Author’s response to reviews

Title: Identification of priority areas for surveillance of cutaneous leishmaniasis using spatial analysis approaches in southeastern of Brazil

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To BMC Infectious Diseases

Dear Editors,

On behalf of the authors of the manuscript "Identification of priority areas for surveillance of cutaneous leishmaniasis using spatial analysis approaches in southeastern Brazil" (#INFD-D-18-00295), I would like to thank you for your message of November 13, 2018. We also would like to thank the reviewers for their thoughtful comments that helped us to improve our paper. We carefully examined all the reviewers’ comments and felt encouraged to revise and resubmit the manuscript taking their recommendations in consideration. Following are the answers and comments to each of the comments/questions they have raised. We hope we were able to meet your requirements. Please do not hesitate to contact us if you need any further explanations.

The changes are clearly outlined in the revised manuscript in track change. As requested, we have prepared a list responding to each of the comments, which are in bold italic.
Response to Reviewer #1:

1. Could you please do a statistical analysis between different age groups and genders?

We understand the reviewer’s suggestion regarding the age groups and genders variations considering the epidemiological profile of the disease, however the present study aimed to analyze the spatiotemporal distribution of CL in the state of Minas Gerais between 2007 and 2015 using different methodologies to further understand, characterize, and quantify the expansion of the disease. The results of this study identify, within the state, the areas that could be prioritized by the control and vigilance. We believe that the results describing the spatiotemporal pattern of CL expansion in this vast geographic area may be relevant to researchers following the disease in other regions of Brazil and beyond. The spatial and temporal analysis techniques applied here are relatively simple and intuitive and can be developed using free software, which facilitates the diffusion and application of such an approach in most of the highly endemic regions in Brazil.

It was not the aim of the study to evaluate risk factors involved in the transmission using spatial and temporal analysis. However, this is an important approach that will be evaluated later, using another statistical model to evaluate the risk of CL in the state of Minas Gerais.

Conclusion

2. It needs a review. Some parts are vague and inaccurate

We thank the reviewer for the comment. We have now thoroughly revised the manuscript, including a professional revision of English language (see attached certificate), and tried to be more precise in our epidemiological description and evaluation. All the changes are highlighted in the new version.
Minas Gerais presents with high incidence rates of CL, with most cases concentrated in the southeastern region. In our study, 124 municipalities in Minas Gerais were classified as high priority in at least one triennium, of which 36 municipalities were classified as high priority during the whole study period and which were located in the mesoregions North of Minas, Jequitinhonha, and Vale do Rio Doce. These 36 municipalities deserve special attention for control, since they can influence neighboring areas, and might contribute to the expansion of CL within and beyond the state.

Our calculations of Global Moran’s Index and LISA risk mapping allowed the identification and quantification of stable and expanding areas of CL cases over time, as well as the identification of regions that share similar spatial patterns. The results reported herein may assist and guide the implementation of disease control measures in the state of Minas Gerais. In addition, the presented approach to detect and describe regions of high priority for CL in this vast geographic area might be applied to other regions, or diseases, in Brazil or beyond.

We would like to thank the reviewer#1 for her/his suggestions.

Reviewer #2:

Question/suggestion#1. The study shows an interesting analytical approach to describe CL incidence distribution on time and space in MC State, Brazil, from secondary data in municipality and three-year scales. However, the authors should better discuss why these descriptive data could be of interest for an international reader. Some examples below:

Lines 242-247 the authors stated: "CL steady increase", MG "new CL cases … more than in the neighboring states", "we tried to understand spatial and temporal changes of the disease". But, the understanding supposes the association between CL trends and environmental or climatic factors or other explanation or hypothesis sustained by analytical results.
We would like to thank the reviewer for his comments. We have tried to put the results and discussion into a more international context. In our view, the used methods and strategies might be used in other countries or regions, in order to identify priority areas and help to guide control measures. With existing alerts on the expansion of CL in Brazil and other Latin American countries, the present spatio-temporal analysis of the expansion of CL in the vast geographical area of Minas Gerais might be of interest for other researchers, who work on the disease in other parts of the world. The applied utilities (GIS) are relatively simple to use, intuitive, and can make use of free software. As such, GIS can be used in any endemic region of the world in order to identify and characterize priority areas and verify the temporal expansion of CL.

We made some changes considering the reviewer’s suggestion in Lines 231-245.

“Since the 1980s, incidence rates for CL in Brazil showed a steady annual increase, and an important spatial diffusion to almost all of the 27 Brazilian member states, turning this protozoan infection into a problem for public health services. In terms of total numbers, confirmed CL cases rose from 3,000 in the 1980s to 20,000 newly registered annual human cases in 2014 [4]. In Latin America, taking advantage of GIS utilities and indicating most-affected regions, CL was reported in fourteen countries between 2001 and 2011, with an increase of 30% in reported cases [3]. In the southeastern region of Brazil, the State of Minas Gerais is of importance, not only because of its geographical extension, but also because of more than 1,000 new CL cases per year, which is much more than in neighboring states, and even in comparison to whole Latin American countries, such as Costa Rica, Honduras and México [3]. Thus, within the national context, this region turned into an endemic area of special attention for the Brazilian Ministry of Health [4]. Here, during the period of our study, we were able to observe an overall tendency for a reduction in CL cases in the State of Minas Gerais. However, by using GIS and smaller functional units, priority areas with increasing incidence rates were detected”.

We understand the concern of the reviewer to seek for environmental or climatic associations with the expansion of the disease. However, this is beyond the goal of the present work, where merely priority areas were identified and described. It was not within our objectives to describe risk factors, however, some possible risk factors were included in the discussion. In fact, the identification of risk factors is importante and will be dealt with in a future analysis, using a different statistical model for Minas Gerais.
Question/suggestion#2. Lines 304-307: "In general, exploratory techniques such as the calculation of the Global Moran's Index in association with LISA are very useful in identifying priority areas for the implementation of public policies related to disease monitoring and control and might be superior and more detailed than the indication of priority circuits, as proposed by others." Please reference or document the improvement of the proposed approach in actual operational scales despite the difference in the number of areas identified.

Thank you for this suggestion. In this study, we have tried to emphasize that for CL the proposed utilities have been explored yet only to a small extent. As such, techniques for spatial analyses, using Moran’s Global and LISA, might be useful for vigilance and control activities in public health services in Brazil and in other Latin American countries.

In Brazil, up to now, production circles are being used for the identification of priority áreas and regions. In doing so, only three priority áreas were identified in three mesoregions of the state of Minas Gerais. However, using our approach with Moran’s global and LISA, we were able to identify priority áreas in eight mesoregions, which resulted in a much more detailed and differentiated identification of priority áreas.

The above mentioned methods and results have been highlighted, compared and discussed in the Discussion part (lines 290-301).

“Here, we identified out 8 mesoregions of importance for CL surveillance and control, and which contained a varying number of high-priority municipalities with elevated incidence rates and considerable degrees of clustering within or between mesoregions. Some former, but also very informative, studies on the epidemiology of CL in Brazil calculated the cases of CL per km² and identified poles or circuits of aggregated human cases in more restricted urban or rural areas [33, 34]. The Brazilian Ministry of Health adopted this method to identify areas of concentration of CL cases [4]. Using this former method, 31 production circuits of CL were identified in Brazil, of which the state of Minas Gerais contained 3 production circuits for the time period from 2007 to 2013, being located in the mesoregions Metropolitan of Belo Horizonte, Vale do Rio Doce and North of Minas [4]. In comparison, in the present study, LISA was applied and it was possible to identify clustered high-priority areas in eight mesoregions, instead of only three in the former study, but including the formerly cited mesoregions, as well”
Discriminate the spatial scales of the results obtained by the cited references, which demonstrated the spread of vectors and infected reservoirs between municipalities. Further, to better support the author's statement, the changes of the article own results in time should be discussed in the frame of a "contagion" trend analysis, and if there are any environmental modifications during the studied period that could explain this trend in some places and not in others at the proper scale.

In the revised version of the manuscript, we have reformulated the lines 306-328 and have tried to improve discussion parts, especially the ones with the mentioned citations, which showed the dissemination and expansion of vectors and reservoir hosts between different municipalities. We have also included a description of the spatial scale, that was used in these former studies.

“The monitoring of municipalities classified as high priority for surveillance is important because these municipalities may influence their neighbors, and spreading of reservoir hosts or vectors for CL may take place, as reported, for example, for the state of Rio de Janeiro [36]. One important factor for the increase of incidence rates and expansion of high priority areas for CL could be migration of reservoir hosts to the close vicinity of housing, as was already reported for Minas Gerais and Rio de Janeiro [14, 36]. Importantly, one of those studies indicated that the expansion of CL between neighboring municipalities or even smaller geographical units occurred independently from deforestation or human migration [36]. Even though that study used a different scale for the distribution of CL [36], we should not exclude that the latter hypothesis for the expansion of CL might also hold true for some municipalities in Minas Gerais. In this respect, small cosmopolitan rodents were shown to have a certain affinity for humans, and their food resources were of great importance for the maintenance of both the wild and the peri-domestic cycles of CL [37]. Due to their mobility of these small rodents, process of disease spread may be related to them due to the circumstance the they move between regions and being thus able to transport it to nearby regions [34, 36–39].

In Minas Gerais, several wild animal species were reported to be infected with L. braziliensis. Interestingly, the main mammalian species encountered were Rattus rattus and Mus musculus, cosmopolitan rodents with a history of living in close proximity to humans [38]. Other studies also pointed out the importance of rodents and small wild mammals as natural hosts for different Leishmania species, and for their roles in the maintenance of the CL parasite lifecycle and transmission [14, 39]. In the southeastern region of Brazil, these reservoir hosts were mainly infected with L. braziliensis, which also was incriminated as the main cause of CL in humans in this region [13, 14, 38].
We would like to emphasize, that it was not the objective of our study to evaluate the environmental changes, that could have happened in our study area during the period of investigation. However, we know that such changes could be decisive for the expansion of leishmaniasis. As such, they have been included in the Discussion in line 271 -281 part as a kind of hypothesis and this issue might be addressed in further studies.

Lines 271 – 281: “In 2009-2010, there was an occurrence of the El Niño-Southern Oscillation, and other studies have associated temporal fluctuations and high incidence rates of CL cases subsequent to this phenomenon [25, 26]. Increased CL incidence is supposed to occur due to an increase in sandfly populations during and shortly after El Niño events [26]. According to Brazilian national weather data, there was an increased amount of precipitation from 2007 to 2009, above the historic average, something that did not occur in 2010 [27]. Also, above-average precipitation was again observed in 2013 [27]; although with no major increase in CL incidence rates in Minas Gerais. Nevertheless, this phenomenon, and the effects on local climatic factors, might have played a role in the epidemiology and peak incidence rates of CL in Minas Gerais in 2010, as also shown by others during earlier studies [28].”

Formal comments

The spatial scales and analytical units are mesoregions and municipalities, so define mesoregion (or the criteria used to define it) in the materials and methods-study area section.

We agree with Reviewer #2 and apologize for the inaccurate definitions. We have now added a sentence on that in the Material and Methods section Lines 99-100: “i.e., geopolitical subdivisions that encompass several municipalities with economic and social similarities”

The sentences 105-106n seems that not add additional information to the previous paragraph, so it could be deleted.

We are sorry for repetitive sections. The above-mentioned sentences have now been deleted.
Check Leishmania braziliensis spelling through the text

We apologize for the typographical errors and wrong spelling. We have thoroughly revised the new version of the manuscript and Leishmania braziliensis has now been corrected throughout the text.

Line 322 L. brasiliensis corrected for L. braziliensis

Line 327 L. brasiliensis corrected for L. braziliensis

We would like to thank the reviewer#2 for her/his kind comments