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 needing to be revised again, please let us know.

According to your comments, we added the introduction of the paper written by Han Si et al. (BMC Infectious Diseases 2008, 8: 113), and emphasized our purpose and contribution. In fact, since 2005 China CDC have planed and began to carry related works, and all the surveys and researches are strictly planed and seriously carried out. Although the date about human rabies in China 96-06 is not new, we analyzed the date more materially and comprehensively. In addition, the date about the status of rabies infection and vaccination in Chinese dogs is original, reliable and authoritative. Furthermore, the status of rabies PEP treatment in the three most seriously affected provinces (Guizhou, Guangxi and Hunan) were described and analyzed systemically. We believe that the publication of this manuscript will be benefit and helpful for prevent and control rabies in China.

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 to 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.

(1) The manuscript could be made a bit shorter and the English needs some serious attention from the English department at their university.

Response: Thanks for your kind suggestion, and we revised our manuscript in language and length according your advices.

(2) I have a very serious problem with an item in METHODS. The authors state that brain specimen of domestic dogs were RANDOMLY COLLECTED AND TESTED BY FAT. They
found the rabies infection rate in dogs to be 8.2% !!!! This is incredible if the samples were truly random (captured or collected and killed at random). I assume that in reality they took randomly from dogs submitted for testing. This surely would not be a random sample but one where the dogs had either died naturally or were killed for some reason (usually sick or mean). The authors must address these issues in some detail.

**Response:** Thanks very much for your question, and it is this question make us find that the rabies infection rate in dogs is mistake in this version of the manuscript. We are very sorry for making so big mistake and very thankful to your advice. In fact, the rabies infection rate in dogs according to our survey is 2.3%, and we have corrected it in the parts of Abstract, Results, Discussion and Table 2. As you mentioned, it is impossible that we collected and killed dogs at random. There are customs of eating dog meat in the three provinces, and dogs slaughtered for meat in restaurants are collected from local farmers. So, we think that dogs killed for meat in local restaurants nearly means local domestic dogs, and we explained it in Methods part (Page 5, revised manuscript). We hope that you’ll be satisfied with our response, and thanks again your kind comments.

**Reviewer 2:** Philippe Gautret

**Response:** Thanks for your detailed review. It’s a fact that we choose a topic similar with the paper written by Han Si et al. (BMC Infectious Diseases 2008. 8: 113), which shows that these date and analysis are very significant and important to prevent and control rabies. In fact, since 2005 China CDC have planed and began to carry related works, and all the surveys and researches are strictly planed and seriously carried out. Although the date about human rabies in China 96-06 is not new, we analyzed the date more materially and comprehensively. In addition, the date about the status of rabies infection in Chinese dogs is original, reliable and authoritative. Furthermore, the status of rabies PEP treatment in the three most seriously affected provinces (Guizhou, Guangxi and Hunan) were described and analyzed systemically. As you suggested, there are no conflict between this manuscript and the paper written by Han Si et al. (BMC Infectious Diseases 2008. 8: 113), which illustrates that both our and Han’s works are very reliable and excellent. We believe that the publication of this manuscript will be benefit and helpful for prevent and control rabies in China. Thanks again for your hard work.

**Reviewer 3:** Millicent Eidson

**Response:** Thanks for your detailed and particular review, and the suggested wording is very helpful for improving the language and making the readers more easily understand our opinions. Thank you very much for your hard and excellent work, and next is a point to point response to your suggestions.

1) In most of the article, the term ‘cities’ is used for the lettered subdivisions of the provincial map. However, the term ‘county’ is used in the middle of page 12. Because the article discusses the preponderance of peasants being infected, and rural areas, perhaps the word ‘county’ should be substituted more widely in the manuscript when referring the lettered subdivisions of the map?

**Response:** Thanks for your comments. According to your suggestion, we have changed the AL country to ZJJ city corresponding to Figure 1. (Discussion, Line , Page 12)

Revised sentence: Many areas that no human rabies report since 1996 occurred outbreaks of rabies
in recent years, such as ZJJ city, Hunan province, where 34 rabies cases were reported in 2005 while there were no cases reported in 1996 to 2004.

2) The following suggestions for the text should be considered to make the wording clearer for the readers. The specific wording I have suggested is not required, but the authors should consider language such as this or other language to clarify the wording. Suggested rewordings are as follows:

p. 3 bottom, For humans after rabies exposure, the rate of prophylaxis . . .
Response: Thanks for your suggestion, related contents have been revised. (Line 21, Page 3)

p. 4 top, Our study shows that the number of human rabies deaths increased rapidly and the prevalence area began to expand in western and . . .
Response: Thanks for your suggestion, related contents have been revised. (Line 2, Page 4)

p. 4 top, Thus, the public education of rabies should be strengthened. The management and vaccination of dogs, and the government financial support for PEP, may also . . .
Response: Thanks for your suggestion, related contents have been revised. (Line 6, Page 4)

p. 4 middle, In the 1980s, . . .
Response: Thanks for your suggestion, related contents have been revised. (Line 13, Page 4)

p. 4 middle, . . . and factors related to the local prevention and control of rabies.
Response: Thanks for your suggestion, related contents have been revised. (Line 1, Page 5)

p. 4 bottom, . . . were collected from the annual reports of the Chinese . . .
Response: Thanks for your suggestion, and Chinese Center for Disease Control and Prevention is the formal name of China CDC, so we think there should be no revision. (Line 6, Page 5)

p. 5, top, . . . by the number of vaccinated dogs/the number of all dogs . . .
Response: Thanks for your suggestion, related contents have been revised. (Line 10, Page 5)

p. 5, middle, After the wound has been thoroughly cleansed, rabies vaccine is administered for Category II and III contacts, and rabies immune globulin (RIG) is administered for Category III contacts. There are two types of RIG used in China, equine RIG (purified . . . The dose of equine RIG is 40 international units . . . for Rabies Postexposure Prophylaxis of Humans based on the WHO criteria above.
Response: Thanks for your suggestion, related contents have been revised. (Line 18, Page 5)

p. 5 bottom, . . . were collected by the local CDC . . .
Response: Thanks for your suggestion, related contents have been revised. (Line 7, Page 6)

p. 6 top, . . . the traditional standard in rabies diagnosis, was used . . .
Response: Thanks for your suggestion, related contents have been revised. (Line 11, Page 6)
p. 6 middle, . . . three selected provinces. The status of . . .
a logistic regression model was used to analyze . . .
Response: Thanks for your suggestion, related contents have been revised. (Line 14, Page 6)

p. 6 bottom, . . . per 100,000. The fewest cases . . .
Response: Thanks for your suggestion, related contents have been revised. (Line 4, Page 7)

p. 7 top, . . . to 2006 are presented in Table 1. Male cases were more than twice
as frequent as female cases. Nearly 1/3 of the cases were under 15 years old. In
all the patients, peasants (rural agricultural workers) represented 61.9%, . . .
Response: Thanks for your suggestion, related contents have been revised. (Line 14, Page 7)

p. 7 middle, . . . of 846 cases was reported compared to 2002, which had a
71.0% increase. In 2005, . . .
. . . increase of 5,841 cases over the 10 years from 1996, an average increase of
35.4% per year.
Initially and until now, most . . .
Response: Thanks for your suggestion, related contents have been revised. (Line 21, Page 7)

p. 8 bottom, . . . dog brains were tested for rabies virus antigen by DFA in 15 of
the X cities in the three provinces . . .
The infection rate of rabies is 8.2% of dogs tested.
All 15 cities showed an infection rate of 1.0-18.9% in the 11-year period. The
infection rate was significantly different among . . .
Response: Thanks for your suggestion, related contents have been corrected and revised. (Line 2, Page 9)

p. 9 top, Of these, 1,157 dogs were male with 20 rabies positives (1.7%) and 761
were female with 23 rabies positives (3.0%). There was no significant difference
between the genders on rabies positivity . . .
. . . was collected in 10 of the 15 cities with dog rabies testing data . . .
The highest rabies vaccination rate was in GG (93.0%), and the lowest rate was
in LZ (10.0%).
Response: Thanks for your suggestion, related contents have been revised. (Line 11, Page 9)

p. 9, middle, . . . showed a non-significant relationship . . . There is also a
non-significant relationship . . . and the vaccination rate of dogs, and between the
infection rate in dogs and the vaccination rate of dogs (r= . . .
Response: Thanks for your suggestion, related contents have been revised. (Line 22, Page 9)

p. 9, bottom, We collected detailed information on 711 of the 7,046 human rabies
cases (X%) from the local CDC . . .
. . . were female. The youngest . . .
Response: Thanks for your suggestion, related contents have been revised. (Line 2, Page 10)
Revised sentence: We collected detailed information on 711 of the human 2956 rabies cases from Guangxi, Hunan and Guizhou provinces in 2005 and 2006 (24.1%).

p. 10, top, . . . 6.3% of the patients . . .
. . . 15.1% had exposures to the head . . .
Response: Thanks for your suggestion, related contents have been revised. (Line 12, Page 10)

Revised sentence: . . . . . occupation, species of attacking animal, animal vaccination status, . . .
Response: Thanks for your suggestion, related contents have been revised. (Line 7, Page 11)

p. 11, top, To clarify these results, we further analyzed the factors . . .
The rate of wound handling (P<0.001) and vaccination . . .
Response: Thanks for your suggestion, related contents have been revised. (Line 13, Page 11)

. . . were not vaccinated because they could not afford . . .
Although the atypical pneumonia pandemic in 2003 in China caught the attention of the world, in the same time period the number . . .
Perhaps the huge number of resources directed to atypical pneumonia influenced . . .
Response: Thanks for your suggestion, related contents have been revised. (Line 24, Page 11)

p. 12 top, . . . incidence decreasing in 2005 may be due to rabies control being emphasized and strengthened by local governments in . . .
This indicates that the attention and participation of the government may improve control of infectious diseases.
Response: Thanks for your suggestion, related contents have been revised. (Line 11, Page 12)

p. 12 middle, . . . as the economic condition is improving in China . . .
Many areas that had no previous human rabies reports have reported outbreaks of rabies since 1996, such as AL county . . .
Response: Thanks for your suggestion, related contents have been revised. (Line 22, Page 12)

p. 12 bottom, . . . occurred in the rural areas of the counties.
. . . and to a low vaccination rate in dogs . . .
Affected populations are primarily peasants, students and unattended children, probably due to increased chance of dog contact, lack of prevention awareness, and reduced capability of defending against dog attack.
Response: Thanks for your suggestion, related contents have been revised. (Line 2, Page 13)

p. 13 top, However, dog rabies surveillance often hasn’t been carried out
because the dog isn’t an important economic animal in China. Insufficient data was obtained to fully address the relationship . . .
In our research, the rabies infection rate (8.2%) in dogs was higher than in other investigations . . .
The vaccination rate was lower in most areas, and the attacked animal primarily was the dog. The rise of . . . in these areas, although this association was not statistically significant in our research.
**Response:** Thanks for your suggestion, related contents have been revised. (Line 14, Page 13)

p. 13 middle, In 2006, the estimated number of dogs in Chinese homes was over 75,000,000. Among those, over 11,000,000 dogs are raised by urban families . . .
[delete, because modified and moved above to earlier para.: So the correlation between the DFA positive rate of rabies and the rate of vaccination in dogs in the investigated areas showed non significant relationship.]
As suggested in previous studies, low dog vaccination rates is one of the . . .
The vaccination coverage in dogs needs tremendous improvement.
**Response:** Thanks for your suggestion, related contents have been revised. (Line 25, Page 13)

p. 13 bottom, In China, there are no official administrative rules . . .
**Response:** Thanks for your suggestion, related contents have been revised. (Line 11, Page 14)

p. 14 top, . . . concerning the animals attacking humans. In some areas, the dog would be killed after attacking humans, with few receiving observation and rabies detection. The status of animals after attacking humans was not always obtained.
**Response:** Thanks for your suggestion, related contents have been revised. (Line 12, Page 14)

p. 14 middle, In our study the rate of PEP in patients with rabies exposure in the three provinces is extremely low. Among the investigated . . .
One of the reasons for the low rate of rabies PEP might be related to the low level . . . and the rates of wound treatment and vaccination administration . . .
**Response:** Thanks for your suggestion, related contents have been revised. (Line 19, Page 14)

p. 14 bottom, This illustrates that with serious exposures at sites close to the head, face and neck, the patients were more likely to seek medical assistance. Those patients with a lower category of exposure or exposure sites on the limbs more often handle the wound by themselves without wound treatment and vaccination, which is often inappropriate. Thus, education on rabies and its prevention is necessary and important in endemic areas . . .
**Response:** Thanks for your suggestion, related contents have been revised. (Line 4, Page 15)

p. 15 top, . . . economic development . . .
. . . total of the cost for PEP/person . . .
Thus, the lower cost intradermal regimens are being considered in China.

**Response:** Thanks for your suggestion, related contents have been revised. (Line 12, Page 15)

p. 15 middle, In addition, some cases receiving PEP still died of rabies. Almost none of them received adequate PEP. For example, many Category II exposure cases only washed the wound without visiting medical doctors. Some category III exposure cases were vaccinated but received no RIG, and some of the patients died quickly . . . [Can the number of cases be added here instead of ‘many’ and ‘some’?]

. . . resulted in these patients dying of rabies. Knowledge of rabies prevention . . .

In summary, comprehensive steps including . . . proper rabies exposure PEP, and increasing the knowledge of rabies prevention, as well as government financial support for PEP, are necessary for . . .

**Response:** Thanks for your suggestion, related contents have been revised. (Line 19, Page 15)

p. 15 bottom, Our study shows that human rabies numbers have increased rapidly . . .

Thus, the public education of rabies should be strengthened. The management and vaccination of dogs and the government financial . . .

**Response:** Thanks for your suggestion, related contents have been revised. (Line 6, Page 16)

p. 16 top, . . . may also play a huge role in reducing the rate of human rabies deaths.

**Response:** Thanks for your suggestion, related contents have been revised. (Line 12, Page 16)

3) Suggested changes for Figure titles:

Figure 1 – Location of Guangxi, Hunan and Guizhou provinces within China.

data on human cases and dogs was included for highlighted counties.

**Response:** Thanks for your suggestion, related contents have been revised. (Line 2, Page 19)

Figure 2 – Number of human cases and incidence rate between 1996 and 2006 in China

**Response:** Thanks for your suggestion, related contents have been revised. (Line 4, Page 16)

Figure 3 – Changes in the number of cases of human rabies . . .

**Response:** Thanks for your suggestion, related contents have been revised. (Line 6, Page 16)

4) Suggested changes for Table titles and column/row headings: Table 1 – The demographic characteristics of all the human rabies cases in China (n=14,065) and in the three affected provinces (Guangxi, Hunan and Guizhou, n=7,046) from 1996 to 2006

**Response:** Thanks for your suggestion, related contents have been revised. (Line 2, Page 20)

Table 2 – The infection rate and vaccination rate in dogs and incidence of human rabies in 15 investigated counties Change 4th column title: Incidence of human cases (1/100,000)
Response: Thanks for your suggestion, related contents have been revised. (Line 28, Page 20)

Table 3, Change ‘Exposure degree’ to ‘Category of Exposure’ to match the terminology in the text.
Response: Thanks for your suggestion, related contents have been revised. (Line 4, Page 21)

Reviewer 4: Paata Imnadze
Response: Thanks for your professional, detailed and encouraging review, and we also hope that the date can be used as the basis for the development of an appropriate prevention plan. Thanks for your hard and excellent work again.