Author's response to reviews

Title: Potential and Actual Rabies Exposure in People and Domestic Animals, Upstate South Carolina, 1995-2003: A Surveillance Study

Authors:

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Author's response to reviews: see over
We respectfully submit the attached revised manuscript entitled “Potential and Actual Terrestrial Rabies Exposure in People and Domestic Animals, Upstate South Carolina, 1994-2004: A Surveillance Study” for your second review. We extensively changed the manuscript according to the reviewers’ comments. We comment on these changes following this letter. We are confident that these changes are satisfactory. We hope you enjoy reviewing the revised manuscript and thank you for your time and consideration.

Sincerely,

IF
Synopsis of changes

- We revised the manuscript according to the reviewers’ suggestion where deemed appropriate. See detailed comments below.
- Instead of AIRIR we use the full term Animal Incident/Rabies Investigation Reports.
- All analyses were redone and a few minor errors associated with the exclusion/inclusion of observations were corrected. The revised results, even when not affected by the removal of bat-associated incidents, are therefore slightly different from the ones in the first version.

Reviewers’ comments are quoted; our responses are set in bold.

Reviewer: Millicent Eidson

Major compulsory revisions:

1. It appears the paper primarily focuses focus on terrestrial rabies, but occasionally it includes some bat data. The paper could focus exclusively on terrestrial rabies, leaving the bat data out. If including some bat data, then a bit more should be added in each section that puts the bat data in perspective related to the terrestrial data. For example, in table 1, bats account for more exposures than skunks, but skunks are addressed more in the text. In table 4, rabid bats account for more exposures than rabid dogs, but dogs receive more focus in the text and in the discussion. The issue of the relative contribution of bats (which have caused almost all of the recent human cases) versus terrestrial wildlife is a big one, and where resources should be directed. With bat data available in SC, more contrasts of bat exposures/risks with the terrestrial species would be helpful, including implications for prevention and control.

We appreciate this helpful suggestion. We revised the manuscript as follows:

a. Change of the title to ”Potential and Actual Terrestrial Rabies Exposure in People and Domestic Animals, Upstate South Carolina, 1994-2004: A Surveillance Study”. Note that the dates were changed as reports from 1994 and 2004 are included in the study.
b. We added the following sentence to the first paragraph of the Method section: “As we were only concerned with terrestrial rabies, we excluded incidents involving bats.“
c. We removed the bat data from Table 1 and changed “rabies” to “terrestrial rabies” in the caption.
d. We removed the bat data from Table 3 and 4 as well as from all other analyses.
2. Abstract, results section: I did not find the statement about dogs and cats contributing 90.1% of the incidents in the results section of the paper, but it could be calculated from the table. I would recommend only including a statistic in the abstract if it has also been presented in the text of the paper. 

Ok–requested change made.

3. Abstract, conclusion section: First sentence about wildlife contributing the majority of confirmed rabies exposures for human victims doesn’t fit with the 3.8% and 0.5% numbers given in the Abstract results section. 

The sentence in the abstract, result section, was misleading–it referred to the proportion of incidents with wildlife in people (3.8%), among which about 13% (=0.5/3.8) were rabid. We restated the whole paragraph to avoid the confusion.

Minor essential revisions:

4. Background section, page 4: 2nd para., definition of exposure, change ‘blood’ to ‘nervous tissue’

Ok

5. Methods section, page 5. In the background section, it was mentioned that animal to animal exposures were being included, but they are not mentioned in the first paragraph of the methods section. Unless they are reported only if there is also a human exposure victim? If so, make that clear.

No, incidents may concern only animal victims. To clarify this we modified the concerned sentence in the following way: “[…] reported by staff of medical treatment facilities, victims or bystanders (when animal victims are concerned)

6. 2nd para., make clear whether the animal categories (stray, pet, family pet) apply both to the exposure animal and the animal victim. I’m not clear on the difference between the pet and family pet categories. Further explanation of why wildlife pets were excluded needs to be provided.

The sentence “Domestic exposure animals were categorized according to ownership status (stray, pet)” states that only exposure animals thus were classified. Because the “family pet” category was not used in this analysis we omit it from the paragraph. “Wildlife pets” were only excluded from the analysis of ownership status.

7. Results section, para. 4, the text says overall positivity was three quarters of a percent, but Table 3 says 7.5%. Also clarify in the table that the N represents the denominator of those tested, not the numerator of those positive. Perhaps provide both?

Ok–we provide a footnote clarifying the denominator.
8. Discussion: Some reports have indicated species other than dogs associated with the majority of reported incidents (see Chang, EID, Sept. 2002). So 1st sentence should be modified to “Our results are consistent with some previous reports . . .”

*In our understanding, the Chang paper focused on PEP, not on animal incidents; we therefore choose the leave the sentence as is.*

9. 2nd paragraph: “rabies cases are considered rare in the United States”, what rabies cases? humans, animals? The argument about cats having similar prey animals with wildlife is unclear. Couldn’t both dogs and cats prey on smaller animals just like wildlife do (rodents, lagomorphs)?

*We changed the passage to “[…] rabies is considered rare […]”. We modified the sentence involving prey animals to “While cats may not commonly be considered a potential source of rabies, outdoor domestic cats are often loosely owned and free roaming, potentially bringing them into contact with rabid wildlife“.*

10. page 10, paragraph about skunks: This paragraph emphasizes the role of skunks, but they account for fewer exposure incidents than foxes in the study. It would help to clarify the relative importance of foxes and skunks in SC.

*We modified the passage to:”Raccoons were the most frequently tested exposure animals and foxes were the most common source for rabies exposure to people. Skunks, however, were most commonly rabid when tested. “*

11. “Cross-species transmission or spill-over of rabies to domestic animals in South Carolina is occurring from wildlife species” Level of evidence for this statement is a bit unclear. Information is included about animals being confirmed with raccoon variant, and the number of domestic animals interacting with wildlife species. But it’s very difficult to determine which wildlife species actually infected domestic animals, other than raccoons with raccoon variant. Other wildlife species such as skunks might be transmitting the raccoon variant in SC, but the evidence is not clear. Sentence could be simplified by changing ‘wildlife species’ to ‘raccoons’.

*We changed the sentence to “The evidence of spill-over transmission of raccoon rabies to domestic animals in South Carolina is consistent with previous studies“ thus avoiding to name a specific source of spillover infection.*

12. Sentence about ‘cats expose human victims to rabies about as frequently as raccoons’, clarify with ‘rabid cats expose human victims to rabies about as frequently as rabid raccoons’

*Ok*

13. page 11, top, ‘rabies vaccination coverage for both dogs and cats was lower’ [change ‘were’ to ‘was’]
14. Statement that it is unlikely that puppies and kittens were disproportionately included; I’m unsure of the evidence. Similarly with the statement that ‘it is unlikely that large numbers of stray cats were pets with current rabies vaccination’, after noting that some may be cats that owners let outside. More information is also needed to clarify the final sentence about vaccination coverage and explanations by bias (what types of bias, influencing in what way?).

*We modified the statement regarding puppies/kittens to:* “If puppies and kittens were disproportionately included in our study, estimated vaccination coverage might thus be artificially deflated“.

15. ‘Vaccination against rabies will help protect these animals and any mammalian contacts” [word ‘help’ is added, because vaccination is not a guarantee of protection].

Ok

16. The Maryland data cited about vaccination status of free-roaming cats perhaps should be mentioned earlier to help support statements in the previous paragraph.

*As suggested, we moved the sentence to the second paragraph of the discussion.*

17. Conclusions: Given the conclusion about most rabies exposures deriving from rabid wildlife, I think it would be helpful to add a sentence about the importance of research to improve wildlife rabies control methods, such as ORV, and initiatives to reduce human/domestic animal interactions with wildlife.

*We modified the last sentence of the conclusions section to:*”Our results underscore the need for future research to improve wildlife rabies control methods as well as the need for initiatives to reduce interactions of domestic animals, including cats, with wildlife“.

Discretionary revisions:

18. Abstract p. 2, Background, in this section, and on the Background section of the paper itself (p. 4), suggested rewording for the Abstract: “Although there has been a reduction of rabies in pets and domestic animals during recent decades in the United States, rabies remains enzootic among bats and several species of terrestrial wildlife. Spillover transmission of wildlife rabies to domestic animals therefore remains a public health threat.” Consider similar change in Background of paper to clarify.

*Abstract and Background section were revised accordingly.*
19. **Abstract, conclusion section:** Consider changing the word ‘significantly’ in referring to stray cats. Perhaps “stray cats were an important contributor”? Education about risks from wildlife is mentioned here, but not in the conclusion in the text. Similarly, the sentence about ‘surveillance of animal victims’ is not based on similar wording in the text conclusion, which needs to be fleshed out if this concept is provided in the abstract.

**The word “significantly” was replaced by “substantially”. The conclusion section of the abstract was adapted to the conclusions from the text.**

20. **Background, page 4, , suggested rewording:** “Although rabies in pets and domestic animals has been successfully reduced in the United States since the 1960s with vaccination programs, oral rabies vaccination (ORV) and other control programs in wildlife have had limited success [1,2]. Rabies remains endemic among bats and several species of terrestrial wildlife {Rupprecht, 1995 #2727; Groseclose, 2004 #9771}, including …”

**Ok—the passage was reworded:** “Rabies in pets and domestic animals has been successfully reduced in the United States during recent decades with vaccination programs. Oral rabies vaccination (ORV) and other control programs in wildlife, on the other hand, have had limited success. Rabies remains enzootic among bats and several species of terrestrial wildlife {Rupprecht, 1995 #2727; Groseclose, 2004 #9771}, including …”

21. **Same para:** “As wildlife rabies is mostly captured by passive surveillance programs”; suggestion to clarify: “Because there are few active surveillance efforts to find rabies in wildlife populations (with the exception of ORV areas), actual disease burden . . .”

**The sentence was modified to:** “Because there are few active surveillance efforts to find rabies in wildlife populations, the actual disease burden is likely underestimated in these populations”

22. **2nd para., 2nd sentence, Consider** “While reporting of human victims is mandated in South Carolina, animal victims are reported voluntarily.”

**Ok**

23. **3rd sentence, ‘reported animal incidents’ is unclear, recommend:** “incidents in which an animal has potentially exposed another animal or human to rabies.”

**Ok**

24. **Results section,** consider referring the reader to Table 1 sooner, e.g., at end of 1st sentence.

**Ok**

25. **Paragraph 2 and figure 1:** I’m not clear whether the dogs and cats mentioned here were the exposure animal or the victim animal, and whether they were rabid as indicated by the Figure caption. The figure title is confusing, because it mentions victim type and exposing animal. The figure is not including other
species, so it’s a partial subset of the data, and that needs to be made clear in the title.

The caption was corrected. It should read:”Ownership status of dogs and cats implicated in animal incidents, Upstate South Carolina, 1994-2004”

26. paragraph 3 and table 2: in the paragraph, it’s not clear that the information is referring to exposing animal (as opposed to victims), although that’s clear in the table. Make that clarification in the para. also. In the methods section, it was stated that strays were by definition coded as unvaccinated, so I don’t understand the vaccination data in the table for them.

We made the clarification and excluded stray animals with stated current rabies immunization status from the analyses.

27. para. 5, it would be helpful to move the reference to Table 4 up to the first sentence. Second sentence, clarify: “Almost 90 percent of all incidents involving rabid animals were due to wildlife exposures.” It would help to label the top and side axes in the table (‘Victim Species’, for top axis, ‘Species of Exposure Animal’ for side axis). Consider changing the word ‘type’ in title to ‘species’.

Ok

28. Discussion, 1st para, next to last sentence, “Reporting of incidents involving human victims is mandated” [change ‘are’ to ‘is]. This reporting requirement for human victims is unusual, so it might be helpful to the readers to give a few more details about it (perhaps the exact wording of the requirement, and whether it is in law or regulation?). I realize it’s provided in reference 10, but readers may appreciate a sentence or two about it in the text. It would also be helpful to provide reference 10 when mandated reporting is first mentioned in the background section, although that would require renumbering the references.

Ok—the typo was corrected and the reporting requirement is briefly explained.

29. Discussion, page 10: Sentence about ‘potential role of domestic cats as reservoirs of rabies’; I’m not seeing sufficient evidence to warrant the word ‘reservoir’.

We change to sentence to emphasize the speculative nature of this statement and say that the observations “raise[s] the question about the capacity of feral cats to act as rabies reservoir”

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published
Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests: I declare that I have no competing interests.
Reviewer’s report  
Reviewer: Philippe Gautret

Discretionary Revisions

1. Introduction: Reference 5 should be updated (new version in 2008)  
The reference was updated.

2. Discussion: P 11: protocols for rabies preventive vaccination in cats and dogs should be detailed.  
Ok—a reference to the Compendium of Animal Rabies Prevention and Control, 2008 is provided.

3. General comment: The authors should read the paper by O’Bell et all: Human rabies exposures and post exposure prophylaxis in South Carolina 1993-2002. Public Health Report 2006-121, and comment their results in view of this larger study.  
OK—see our response to reviewer 3, first comment.

4. Conclusion: Given the bias in the, it should not be concluded that domestic animal victims are “sixteen” times more likely to be exposed to rabies than people.  
Ok—we modify the sentence to “Given a reported incident, domestic animal victims are much more likely to be exposed to rabies than people”.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests: I declare that I have no competing interests' below
Reviewer’s report

Reviewer: Jesse Blanton

Reviewer's report: This study provides a unique look at domestic animal exposure and the role of pets as rabies vectors from wildlife species (and underlines the importance of domestic animal vaccination as the front line in preventing human rabies exposure). However, the some discussion of the findings in regards to human rabies postexposure prophylaxis would strengthen the paper.

Major Compulsory Revisions

1. Could the authors provide some insight into their findings in regards to human rabies postexposure prophylaxis. Some discussion regarding potential exposure and human PEP administration would strengthen this paper, as this is the ultimate public health and financial burden of exposure. Similarly regarding euthanasia, quarantine and observation of potentially exposed domestic animals. Did PEP administration reflect the relative rate of exposure in the study area over the time studied? For reference O’Bell SA, McQuiston J, Bell LJ, et al. Human rabies exposure and postexposure prophylaxis in South Carolina, 1993-2002. Public health rep. 2006; 121: 197-202.

PEP, although of great public health importance, was not the focus of this study. As the animal incidence/rabies investigation reports on which this study was based did not contain reliable information on PEP, nor on the other issues mentioned (quarantine, euthanasia, etc) we cannot address them. We appreciate the reference to O’Bell et al which we incorporate into our discussion.

2. Pg10, 3rd paragraph – Please provide additional support for cats as reservoirs vs vectors of rabies or clarify meaning. To date there has been no evidence of cats acting as a primary reservoir of rabies or any Lyssavirus. Additional viral characterization and laboratory support should be provided and would constitute a separate publication if so.

The distinction between rabies reservoir and vector clearly is extremely important. We do not have any additional evidence for domestic cats currently serving as a reservoir. Therefore, we changed the sentence to “Previous studies found that incidence of rabies in cats remained unchanged after the primary epizootic in raccoons subsided {Gordon, 2004 #897}, which raises the question whether feral cats might also act as rabies reservoir.” We hope thereby to clearly indicate the speculative nature of the statement.

Discretionary Revisions
1. Background / Second paragraph – May want to clarify South Carolina surveillance vs. national surveillance. Currently there is no national surveillance for human or animal exposure or for rabies postexposure prophylaxis.

   Ok – the requested clarification was made.


   The suggested sources are cited.

3. Results / Could the authors also provide the rate of human exposure for the study population?

   An incidence rate of human exposure is provided.

4. Results / Pg7, 4th paragraph – by “exposed to rabies” do the authors mean exposed to animals with a laboratory confirmation of rabies?

   Yes – the sentence was changed to: ”Animals were far more commonly exposed to rabid animals than people “

5. Results / Pg7, 4th paragraph – in the third sentence please specify exposures to animals, in 4th sentence why are skunks and bats lumped together?

   Upon suggestion of the first reviewer, bats were excluded from the analyses.

6. Discussion / Pg9, 2nd paragraph – The authors state that dogs are more frequently reported as victims of animal incidents than cats. Could the authors comment on bias due to ownership status as well as relative population difference between dogs and cats.

   This is good point: we added the sentence: ”It remains to be determined to what extent that difference may be due to differences in population sizes, differences in ownership distributions or other factors.”

7. Discussion / Pg10, 2nd paragraph – In the first sentence regarding rabies virus variant. Did no human or animal exposure to a confirmed rabid bat occur in this study population?

   As stated above, we excluded bats from the analysis (upon suggestion of the first reviewer)