Author's response to reviews

Title: Epidemiological investigations of human rabies in China

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Author's response to reviews: see over
Dear Iratxe Puebla,

Thanks for your inspiring mail and the reviewers’ thoughtful comments to us. The suggestions are very important and useful for the improvement of our manuscript, and we have revised the manuscript according to the kind advices. Enclosed please find the response to the reviewers. If there are some places need to be revised again, please let us know.

In this revision, the human rabies data in China in 2007 and 2008 were added, for the general analysis about characteristics of human rabies in recent years. In addition, all the date and calculation were proofed, and the written English was improved.

In addition, the reviewer 4’s comments are more likely to the paper written by Han Si et al. (BMC Infectious Diseases 2008. 8: 113), and we still revised our manuscript according the comments.

Thank you once again for all your help and looking forward to hearing from you soon. We sincerely hope this manuscript will be finally acceptable and be published on BMC Infectious Diseases.

Best regards

Yours sincerely
Miao Song, M.D.

**Reviewer 1:** Henry Wilde

**Response:** Thanks for your detailed and encouraging review, and your comments and questions are very critical for improving our manuscript. Next is a point to point response to your suggestions.

They found that over 2% of the dogs "randomly" collected, apparently from restaurants specializing in dog meat, were positive by FAT for rabies. The FAT test is not positive until encephalitis is well underway; the animal is symptomatic. This would suggest that sick dogs are sold to the restaurants for dinners. If that is so, I can only hope that all meals are well cooked before served to people. Also, if this is true and FATs are not over-read, this would not be a random sample of the general dog population. The authors can not avoid not to discuss this subject further and look for some reliable references regarding the appearance of FAT positive brain RNA in relation to clinical onset.

**Response:** Thanks for your suggestions. To answer your questions, essential explanations were added in Methods (middle, Page 6) and Discussion (middle, Page 13) parts in the revised
In fact, not only in China but also in other countries, the reports about identification or isolation of rabies virus in apparently healthy dogs repeated. Although no date are available concerning how long such dogs survive and no adequate evidence are provided, the phenomenon may be explained that rabies virus has reached the central nervous system before clinical signs appear rather than there are carrier or asymptomatic rabies state exists. About the dogs purchased by restaurants, they will be slaughtered soon and no time to transmit rabies virus to other dogs and humans but the butchers. Up to now, the dog meat consumers are considered no risk of rabies infection for no related reports appear. In the three provinces, there are many restaurants selling dog meat here and there, for people in southern China are accustomed to eat dog meat to resist dampness and cold in winter, and almost all the dogs collected for meat consumption are local domestic dogs free-ranging and unvaccinated in rural areas which are majorly accounted for human rabies. So the brain specimens from apparently healthy dogs in different restaurants in the 15 principal cities can be regarded as from random domestic dogs.

**Reviewer 4: Paata Imnadze**

**Response:** Thanks for your detailed and encouraging review, and your comments and questions are very critical for improving our manuscript. Next is a point to point response to your suggestions.

Results of analysis of data obtained from all provincial administrative regions of China for the period 1990-2007 clearly showed increasing trends of human rabies in some China provinces. However, it remains unclear, what kind of mortality rate was calculated during the study and what for, as in cases of human rabies both incidence and mortality rates must be the same. This part should have more detailed explanation or just be excluded from the manuscript as I could not find any figures of mortality rate inside.

**Response:** Thanks for your suggestions. For the general analysis about characteristics of human rabies in recent years, the human rabies data in China in 2007 and 2008 were added, and the human rabies data in China between 1996 and 2008 were analyzed in detail in our manuscript. For human rabies, once clinical signs appear, the disease is essentially 100% fatal. So the mortality is identical to the incidence rate, and incidence rate was calculated in this study. The explanations above have been added in Methods part (bottom, Page 6).

1. Data indicated in part of "analysis of post-exposure treatment failures" are unclear, as if 50 of 80 patients had only washed wounds by themselves and 30 of 80 went to hospitals or local CDCs to have treatment of their wounds, it is not clear who are those 38 of 80 patients who received between one and four shots of rabies vaccine.

**Response:** Thanks for your suggestions. More detailed and exact descriptions about PEP were added in Results part (middle, Page 10), and there was analysis in detail in Discussion part (Page 15).

2. These data also don't match figures in Table 1.

**Response:** Thanks for your suggestions, and all the date and calculation were proofed in the
3. In my opinion results of study do not fully reflect the objective 2, as in order to define better recommendation for improving the post-exposure prophylaxis schedules delivered to rabies patients it necessary to obtain evidences that cause of human rabies incidence rate increasing was inadequate schedule of PEP. And for this purpose they had to conduct evaluation of reasons of inadequate or insufficient treatment, could not find any evidence-based explanation of it the manuscript. There are some assumptions, but they are not supported by data. If authors have these kinds of data, it will be better to include it in the manuscript. As to discussions and conclusions they are well balanced, but might need some corrections if authors would take into account comments described above.

**Response:** Thanks for your suggestions. In Results part (middle, Page 10), More detailed and exact descriptions about PEP were added, and these data were fully discussed (Page 15). Based on the analysis above, some suggestions were provided in Conclusions part (top, Page 17). Hope the revision will satisfied you.