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Title: Urban and rural trench fever associated with culture negative endocarditis and systemic embolization in Manitoba, 2010–2020: a retrospective case series of *Bartonella* serologies

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Reviewer 1: Dr. Stanley Houston

Institution: Walter C. MacKenzie Centre

General comments (author response in bold)

I applaud the authors' efforts to take a more systematic look at this under studied disease and raise awareness around it.

Thank you for your interest and your support. As you are well aware, it is a difficult disease to study as Bartonella species are not identified on routine culture and B. quintana exclusively affects populations with substantial barriers to medical care.

The authors could express more strongly, the shamefully extreme degree of disadvantage required to enable susceptibility to body louse infection. While the solution would ideally involve a broader response to social determinants of health, relatively simple interventions to enable safe access to a shower and clothes washing could be implemented immediately.

Thank you very much for this comment. We agree that B. quintana acts as an “indicator species” of extreme conditions of poverty that are preventable. Please see our addition on page 13 (lines 476-478). We have also addressed the importance of simple interventions to interrupt transmission (accessible washing facilities) on page 15 (lines 552-553).

In the introduction, it might be helpful to readers to mention that “habitat” of the body louse is clothing, not skin or hair.

Thank you. This has been done (see page 5, lines 99-101).

The authors might comment on whether limiting clinical information to charts from 2 hospitals might limit information available on non-endocarditis patients.

Thank you. We have included this in our limitations (please see page 16, lines 422-435).

It is important that criteria used in interpretation of serology titers be clarified, for example when titers were positive for both species, how was that handled and based on what evidence/recommendations? I was unable to find criteria for diagnosis of Bartonella, cat scratch disease or trench fever in the 1997 CDC reference listed.

Thank you. Bartonella serology is cross-reactive between both species (please see page 7, lines 181-183). Positivity for both species is the rule, not the exception. Since speciation is impossible based on serology alone, the use of epidemiologic exposure indicates species, in the absence of tissue for molecular diagnostics (please see page 8). Exposure to cats indicates B. henselae. Strong serologic positivity with homelessness and no cat exposure indicates B. quintana (please see page 8). Until a third species of Bartonella has a confirmed human infection in Canada, these are the only 2 options.

The CDC reference provides guidance on case definitions for infectious diseases (confirmed, probable...). We have extrapolated from these definitions and have changed the wording to clarify this (please see page 8). As Bartonellosis is generally neglected and not reportable, there is a lack of existing guidelines. Thank you.

p. 14. 11 quintana, 4 henselae/16 total. The authors should say something about the speciation of the one missing organism.

Thank you. One low-titer Bartonella serology without a clear epidemiologic exposure and without a common clinical syndrome was deemed to be a false positive (patient 8 in tables 2 and 3). His B. henselae titer was at the cut-off of positivity (1:256) and his B. quintana was negative. He did not have a syndrome indicative of Bartonella infection and improved without anti-Bartonella therapy. We have clarified this issue. Please see page 3 (abstract) and page 10 (lines 292-294).

Lines 160 and 169: 24 positive serologies, then 16 patients. Needs clarification of what happened to the other 8 results

Thank you. Table 1 indicates aggregate data of both adults and pediatric patients. However, chart review only occurred on adult patients. Thus, 8 (24-16=8) pediatric cases with positive Bartonella serologies were excluded. We have clarified this throughout the text (eg: page 9, lines 262-264).

Line 173: specify that the characteristics of endocarditis were limited to B. quintana cases, not the 2 B. henselae cases.

Thank you. This has been done.

***P. 33 (? Table 2) As currently structured, the tables are extraordinarily difficult to read. At the very least, each of the 4 tables containing patient information needs to have the patient number attached. Ideally, this should all be in 1 table, but that might require limiting the information provided or might not be logistically feasible.

Thank you. We agree. It was impossible to include all information in one table. At the request of other reviewers/editorial staff, we have divided the table into 2 separate ones, and kept the same patient number.

Reviewer 2: Dr. Kevin Fonseca

Institution: Alberta Health Services Board

General comments (author response in bold)

This manuscript catalogues cases of Bartonella infections over a 10 yr period in MB, focusing on those caused by B. quintana. As serology is used as the primary identifier, these cases likely represent a fraction of the total, in part because this infection was not suspected, or testing not performed or possibly the titre was not high enough at the time of testing to flag it as a case?

Thank you. Yes, this is correct. This is an under-estimate of total Bartonella infections in Manitoba due to the issues you've raised (this is addressed in the last paragraph of the interpretation, page 16).

A point for the authors to comment upon is 1> is or are there titre(s) at or above which a B. quintana infection is more likely, 2> in the course of infection how soon do these antibody titres appear and are they sustained for long periods after treatment?

Thank you. As described in table 3 (new table), titer magnitude is linked to severity of disease/clinical manifestation with higher titers associated with endocarditis (titers above 1000 and often 4000 or upper limit of detection at 8000). Cat scratch disease seems to be associated with mid-level titers (500-1000) and ectoparasitosis-linked exposure and mild trench fever seems to be associated with low level titers (256-565). This is described on page 11 (link between elevated titer and endocarditis).

Since serial Bartonella serologies were rarely ordered and not included here, we cannot comment on the chronology of antibody appearance and decline. In our anecdotal experience of treating individuals with Bartonella endocarditis, the titers decline slowly over many months. Thank you.

In Table 1, the numbers of samples/cases tested in 2020 is markedly upwards compared with 2019, but somewhat comparable to 2018 (140 samples) – any reason(s) for this increase?

Thank you. We do not know why the test volume was increased in 2018 and 2020. The publicity of our B. quintana case series occurred in Dec, 2020 and thus would not explain these increases.

Table 2 documents 16 cases although in Results pg 9 line 160 there are 24 positive cases – no explanation given for the difference.

Thank you. Please see comments above. 24 cases included both adults and peds. 8 pediatric cases were excluded as we did not have REB for peds.

Table 2 – case 8 was considered to be a false positive, so I am assuming it should be may be in Table 3?

What about case 10 which has a titre of 256 to B. henselae but negative to B. quintana – could that be a false-pos analogous to case 8?

Thank you. We have removed table 3 (equivocal case) but have explained that we counted patient 8 as a false positive (no clinical syndrome, no epi exposure). Patient 10 had a diagnosis of culture-negative endocarditis and cat exposure, and thus we did not count this patient as a false positive as it is possible that it was simply waning titers. Please see page 8 (line 323-324).

In Table 3, which I assume are the equivocal cases, there are 38 persons listed but 94 cases in the statement in the Results section pg 9, line 161 – no explanation given?

Thank you. We have removed the table of equivocals (previously table 3) as it is not clearly of clinical significance.

In Table 3, cases 4, 17, 23 & 25 – comments are made in the interpretation “possible cross reaction – syphilis”. These two agents are not closely related taxonomically & serologically, so is the assumption of a possible cross reaction based upon the clinical presentation “visual changes” & findings of a high RPR titre, not given in the Table ? There are a number of other cases with “visual changes” such as cases 18, 19 & 20, but are classified as unclear in the interpretation?

Thank you. We have removed the table of equivocals (previously table 3) as it is not clearly of clinical significance. We agree that it is unclear about cross-reaction with syphilis, however in the equivocals, there were many ocular syphilis cases with low-grade Bartonella seropositivity. We have deleted this table.

Table 3, case 23, “syphilis” listed as antimicrobial therapy – I would hope this is an error and not a new radical alternative treatment instead of tried and tested antibiotics ??

Thank you. We have removed the table of equivocals (previously table 3) as it is not clearly of clinical significance. This was an error. Thank you.

As I read the Conclusion I get the impression that B.quintana infections are solely attributable to a lack of suitable housing which is just one part of the larger problem of being disadvantaged. Other contributing factors are attention to personal hygiene, access to clean clothing and laundry, overcrowding and lack of supportive care for substance abuse and personal issues. Societal and medical factors are also significant contributors to the lifestyle of these disadvantaged persons.

Thank you. You are correct. We have included a description of the importance of accessible washing and laundry facilities as a quick way to interrupt B. quintana transmission (page 15, lines 453-455).