## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Spatial analysis on human brucellosis incidence in mainland China: 2004-2010 |
| **AUTHORS** | Zhang, Junhui; Yin, Fei; Zhang, Tao; Yang, Chao; Zhang, Xingyu; Feng, Zijian; Li, Xiaosong |

## VERSION 1 - REVIEW

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| **REVIEWER** | Ahmad Athamneh<br>Purdue University, USA |
| **REVIEW RETURNED** | 28-Dec-2013 |

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| **GENERAL COMMENTS** | Zhang et. al. apply exploratory spatial data analysis and empirical Bayes smoothing technique to examine spatial patterns of county-level incidence rates of human brucellosis in mainland china from 2004-2010. The manuscript reads well and presents the results in a clear and concise manner. However, the reviewer could not identify any advancement in the methodology or knowledge presented in the manuscript compared to previous reports.<br><br>Major concerns:<br>The author retrieved the dataset from the internet-based disease-reporting system of the China Information System for Disease Control and Prevention and applied statistical analysis techniques similar to previously published studies (References 14-17). The reviewer could not identify any advancement in the analytical methodology compared to previously published studies.<br><br>The same dataset analyzed in this manuscript and the main conclusion (high-risk cluster on counties) has been described in a previously published article cited by the authors (Reference 31). Although the authors discuss the differences between the two studies, the data presented and the overall conclusions are essentially the same. |

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| **REVIEWER** | Ian Kracalik<br>Spatial Epidemiologist<br>Emerging Pathogens Institute<br>University of Florida, U.S.A. |
| **REVIEW RETURNED** | 03-Jan-2014 |

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| **GENERAL COMMENTS** | The authors provide a good descriptive analysis of human brucellosis in mainland China during the period 2004-2010. However, there are several items that need to be addressed before publication. |

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| | In the abstract the authors state that there was one cluster identified in the north. There are actually several clusters that make up the general pattern of clustering in the north. This needs to be corrected to accurately describe the results.<br><br>METHODS<br><br>The reporting system needs to be better described to address potential biases. Are these data passive surveillance, serology, bacterial isolation, clinical diagnosis etc.<br><br>The estimation of raw incidence rates is not clear. The authors state they use demographic information from the year 2000. What demographic information exactly? If the data obtained were reported incidence rates how were the incidence rates calculated? What denominator data are used i.e. population from the year 2000 or something different. The authors state "We used<br>seven-year reported human brucellosis cases to provide a stable measure of<br>disease incidence rate by time and location at the county level" Is this an average incidence? This section needs to be more clearly written to avoid confusion.<br><br>Although the authors recognize the issue of multiple hypothesis testing I suggest stating what method was used to address this issue e.g. False discovery rate (FDR) correction<br><br>DISCUSSION<br><br>The authors describe potential changes in the reporting of brucellosis over time however, these findings need to be discussed in the context of changing populations. Further clarification of the incidence estimations aforementioned in the methods may help reconcile this issue.<br><br>How does the density of livestock compare to the distribution of human cases? Is livestock brucellosis more prevalent in these areas?<br><br>Were changes in the incidence of brucellosis over time associated with changes in the methods of detection or reporting?<br><br>Clustering was identified in the north but it would be useful to discuss how healthcare seeking behavior may differ in these areas? Is there equal access to hospitals and healthcare? A better description of the reporting system would help address potential systematic and other biases.<br><br>Minor Corrections<br><br>Grammar and journal citation formatting should be reviewed. |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer #1:
1. The author retrieved the dataset from the internet-based disease-reporting system of the China Information System for Disease Control and Prevention and applied statistical analysis techniques similar to previously published studies (References 14-17). The reviewer could not identify any advancement in the analytical methodology compared to previously published studies.
Response: Thank you for pointing this out. However, the purpose of this paper is to apply the appropriate spatial analysis methods for data analysis to reveal changes in the spatial pattern of human brucellosis. Therefore, we did not involve innovative methods.

2. The same dataset analyzed in this manuscript and the main conclusion (high-risk cluster on counties) has been described in a previously published article cited by the authors (Reference 31). Although the authors discuss the differences between the two studies, the data presented and the overall conclusions are essentially the same.
Response: Our work is very different from reference 31. Firstly, although both reference 31 and our work analyzed county-level human brucellosis cases in mainland China from 2004 to 2010, reference 31 performed cluster detection by using a seven-year average human brucellosis cases which merely reflected the average spatial aggregation. In this paper, we performed the cluster detection year by year by using the annual human brucellosis cases from 2004 to 2010 which fully reflected the year-by-year changes in spatial pattern of human brucellosis incidence rates from 2004 to 2010. Secondly, Spatial cluster detection method used in this paper is the local Moran's I, while reference 31 used the spatial scan statistic. The results of these two methods differed slightly and complemented each other. Furthermore, reference 31 is just a letter, the results of which is very simple and rough and provided very limited information.

Reviewer #2
In the abstract the authors state that there was one cluster identified in the north. There are actually several clusters that make up the general pattern of clustering in the north. This needs to be corrected to accurately describe the results.
Response: We are very sorry for our incorrect writing. The error has been corrected.

METHODS
The reporting system needs to be better described to address potential biases. Are these data passive surveillance, serology, bacterial isolation, clinical diagnosis etc.
Response: Human brucellosis is a reportable disease in China; suspected or confirmed cases must be reported to local and provincial Centers for Disease Control and Prevention (CDC) and then to Chinese CDC (CCDC) through the National Notifiable Disease Surveillance System. To meet case definitions, disease in persons must be accompanied by clinical signs and must be confirmed by serologic tests or isolation in accordance with the case definition of the World Health Organization. These contents have been added in our paper.

The estimation of raw incidence rates is not clear. The authors state they use demographic information from the year 2000. What demographic information exactly? If the data obtained were reported incidence rates how were the incidence rates calculated? What denominator data are used i.e. population from the year 2000 or something different. The authors state "We used seven-year reported human brucellosis cases to provide a stable measure of disease incidence rate by time and location at the county level". Is this an average incidence? This section needs to be more clearly written to avoid confusion.
Response: 1) The purpose of this study was to examine the spatial pattern of human brucellosis. Many studies proposed that raw incidence rates are inappropriate to be used to examine the spatial pattern because of their intrinsic defects. EB smoothed incidence rates are more appropriate to be used to examine the spatial pattern of human brucellosis. Therefore, we didn't provide raw incidence

rates. 2) Since 1990, China's population census conducts once every 10 years. And the population of the rest year is inferred from population of the census year in combination with the natural population growth rate. China's fifth and sixth population census conducted in 2000 and 2010, respectively. Therefore, the population from 2001 to 2009 is inferred from population of the census 2000. To avoid confusion, “based on the 2000 census” has been deleted. 3) For the estimate of the incidence rates, the denominator is the number of National Bureau of Statistics from 2004 to 2010 which increased over time, and the numerator is the reported number of human brucellosis cases obtained from the CISDCP. 4) The sentence "We used seven-year reported human brucellosis cases to provide a stable measure of disease incidence rate by time and location at the county level" has been deleted, because it was incorrect.

Although the authors recognize the issue of multiple hypothesis testing I suggest stating what method was used to address this issue e.g. False discovery rate (FDR) correction
Response: Several methods can be used to counteract the problem of multiple hypothesis testing, one of which is adjustment of the significance level. Future research may consider FDR.

DISCUSSION
The authors describe potential changes in the reporting of brucellosis over time however, these findings need to be discussed in the context of changing populations. Further clarification of the incidence estimations aforementioned in the methods may help reconcile this issue.
Response: In this paper, the population from 2004 to 2010 increased over time. We examined the spatial pattern of human brucellosis by using incidence rates instead of incidence cases. Therefore, we think we do not need to consider changes in population data.

How does the density of livestock compare to the distribution of human cases? Is livestock brucellosis more prevalent in these areas?
Response: Currently, cross-organizational collaboration (between public health, clinics, and hospitals) has been very efficient within the healthcare system; however, information-sharing between healthcare organizations and non-health departments, such as the government’s agriculture department, has not been extensive. Animal and human health disease surveillance databases are not currently linked. Additionally, we can’t obtain the data of animal brucellosis because of confidentiality restrictions. Therefore, we didn’t analyze the density of livestock compare to the distribution of human cases.

Were changes in the incidence of brucellosis over time associated with changes in the methods of detection or reporting?
Response: There was little association between changes in the incidence of brucellosis over time associated with changes in the methods of reporting. But there may be association between changes in the incidence of brucellosis over time associated with changes in the methods of detection.

Clustering was identified in the north but it would be useful to discuss how healthcare seeking behavior may differ in these areas? Is there equal access to hospitals and healthcare? A better description of the reporting system would help address potential systematic and other biases.
Response: These contents have been added in our paper.

Minor Corrections

Grammar and journal citation formatting should be reviewed.
Response: The grammar and journal citation formatting have been checked and corrected.