA	0.0	
001	[34]	US	Intravenous drug users	204	2.0	NA	2.0	
001	[19]	France	Homeless patients cutaneous parasitic	57	54.4	5.3	54.4	< 0.00
			Blood donors	53	1.9	0	1.9	
2001	[22]	Sweden	Elite orienteers	1136	1.4	NA	1.4	>0.05
			Blood donors	322	0.3	NA	0.3	
2002	[3]	France	Homeless blood culture positive	40	65.0	NA	65.0	< 0.05
	50 F3		Homeless blood culture negative	82	19.5	NA	19.5	
2002	[35]	Korea	Patients regional lymphadenopathy	31	64.5	NA	64.5	
.002	[36]	US	Patients	200	9.5	NA	9.5	
2003	[20]	France	Patients pericardial effusion	204	0.5	NA	0.5	>0.05
	52.53	a 1	Blood donors	260	0.0	NA	0.0	
2003	[37]	Sweden	Autopsy of heroin addicts	59	3.4	NA	3.4	NA
	51.03	~	Forensic autopsy	44	0.0	NA	0.0	
2003	[10]	Greece	Blood donors	500	15.0	0	15.0	
2003	[38]	Poland	Bartonellosis patients	265	1.5	0.4	1.9	
2004	[39]	Denmark	Elite orienteers	43	0.0	0	0	NA
			Blood donors	159	0.0	0	0	
0.0.1	E 4 6 3	<b>.</b> .	Elite indoor sportsmen	63	0.0	0	0	
004	[40]	Jordan	Children patients	482	4.1	NA	4.1	
005 005	[8]	Brazil	Healthy individuals	437	12.8	NA	12.8	
	[41]	Algeria	Suspected endocarditis	61	11.5	NA	11.5	

Contd...

Mai.: Seroprevalence of bartonella quintana infection: A systematic review

Year	References	Countries	Subpopulations	п	lgG (%)	lgM (%)	Percentage	Р
2005 [7] France	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	2007 [46] Polar	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	008 [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 applicated

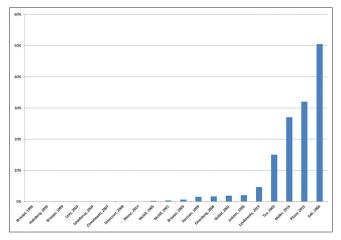


Figure 3: Seroprevalence diagram of blood donors

of transmission among this primate.<sup>[60]</sup> 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.<sup>[61,62]</sup> Thus, various reservoirs, vectors, and transmitted ways were detected

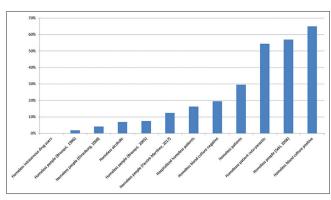


Figure 4: Seroprevalence diagram of homeless people

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

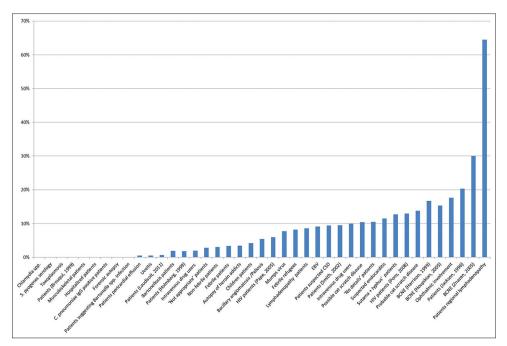


Figure 5: Seroprevalence diagram of symptoms/diseases

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/).

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#### **Conflicts of interest**

There are no conflicts of interest.

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