

REVIEW

REVISED Epidemiology of zoonotic tick-borne diseases in Latin America: Are we just seeing the tip of the iceberg? [version 2; peer review: 2 approved, 1 not approved]

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Abstract

Ticks are responsible for transmission of multiple bacterial, parasitic and viral diseases. Tick-borne diseases (TBDs) occur particularly in tropical and also subtropical areas. The frequency of these TBDs has been increasing and extending to new territories in a significant way, partly since ticks' populations are highly favored by prevailing factors such as change in land use patterns, and climate change. Therefore, in order to obtain accurate estimates of mortality, premature mortality, and disability associated about TBDs, more molecular and epidemiological studies in different regions of the world, including Latin America, are required. In the case of this region, there is still a limited number of published studies. In addition, there is recently the emergence and discovering of pathogens not reported previously in this region but present in other areas of the world. In this article we discuss some studies and implications about TBDs in Latin America, most of them, zoonotic and with evolving taxonomical issues.

Keywords

Tick-borne disease, zoonoses, Anaplasma, Babesia, Borrelia, Ehrlichia, Rickettsia, epidemiology, public health

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This article is included in the Disease Outbreaks gateway.

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Any reports and responses or comments on the article can be found at the end of the article.

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REVISED Amendments from Version 1

This new version considered interesting comments of the reviewers regard the taxonomy, the species, particularly focusing more on the situation in Latin America, improving the table, as well as adding news references to the article. Also was edited and improved in terms of writing with the help of the software Grammarly.

In this version, Álvaro A. Faccini-Martínez contributed and participated actively and so they have been added as an author.

See referee reports

Over the past decades, there have been significant achievements in the understanding of tick-borne diseases (TBDs), which are mostly zoonoses and classed as neglected diseases¹⁻⁵. Their occurrence is significant in tropical and subtropical areas, leading to an important impact on public health as well as the economy, as they affect humans, domestic animals, and livestock, among others⁶. Knowledge of the occurrence of these diseases in animal species is of utmost importance for the understanding of the risk for human infection⁷. Ticks, and animals, including human beings, interact with nature, and their environmental and ecological interactions regulate the populations of ticks and vertebrates, determining their contact rates and the circulation of the diseases8. Regarding TBDs that affect humans, those that are caused by Rickettsia genera, known as spotted fever group rickettsioses, are the most studied and recognized in Latin America. Nevertheless, case reports and preliminary field studies published in the last two decades, suggest that ehrlichiosis, anaplasmosis, babesiosis and relapsing fever group borreliosis, would also be present but probably are underdiagnosed.

After the first description of Rickettsia rickettsii in North America in the first half of the twentieth century, this species also was recognized as a human pathogen in Latin America9. Currently, R. rickettsii rickettsiosis is the most important and deadly TBDs in México, Panamá, Colombia, Brazil, and Argentina, where is transmitted to humans by different ticks' species as Rhipicephalus sanguineus, Amblyomma mixtum, A. patinoi, A. sculptum, A. aureolatum, and A. tonelliae^{9,10}. Unfortunately, only in Brazil, this disease is of officially mandatory reporting⁹. Moreover, in the last years, other rickettsiae have been pointed as emerging pathogenic species, causing febrile rickettsiosis (R. parkeri and R. massiliae) or asymptomatic/mild illness (R. amblyommatis)^{9,10}. Currently, R. parkeri, transmitted by A. ovale, A. tigrinum, and A. triste, is the main agent relate to eschar-associated rickettsiosis in Brazil, Argentina and Uruguay^{11–13}. Clinically is less severe compared to R. rickettsii rickettsiosis, and no related deaths have been reported¹¹⁻¹³.

On the other hand, although *Amblyomma americanum* and *Ixodes scapularis* ticks, which are recognized as main vectors of human pathogenic *Ehrlichia* and *Anaplasma* species in the United States, are not presented in Latin America¹⁴, some confirmed *E. chaffeensis* infections have been reported in patients from Venezuela and Mexico^{15,16}. The above suggests that probably

other ticks' species could be competent vectors in tropical regions. Thus, is worth to mention the recent descriptions of *Ehrlichia* spp. detected in anthropophilic ticks (*A. tigrinum* and *A. parvum*) in Argentina^{17,18}. Furthermore, particularly in Venezuela, few studies point *Anaplasma platys* and *E. canis* as a human pathogen^{19,20}, a concern that actually discusses, but contrast with the recent description of a novel genotype of *E. canis* detected in samples of human blood bank donors in Costa Rica²¹. The significance of the above requires future investigations.

Babesiosis is another tick-borne disease, caused by protozoal hemoparasites of the phylum Apicomplexa. Presently, three species of the genus *Babesia* (*B. microti*, *B. divergens* and *B. venatorum*) are the main human pathogens in The United States, Europe, and Asia, where anthropophilic ticks of the *Ixodes ricinus* complex (*I. scapularis*, *I. ricinus*, and *I. persulcatus*) are the main vectors²². In Latin America, these tick's species are not present, and even though exist some species of the *I. ricinus* complex, they do not human-biting¹⁴. Nevertheless, interestingly, some confirmed *B. microti* infection has been reported in Mexico and Bolivia^{23,24}, and also in the latter and in Colombia serological studies suggest exposure to *Babesia* spp. in rural individuals^{23,25}. Acarological studies attempting to detect *Babesia* species in anthropophilic Latin American ticks are scarce.

Additionally, as occurs with Babesiosis, human-biting I. ricinus complex ticks are also vectors of pathogenic-Borrelia burgdorferi sensu lato (s.l.) species (B. burgdorferi sensu stricto, B. mayonii, B. garinii, B. afzelii), causing Lyme borreliosis in temperate regions of northern hemisphere²⁶. In Latin America, in the last decade, new B. burgdorferi s.l. strains or new related species have been described in countries such as Argentina, Uruguay, Brazil, and Chile, from non-anthropophilic Ixodes tick27. This fact, as well as that B. burgdorferi, has not yet been isolated or cultured from clinical samples from autochthonous patients, is against of Lyme borreliosis presence in Southern hemisphere of America. By contrast, considering the recently first isolation and molecular characterization of a relapsing fever *Borrelia* (B. venezuelensis) in Latin America, recovered from an Ornithodoros rudis tick28, is plausible the occurrence of underdiagnosed human cases, taking to account the historical records of tick-borne relapsing fever in Colombia, Venezuela and Panama²⁹.

Beyond the Americas, in other regions of the world, like in Europe, ticks are the main vectors of animal and human organisms. Ticks transmit several viral agents, called tick-borne viruses (TBV), such as tick-borne encephalitis virus and Crimean-Congo hemorrhagic fever virus, which have reemerged in multiple areas of the world³⁰. TBV have a natural cycle between ticks and wild animals in nature, with humans as accidental hosts^{30,31}. Emerging TBVs are continually discovered, probably related to the increase of tick populations in different regions of the planet and invasion of human beings into areas infested by ticks^{30,31}. The study of tick-borne viruses in Latin America is scarce. Recently Brazilian authors described a genetic characterization of Cacipacoré virus (genus Flavivirus) from *A. cajennense* ticks collected in São Paulo State, Brazil³². The significance of this finding requires future investigations.

Table 1. Examples of selected tick-borne diseases in Latin America.

Disease	Etiological agent(s)	Primary or probable vector(s)
Rickettsia rickettsii rickettsiosis	Rickettsia rickettsii	Rhipicephalus sanguineus, Amblyomma mixtum, A. patinoi, A. sculptum, A. aureolatum, A. tonelliae
Rickettsia parkeri rickettsiosis	Rickettsia parkeri	A. ovale, A. maculatum, A. tigrinum, A. aureolatum, A. triste
Rickettsia massiliae rickettsiosis	Rickettsia massiliae	Rhipicephalus sanguineus
Ehrlichiosis?	Ehrlichia sp. strain San Luis and strain Cordoba	A. tigrinum, A. parvum
Tick-borne relapsing fever	Borrelia venezuelensis	Ornithodoros rudis

Detection and sentinel surveillance of TBDs require molecular tools for diagnosis³³, for example, serological tests have proven to be inconclusive in diagnose Lyme disease³⁴. The use of molecular biology tests in recent years has increased the sensitivity and specificity of the diagnosis of infections caused by Rickettsiales. Molecular diagnosis enables the accurate identification not only at the genus level but species, providing additional characterization on the epidemiology and the evolution of the clinical disease. Furthermore, PCR, as well as enzyme restriction tests of the vector blood meal, can be employed to analyze their feeding source and possibly identify the ecological reservoir of the organisms³⁵.

Conclusions

Besides the number of studies in Latin America on TBDs, the prevalence of these diseases is increasing, triggered by globalization, as well the impact climate change and variability. More surveillance, more diagnostics, with better identification approaches, as well as more research, is needed. Even more, in that way, there is a lack of infrastructure and/or funding to support continued vector surveillance studies in many countries across the region. Tick and TBDs investigators, veterinary doctors, medical and public health practitioners should work to share their expertise on different aspects of TBDs, such as tick ecology, disease transmission, diagnostics, and treatment, in order to face the challenges of scientific, political, and public engagement for

TBD research and control in this region³⁶. Systematic reviews, as well as observational analyses, are necessary in order to understand the current situation of TBDs. In fact, also there is a lack of studies of costs and burden of these diseases, as is clearly available for other vector-borne diseases (e.g. arboviral)³⁷. As is known, also there are clear limitations in the national budgets that are specifically earmarked for vector-borne surveillance and public health efforts. Even more, what part of that is allotted toward TBD research. This should be considered as part of this call to action. For diagnostics, molecular tools can provide valuable information for understanding the evolution of their etiological agents, as well as provide insights into hostpathogen-vector-environment interactions but need to be more widely available as part of routine diagnostics. Probably, what we have seen till now in terms of prevalence, but also in terms of action to reduce the impact of TBD, is just the tip of an iceberg and there is a need for more studies and actions towards control in Latin America about these diseases.

Data availability

No data is associated with this article.

Grant information

The author(s) declared that no grants were involved in supporting this work

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Version 2

Reviewer Report 19 August 2019

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Stefan Vilges de Oliveira (1)



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I would like to highlight some points that could be improved:

The title of the manuscript creates an expectation that is not answered. In the manuscript is finished stating that further studies could help answer this question. Methodologically this is not correct. Suggestion to change the title to: Epidemiology of zoonotic tick-borne diseases in Latin América.

The authors mention that Brazil is the only country in Latin America that TBDs are mandatory reporting. In Brazil Spotted Fever is diseases the mandatory notification. Authors need to provide the correct source of information. They should mention the ordinance that regulates the notification in Brazil and that is available at this Link.

About the title question: Are we just seeing the tip of the iceberg?

Even in Brazil with the best data compared to other Latin American countries it was still not possible to answer this question.

In order to measure these subrecords, it would be advisable to evaluate different sources of information through retrospective studies that include information on patients with clinical suspicions with differential diagnoses for TBDs.

In Brazil different information systems are used for different functionalities. There is a system that records the notification diseases (Notification Disease Information System), another records the deaths (Mortality Information System), another the laboratory diagnosis requests (Laboratory Environment Manager). To evaluate subrecords it would be interesting to crosscheck data that takes into account the information from the different information systems. Ideally a system of clinical suspicion and laboratory investigation based on a syndromic diagnosis would be the most effective for detecting TBDs cases.

Finally, the updated review highlights very important points, such as the lack of information, the need to assess the burden and impact of TBDs and the advances made so far and the challenges, especially in diagnosis, clinical and laboratory. Therefore, I consider this article appropriate for indexing.



Is the topic of the review discussed comprehensively in the context of the current literature? Yes

Are all factual statements correct and adequately supported by citations?

Yes

Is the review written in accessible language?

Yes

Are the conclusions drawn appropriate in the context of the current research literature? Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology and Public Health

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 04 March 2019

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Joyce M Sakamoto

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This second version of the manuscript entitled "Epidemiology of zoonotic tick-borne diseases in Latin America: Are we just seeing the tip of the iceberg?" has undergone edits, the inclusion of more references, and the addition of an author. I have chosen "Approved" because, although there are some minor comments that should be addressed, there is no "minor revision" option available.

Many of the edits that the authors have included have improved readability and flow. However, there are some points that need clarification. Most of these are grammatical/typographical errors, but a few have to do with structural organization of sentences or lack of citations. I would like to point out that, while it is commendable that the authors utilized a tool like Grammarly, the general (i.e. non-academic) version of Grammarly does not work as well for scientific terminology or syntax:

Paragraph 1: "Regarding TBDs that affect humans, those that are caused by *Rickettsia* genera, known as spotted fever group rickettsioses, are the most studied and recognized in Latin America."

1) The wording is a little confusing because of the structure. Start with "The most important tick-borne diseases in Latin America are caused by pathogen spotted fever group *Rickettsia*."



2) Replace "genera". It should be "Multiple species in the genus *Rickettsia*" or "*Rickettsia*" or "

Paragraph 2: "Currently, *R. rickettsii* rickettsiosis is the most important and deadly TBDs in México, Panamá, Colombia, Brazil, and Argentina, where is transmitted to humans by different ticks' species as *Rhipicephalus sanguineus*, *Amblyomma mixtum*, *A. patinoi*, *A. sculptum*, *A. aureolatum*, and *A. tonelliae*"

- 1) Change "where". It should be "which".
- 2) Change "ticks' species as" to "tick species such as".
- 3) Use "Rocky Mountain Spotted Fever" to describe the disease caused by *R. rickettsii. e.g.* "Currently, Rocky Mountain Spotted fever (*R. rickettsii*) is the most important and deadly TBD..."

Paragraph 3: "Furthermore, particularly in Venezuela, few studies point *Anaplasma platys* and *E. canis* as a human pathogen, a concern that actually discusses, but contrast with the recent description of a novel genotype of *E. canis* detected in samples of human blood bank donors in Costa Rica"

- 1) I am not sure I understand the point of this sentence. Grammatically, it seems like you are missing some words in this part of the sentence: "...few studies point *Anaplasma platys* and *E. canis* as a human pathogen..." should be changed to:
- "...studies point to Anaplasma platys and E. canis as human pathogens..."?
- 2) The *E. canis* genotype paper does not "contrast" with the human blood bank donor study. Blood tested from two case studies is a pretty low sample size (N = 2) to make any conclusion. Maybe just stop after " *E. canis* as human pathogens"

Paragraph 5: "This fact, as well as that *B. burgdorferi*, has not yet been isolated or cultured from clinical samples from autochthonous patients, is against of Lyme borreliosis presence in Southern hemisphere of America. "

The structural organization of this sentence is confusing. Maybe: "Because *B. burgdorferi* s.l. has not been isolated or cultured from...It is not thought to be present in..."

Paragraph 5: "By contrast, considering the recently first isolation and molecular characterization of a relapsing fever *Borrelia* (*B. venezuelensis*) in Latin America, recovered from an *Ornithodoros rudis* tick, is plausible the occurrence of underdiagnosed human cases, taking to account the historical records of tick-borne relapsing fever in Colombia, Venezuela and Panama."

Organize this sentence differently. Break this sentence into two, e.g.: "In contrast, tick-borne relapsing fevers have historically occurred in Colombia, Venezuela, and Panama. Recently, the relapsing fever pathogen *Borrelia venezuelensis* has been isolated and molecularly characterized from the soft tick *Ornithodoros rudis*."

Paragraph 7: "Detection and sentinel surveillance of TBDs require molecular tools for diagnosis, for example, serological tests have proven to be inconclusive in diagnose Lyme disease"

There are a couple of things wrong with this sentence.

- 1) "diagnose" should be "diagnosis of" or "diagnostics of"
- 2) I am not sure serological tests are inconclusive, although there are problems with cross-reactivity or poor sensitivity during early Lyme disease onset¹.



Paragraph 7 "... at the genus level but species,

• Change to: "to the species level"

Conclusion: "As is known, also there are clear limitations in the national budgets that are specifically earmarked for vector-borne surveillance and public health efforts. Even more, what part of that is allotted toward TBD research. This should be considered as part of this call to action."

The point of your piece is that there is a growing tick-borne disease problem that needs to be and is currently not addressed. "As is known" is referring to anecdotal information. Please find a reference to support this claim that national budgets are not providing enough funds for vector-borne surveillance and compare (or contrast) this with what you think it should be (probably the Colombian National Public Health Institutions will have information on this).

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Is the topic of the review discussed comprehensively in the context of the current literature? Yes

Are all factual statements correct and adequately supported by citations? Yes

Is the review written in accessible language?

Yes

Are the conclusions drawn appropriate in the context of the current research literature? Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Ticks and microbiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 30 January 2019

https://doi.org/10.5256/f1000research.19300.r42313

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Joyce M Sakamoto

Department of Entomology, The Pennsylvania State University, University Park, PA, USA

This manuscript entitled "Epidemiology of zoonotic tick-borne diseases in Latin America: Are we just seeing the tip of the iceberg?" suggests that more studies on TTBD (ticks and tick-borne diseases) are needed worldwide, and particularly in Latin America, but there is a dearth of available data published.

Because the authors emphasized that their manuscript was not intended to be an extensive review article, but was originally presented as an opinion piece, I reviewed this manuscript as the latter. There is a lack of cohesiveness and transition between subjects within the manuscript and an overall lack of a common theme. There are also some minor errors in terminology and italicization throughout, which I will point out in each paragraph. In summary, while I appreciate the fact that this paper was originally intended to be a superficial review intended to emphasize the lack of research literature on ticks and TBD in Latin America, it does not do so in a cohesive manner, nor does it make a clear case for the need for further resources. Nevertheless, many Latin American countries would benefit from more resources dedicated to TBD research and surveillance. Should the authors reorganize and focus their attention to a specific objective, this might make for a stronger case.

Specific Comments:

The 1st paragraph gives a brief introduction to the impacts of TTBD on human and animal health, particularly in tropical and subtropical areas of the world. While it is interesting to point out that some TBD can be transmitted in other ways besides via ticks, I'm not sure that really supports the point of your manuscript. Make sure to be consistent in whether you use "tick-borne" or "tick borne" throughout the manuscript.

The 2nd paragraph begins with an introduction to Latin America, but then goes directly into rickettsioses, followed by a paragraph each on ehrlichioses, babesioses, and a brief mention of borrelioses. This feels much like a listing of diseases that have no connectivity with the overall purpose of the article. To help this, a sentence or two to introduce what will be discussed in the coming paragraphs might help to outline what a reader might expect to see. Maybe something like..."Here we will briefly review the known literature and highlight the increasing incidence/discovery/etc of tick-borne pathogens..."

- There seems to be a missing word in "Rickettsia rickettsii were reported in rural and urban of Panama"
- "Until some years ago, R. rickettsia was the only tick-borne species of rickettsia present in Latin America. Nowadays" - 'Nowadays' is too colloquial. Perhaps "Presently" or "Currently" are better alternatives?
- There is what looks like an autocorrect error ("R. rickettsia" should be "R. rickettsii").
- Question: Is it possible that other *Rickettsia* spp. were present already, but the older serological diagnostics that identified RMSF (*R. rickettsii*) were cross-reacting with them and were all recorded as RMSF?
- Many Rickettsia spp. are non-pathogenic and are instead obligate symbionts of the ticks in which they reside.

3rd paragraph: "specie" should be "species". The genus "Ehrlichia" should be italicized.

4th paragraph: I refer you to "Rickettsia species". *Rickettsia* capitalized refers to the genus and it should be italicized. If referring to the colloquial term used to refer to Rickettsiales, then it should be lowercase and not italicized (rickettsias). I believe the former applies in this sentence. "sp." indicates that the species designation is not known and is not italicized.



5th paragraph:

- "Till" should be "Until".
- The paragraph is almost entirely about babesioses worldwide, yet the last sentence briefly mentions *Borrelia* and does not flow at all. Borreliosis should be its own section, with a discussion on both Lyme borreliosis and relapsing fever variants. Perhaps the authors could mention the role that soft ticks play in relapsing fever, particularly since this is a problem in Latin America.

6th paragraph:

- If the purpose of this paper is to focus on Latin America and the paucity of work on ticks and tickborne disease relative to other parts of the world, there should be more focus on Latin America. The discussion of other countries detracts from this message. The only exception is in the context of potential TTBD flow between these countries via trade, human or animal migration, and impacts of climate change.
- Further, there is a sudden switch mid-paragraph to tickborne viruses (TBV). Is the purpose of mentioning TBV to say that TBV exist in Latin America, but no one has looked hard enough? There are a few review articles that may provide support for this, but I suggest that as it is here, there is no context and it feels like it was just added after-the-fact.
- Replace "vectorized" with "transmitted". Note "Transmit" = verb, "vector" = noun. "Vectorized" isn't really a word, or at least not commonly used North American medical entomology.

7th paragraph: I'm unclear on the purpose of this paragraph. Is it to highlight the advances in diagnostics that make it possible to detect TBD? If so, how does this support the overall theme of this article?

- The last sentence of the 7th paragraph is not clear and has several errors. "Etiological agents of the group of **Rickettsia**, including those in the **genuses** *Anaplasma*, *Neorickettsia*, *Ehrlichia*, and *Rickettsia*, are relevant and often vector-borne organisms of canines and felines, but also of bovine, live-stock and other animals, which appears to be a wide range of hosts". Could this be moved somewhere else to make a transition or taken out completely?
- "group of "Rickettsial" should be either "rickettsial pathogens in the..." OR "Etiological agents in the Order Rickettsiales"
- "live-stock" should be "livestock"
- "Genuses" should be "genera"
- The Order Rickettsiales is an Order and not italicized. Admittedly this order's taxonomy is problematic, but if you are going to refer to it, don't italicize it.

Table 1:

- Your table is entitled "Examples of selected tick-borne diseases in Latin America," yet contains tick species mostly localized to North America (*D. andersoni*, *D. variabilis*, *D. occidentalis*, *I. pacificus*, and *I. scapularis*). There was a review by Esteve-Gassent et al (2014)¹ that suggests that some of these species could potentially spill over the Mexico-USA border and therefore these species could potentially warrant further study. Your use of this table, however, does not provide any context and feels out-of-place and irrelevant.
- There have been several articles detailing known hard and soft tick species and their epidemiological significance from many different Latin American countries (e.g. Rivera-Páez in 2018 gives updates to Colombian Ixodidae²; Mastropaolo 2014 reviewed both hard and soft ticks of Bolivia³; Lopes in 2016 of Belize⁴, and Witter in 2016 from wild animals of Brazil⁵, just to name a few). There have also been reviews on tick species found in the Caribbean, Cuba, and Mexico. If you can obtain it, a valuable and comprehensive resource is "The Hard Ticks of the World (Acari: Ixodida: Ixodidae)", by Guglielmone et al (2014)⁶, which contains summaries of all known hard tick species worldwide, including host associations and geographic distributions.

Conclusion: I am afraid I don't see the relevance of this conclusion section to the rest of the article. What you need is to tie together what you have written and make a conclusion.



- What is your conclusion? Do we need more surveillance? More research? Better diagnostics? Better identification approaches?
- What are you trying to state that leads to your final concluding statement that this is "just the tip of the iceberg"? To say there is not enough data is sort of vague. More data is always better, but I myself have at least 100 references for literature on TTBD from Central and South America, and my list is not extensive. I would posit that you may need to rethink the purpose of your article. To state that there insufficient work on this topic in Latin America borders on insulting those who have spent careers working on these exact topics.
- There is an element that you have not discussed: the lack of infrastructure and/or funding to support continued vector surveillance studies. Are there reports comparing the estimated costs of these types of studies (surveillance as well as diagnostics)? If so, how does that compare to the estimated proportion of the national budgets that are specifically earmarked for vector-borne surveillance and public health efforts, and what part of that is allotted toward TTBD research? Perhaps this would strengthen your case for a call to action.

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Is the topic of the review discussed comprehensively in the context of the current literature? No

Are all factual statements correct and adequately supported by citations?

Is the review written in accessible language?

Yes

Are the conclusions drawn appropriate in the context of the current research literature? Partly

Competing Interests: No competing interests were disclosed.



Reviewer Expertise: Ticks and microbiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 04 Feb 2019

Alfonso Rodriguez-Morales, Universidad Franz Tamayo/UNIFRANZ, Cochabamba, Bolivia

Dear Dr. Sakamoto

Thanks for your valuable comments. We want to answer all your comments, as we improved significantly our manuscript based on yours as well as on the other reviewer.

This manuscript entitled "Epidemiology of zoonotic tick-borne diseases in Latin America: Are we just seeing the tip of the iceberg?" suggests that more studies on TTBD (ticks and tick-borne diseases) are needed worldwide, and particularly in Latin America, but there is a dearth of available data published.

Certainly, there are more available data published, but our original intention was present an Opinion Article. As an Advisor of this Gateway, called, Disease Outbreaks, I should explain to you that at this open publishing platform where there are Opinion Articles, Review Articles and Systematic Review Articles.

This article is NOT a Systematic Review, it was originally submitted as an Opinion Article, as an invitation from F1000Research as being F1000Research Disease Outbreaks Gateway Advisor, but later classified as Review (narrative review). As you well read, we only referred to some examples of studies in Latin America, including yours (cited, now 36. Sakamoto JM: Progress, challenges, and the role of public engagement to improve tick-borne disease literacy. Curr Opin Insect Sci. 2018;28:81–9. 30551772 10.1016/j.cois.2018.05.011), about tick-borne diseases, that illustrate the problem, in terms of a neglected group of conditions in the region, wherein most of the countries are not under surveillance, and there is still a lack of studies, but even more actions for effective control.

Because the authors emphasized that their manuscript was not intended to be an extensive review article, but was originally presented as an opinion piece, I reviewed this manuscript as the latter. There is a lack of cohesiveness and transition between subjects within the manuscript and an overall lack of a common theme. There are also some minor errors in terminology and italicization throughout, which I will point out in each paragraph. In summary, while I appreciate the fact that this paper was originally intended to be a superficial review intended to emphasize the lack of research literature on ticks and TBD in Latin America, it does not do so in a cohesive manner, nor does it make a clear case for the need for further resources. Nevertheless, many Latin American countries would benefit from more resources dedicated to TBD research and surveillance. Should the authors reorganize and focus their attention to a specific objective, this might make for a stronger case.

We have significantly improved the grammatical and orthography of this paper. We modified the



paper considering your comments.

Specific Comments:

The 1st paragraph gives a brief introduction to the impacts of TTBD on human and animal health, particularly in tropical and subtropical areas of the world. While it is interesting to point out that some TBD can be transmitted in other ways besides via ticks, I'm not sure that really supports the point of your manuscript. Make sure to be consistent in whether you use "tick-borne" or "tick borne" throughout the manuscript.

Well, that's a comment, additionally to the main point of this article. Regard your comment of consistency in the use of tick-borne, we have checked and only left "tick-borne".

The 2nd paragraph begins with an introduction to Latin America but then goes directly into rickettsioses, followed by a paragraph each on ehrlichioses, babesioses, and a brief mention of borrelioses. This feels much like a listing of diseases that have no connectivity with the overall purpose of the article. To help this, a sentence or two to introduce what will be discussed in the coming paragraphs might help to outline what a reader might expect to see. Maybe something like..."Here we will briefly review the known literature and highlight the increasing incidence/discovery/etc of tick-borne pathogens..."

We have restructured the paragraph in that way.

- There seems to be a missing word in "Rickettsia rickettsii were reported in rural and urban of Panama". Corrected.
- "Until some years ago, R. rickettsia was the only tick-borne species of rickettsia present in Latin America. Nowadays" - 'Nowadays' is too colloquial. Perhaps "Presently" or "Currently" are better alternatives? Corrected.
- There is what looks like an autocorrect error ("R. rickettsia" should be "R. rickettsii"). Corrected.
- Question: Is it possible that other Rickettsia spp. were present already, but the older serological diagnostics that identified RMSF (R. rickettsii) were cross-reacting with them and were all recorded as RMSF? Included.
- Many Rickettsia spp. are non-pathogenic and are instead obligate symbionts of the ticks in which they reside. Considered.

3rd paragraph: "specie" should be "species". The genus "Ehrlichia" should be italicized.

Done. All that should be italicized, has been done.

4th paragraph: I refer you to "Rickettsia species". *Rickettsia* capitalized refers to the genus and it should be italicized. If referring to the colloquial term used to refer to Rickettsiales, then it should be lowercase and not italicized (rickettsias). I believe the former applies in this sentence. "sp." indicates that the species designation is not known and is not italicized.

Done. Capitalized where corresponded.

5th paragraph:



- "Till" should be "Until". Ok.
- The paragraph is almost entirely about babesioses worldwide, yet the last sentence briefly mentions Borrelia and does not flow at all. Borreliosis should be its own section, with a discussion on both Lyme borreliosis and relapsing fever variants. Perhaps the authors could mention the role that soft ticks play in relapsing fever, particularly since this is a problem in Latin America. This has been modified. We discussed also relapsing fever.

6th paragraph:

- If the purpose of this paper is to focus on Latin America and the paucity of work on ticks and tickborne disease relative to other parts of the world, there should be more focus on Latin America. The discussion of other countries detracts from this message. The only exception is in the context of potential TTBD flow between these countries via trade, human or animal migration, and impacts of climate change. We have improved this aspect and more focused on Latin America.
- Further, there is a sudden switch mid-paragraph to tickborne viruses (TBV). Is the purpose of mentioning TBV to say that TBV exist in Latin America, but no one has looked hard enough? There are a few review articles that may provide support for this, but I suggest that as it is here, there is no context and it feels like it was just added after-the-fact. We have corrected this.
- Replace "vectorized" with "transmitted". Note "Transmit" = verb, "vector" = noun. "Vectorized" isn't really a word, or at least not commonly used North American medical entomology. Corrected.

7th paragraph: I'm unclear on the purpose of this paragraph. Is it to highlight the advances in diagnostics that make it possible to detect TBD? If so, how does this support the overall theme of this article? We restructured the paragraph.

- The last sentence of the 7th paragraph is not clear and has several errors. "Etiological agents of the group of Rickettsial, including those in the genuses Anaplasma, Neorickettsia, Ehrlichia, and Rickettsia, are relevant and often vector-borne organisms of canines and felines, but also of bovine, live-stock and other animals, which appears to be a wide range of hosts". Could this be moved somewhere else to make a transition or taken out completely? Corrected.
- "group of "Rickettsial" should be either "rickettsial pathogens in the..." OR "Etiological agents in the Order Rickettsiales". Corrected.
- "live-stock" should be "livestock". Done.
- "Genuses" should be "genera". Done.
- The Order Rickettsiales is an Order and not italicized. Admittedly this order's taxonomy is problematic, but if you are going to refer to it, don't italicize it. Ok.

Table 1:

- Your table is entitled "Examples of selected tick-borne diseases in Latin America," yet contains tick species mostly localized to North America (*D. andersoni*, *D. variabilis*, *D. occidentalis*, *I. pacificus*, and *I. scapularis*). There was a review by Esteve-Gassent et al (2014)¹ that suggests that some of these species could potentially spill over the Mexico-USA border and therefore these species could potentially warrant further study. Your use of this table, however, does not provide any context and feels out-of-place and irrelevant. We have extensively changed the table.
- There have been several articles detailing known hard and soft tick species and their epidemiological significance from many different Latin American countries (e.g. Rivera-Páez in 2018 gives updates to Colombian Ixodidae²; Mastropaolo 2014



reviewed both hard and soft ticks of Bolivia³; Lopes in 2016 of Belize⁴, and Witter in 2016 from wild animals of Brazil⁵, just to name a few). There have also been reviews on tick species found in the Caribbean, Cuba, and Mexico. If you can obtain it, a valuable and comprehensive resource is "The Hard Ticks of the World (Acari: Ixodida: Ixodidae)", by Guglielmone et al (2014)⁶, which contains summaries of all known hard tick species worldwide, including host associations and geographic distributions. We have corrected that.

Conclusion: I am afraid I don't see the relevance of this conclusion section to the rest of the article. What you need is to tie together what you have written and make a conclusion.

- What is your conclusion? Do we need more surveillance? More research? Better diagnostics? Better identification approaches? We included those considerations.
- What are you trying to state that leads to your final concluding statement that this is "just the tip of the iceberg"? To say there is not enough data is sort of vague. More data is always better, but I myself have at least 100 references for literature on TTBD from Central and South America, and my list is not extensive. I would posit that you may need to rethink the purpose of your article. To state that there insufficient work on this topic in Latin America borders on insulting those who have spent careers working on these exact topics. Now we have considered that and discussed in the Conclusions.
- There is an element that you have not discussed: the lack of infrastructure and/or funding to support continued vector surveillance studies. Are there reports comparing the estimated costs of these types of studies (surveillance as well as diagnostics)? If so, how does that compare to the estimated proportion of the national budgets that are specifically earmarked for vector-borne surveillance and public health efforts, and what part of that is allotted toward TTBD research? Perhaps this would strengthen your case for a call to action. We mentioned all of that now and tried to make a more deep call for action.

Competing Interests: None.

Reviewer Report 30 January 2019

https://doi.org/10.5256/f1000research.19300.r42312

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Lidia Chitimia-Dobler

Bundeswehr Institute of Microbiology, Munich, Germany

Title and content of this work do not fit together.

What about the taxonomical issues stated at the end of the abstract? It is not discussed in the paper.



For a review, it is not very comprehensive and does not focus on Latin America. The structure of the manuscript is not logical, starting with *Rickettsia*, continue with *Ehrlichia*, coming back to *Rickettsia*. There is too much content about the USA for a short review referring to Latin America.

In the table, there are a number of tick-borne diseases which do not occur in Latin America E.g. Colorado tick fever, Heartland virus diseases or Powassan encephalitis. It is not acceptable to simply transfer data from USA to Latin America.

Is the topic of the review discussed comprehensively in the context of the current literature?

Are all factual statements correct and adequately supported by citations?

Is the review written in accessible language? Yes

Are the conclusions drawn appropriate in the context of the current research literature?

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Ticks and tick-borne diseases

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 04 Feb 2019

Alfonso Rodriguez-Morales, Universidad Franz Tamayo/UNIFRANZ, Cochabamba, Bolivia

Dear Dr. Chitima-Dobler

Thanks for your valuable comments. We want to answer all your comments, as we improved significantly our manuscript based on yours as well as on the other reviewer.

Title and content of this work do not fit together.

Well, we have significantly improved the manuscript, which was originally intended as an Opinion Article. As an Advisor of this Gateway, called, Disease Outbreaks, I should explain to you that at this open publishing platform where there are Opinion Articles, Review Articles and Systematic Review Articles.

This article is NOT a Systematic Review, it was originally submitted as an Opinion Article, as an invitation from F1000Research as being F1000Research Disease Outbreaks Gateway Advisor, but later classified as Review (narrative review). As you well read, we only referred to some examples of studies in Latin America, about tick-borne diseases, that illustrate the problem, in terms of a neglected group of conditions in the region, wherein most of the countries are not under surveillance, and there is still a lack of studies, but even more actions for effective control.



What about the taxonomical issues stated at the end of the abstract? It is not discussed in the paper.

We have improved on the updated taxonomy.

For a review, it is not very comprehensive and does not focus on Latin America. The structure of the manuscript is not logical, starting with *Rickettsia*, continue with *Ehrlichia*, coming back to *Rickettsia*. There is too much content about the USA for a short review referring to Latin America.

As we mentioned, this is not a Systematic Review, is an opinion article, published by decision of F1000Research as a Review (narrative). We focused now more in Latin America.

In the table, there are a number of tick-borne diseases which do not occur in Latin America E.g. Colorado tick fever, Heartland virus diseases or Powassan encephalitis. It is not acceptable to simply transfer data from USA to Latin America.

We significantly changed and corrected the table.

Competing Interests: None.

Comments on this article

Version 1

Author Response 05 Jan 2019

Alfonso Rodriguez-Morales, Universidad Franz Tamayo/UNIFRANZ, Cochabamba, Bolivia

Dear Sergio,

First of all, thanks for your valuable comments as an expert in ticks and tick-borne diseases. Secondly, you probably are not fully aware of the article types of F1000Research. As an Advisor of this Gateway, called, Disease Outbreaks, I should explain to you that at this open publishing platform there are Opinion Articles, Review Articles and Systematic Review Articles.

This article is NOT a Systematic Review, it was originally submitted as an Opinion Article, on invitation from F1000Research as being F1000Research Disease Outbreaks Gateway Advisor, but later classified as Review (narrative review). As you well read, we only referred to some examples of studies in Latin America, including yours (cited), about tick-borne diseases, that illustrate the problem, in terms of a neglected group of conditions in the region, where in most of the countries are not under surveillance, and there is still a lack of studies.

As you stated, this subject remains valid. The intention of this paper, as NOT being a systematic review, was not perform a comprehensive review of the works published in Latin America, a region that has produced a number of scientific articles in recent years, especially on Rickettsiosis, yes, but not in other



tick-borne diseases.

In addition to the above, the current version, is not yet a peer-reviewed article, and your comments, however, will be considered for the next version after peer-reviewer comments.

Finally, we should say that this piece of opinion has been made with the idea to call again for more studies and research, that in fact are still necessary in order to a better understanding of the current situation of tick borne diseases in many countries of region. There are many countries, besides those you mentioned, and we at the article, that in fact, have no studies on much of the tick borne diseases, including Rickettsiosis (e.g. Bolivia), and our comments and call are valid in the way we would say that what we have seen until now is just the tip of an iceberg and there is a need for more studies in Latin America about tick-borne diseases.

Competing Interests: No competing interests were disclosed.

Reader Comment 04 Jan 2019

Sergio Bermúdez Castillero, Gorgas Memorial Institute for Health Studies, Panama

The paper "Epidemiology of zoonotic tick-borne diseases in Latin America: Are we just seeing the tip of the iceberg?" presents a premise that has been discussed by numerous articles in the last years, which is a subject that remains valid. However, despite the title, the paper presents a poor review of the works published in Latin America, a region that has produced a large number of scientific articles in recent years, especially on Rickettsiosis.

An example of this is the reviews described for the cases of spotted fevers by *Rickettsia rickettsii* in Mexico, Brazil, Panama, Colombia or Costa Rica, in addition to several studies published on eco-epidemiology of this and other Rickettsiae in Central and South America.

Similarly, diseases such as relapsing fevers transmitted by Argasidae ticks have recently been discussed for Latin America. This kind of borreliosis is much more relevant to this region than the mention of Lyme disease, despite the findings of *Borrelia burdoferi* s.l. in ticks of South America, which include species where pathogenic capacity has not been proven and that are detected in ticks that have little affinity with humans.

In the case of less common diseases that affect humans (eg babesiosis, ehrlichiosis), the little information available for Latin America is similar to the little information in other regions of the world.

On the other hand, Table 1 does not present valid information for a work in the Latin American region, since no disease, pathogens or potential vector for the region is explained.

In summary, this work should include a better literature review of the scientific articles produced in Latin America and published in indexed journals and local journals.

Competing Interests: No competing interests were disclosed.



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