Reviewer’s report

Title: Human rabies post exposure prophylaxis at the Pasteur Institute of Dakar, Senegal: trends and risk factors

Version: 0 Date: 30 Jan 2018

Reviewer: Ryan M. Wallace

Reviewer's report:

This manuscript is a very clear description of PEP seeking behaviors at a clinic in Senegal. The study is well designed, results clearly presented, and conclusions are largely sound and consistent with the reported results. Given the current interest in regards to the elimination of dog-mediated human rabies deaths, this paper is timely and could potentially have a wide-ranging impact in the development of global rabies elimination recommendations.

GENERAL COMMENTS

1 - METHODS: the authors noted that patients received special counseling on the rationale for this study and signed an informed-consent waiver. This is something that would likely NOT be done for bite victims outside of the context of this study. By providing this additional counseling, could the results be biased? Could people be more sensitive to the risks of rabies, and thereby overinflate the PEP adherence rates reported here? This bias is not adequately addressed in the manuscript.

2 - METHODS: Was this the normal procedure for PEP, or was anything different in the approach of the patient or the physician that would bias these findings?

3 - METHODS: the main conclusions of this manuscript relate to completion of PEP. However, 2 different schedules for PEP were recommended by Pasteur Institute staff: a 3-dose for when the animal was alive after 2-weeks and a 4-dose for when the animal was dead or unknown. It is critical that these two schedules be analyzed separately. The completion rate should be calculated based on the persons compliance with the medical advice they received. The comment in the discussion that the animal could not be independently verified as healthy is not an adequate rationale to ignore this potential association.
4 - METHODS: The model (Tables 4 and 5) did not consider the outcome of the dog, which could have potentially significant associations with a person's perceived risk of the event, and their decision to complete PEP. I highly suggest to re-consider Table 4 and the model (table 5) to include the outcome of the dog: confirmed rabid (n = 51), healthy at day 21 (n = 93) or any other outcomes that the authors captured in their study.

5 - INTRO: There should be some additional description in the introduction of how the Pasteur Institute is engaged with the Senegalese government. This is of particular importance since the discussion includes recommendations for national guidance. Are these recommendations supported by the Senegalese government, or by Pasteur Institute?

SPECIFIC COMMENTS:

INTRO

* Line 50 - This reference is outdated, suggest to reference the updated human burden estimation by Hampson et al. in 2015: 59,000

* A bit more background information on Senegal would be nice. How many human rabies deaths reported? How many estimated? What do we know about these deaths? What do we know about the wider rabies control practices in Senegal?

METHODS

* Line 105 - is a severe wound considered WHO Category III or is at the clinician's discretion as to what is considered "severe"?
* Line 112 - make sure survey is available as supplement or box. I did not see it in the submission documents.

* Line 113 - were persons bitten by an animal that was still alive 10-days after the bite event still recommended to complete PEP? Or were they recommended to discontinue the series? [this question is answered in the discussion, but should be addressed here as well]

* Are ALL dog-bite victims recommended to begin PEP, regardless of the health-status of the dog or circumstances of the bite? WHO defines a rabies suspect animal as one that has symptoms consistent with rabies. Therefore, in some cases a dog bite may not require PEP, particularly when the animal is available for observation. Is this perhaps why some people chose not to initiate PEP / or perhaps they were not recommended PEP? More description of the PEP recommendations in Pasteur Institute are indicated.

RESULTS

* Figure 1: I do not see the exclusion of persons without mobile phones in this figure. Were any people excluded, as it seems to be indicating in the methods?

* Figure 1: suggest to include the percentages of persons receiving PEP to the flow diagram (ie 678 of 905 completed 3rd dose / 493 of 905 completed 4th dose, etc.). Also, suggest to separate the flow chart by those recommended the 3-dose series and those recommended a 4-dose series.

* Line 174 - what is the significance of noting that the animals were 'healthy' 7 days PRIOR to the bite? All global recommendations focus on the observation of the animal AFTER the bite event. I know of no guidance related to rabies risk if the animal appeared healthy in the days PRIOR to the bite event.
* Table 2: suggest to include a row indicating the outcome of the biting animal by PEP behavior. What were the PEP practices of persons with exposures to confirmed rabid dogs (n = 51)? What were PEP practices for persons exposed to animals that died or were not available shortly after the exposure?

* Line 187: what is the financial cost to the bite victims for PEP at the Pasteur Institute? This should be noted in the methods. [this is mentioned in the discussion, but should also be noted earlier in either intro or methods]

* Linen 195: how far did the study period extend for health checks? Deaths would be expected to occur 3 weeks to 3 months after exposure. Given a 21 day vaccination series was used, few (if any) deaths would be expected in this time period regardless of PEP practices. Were additional efforts undertake to assess the health status of bite victims AFTER the 4th dose of vaccine? If not, how meaningful is this finding?

* Line 198: the methods need to clarify if the Pasteur Institute recommends to discontinue vaccination if the dog is "alive 2 weeks after bite". If this is the formal recommendation, then these individuals should have been considered to adhere to medical advice, and the true "completion rate" is much higher than 55%

* Line 200: spelling mistake

* Line 201: this is a problem for the analysis. What you should truly be displaying is the "adherence to medical advice". If the patients were advised by a medical professional to discontinue PEP after the 3rd dose, then they should be considered to have completed the recommended regimen. Ideally, the analysis and Figure 1 should consider these bite victims separately, since their vaccine regimens were different (3 dose vs 4 dose recommended schedule).

* Line 199: text says 62 people advised not to get 4th dose, but table says 87. It also says in table 3 that 93 people indicated that the animal was still alive. If the national recommendation is to discontinue the vaccination series, then these people did comply with the recommended schedule. Regardless, which is the correct value?
* Table 3: please provide the cost of PEP in the methods or elsewhere in the manuscript and calculate this cost as a proportion of the average monthly salary in Senegal.

* Table 4: people who live further away were significantly more likely to complete PEP compared to people who live closer to PI? That is odd and interesting. It is potentially explained by the finding that delays and lack of wound cleansing were the only associated variables in multivariable analysis. Did you consider interaction terms in the model? Were persons living further away less likely to access medical services in a timely manner? Suggest to re-run the model with at a minimum, an interaction term of distance with delay and distance with wound cleansing.

DISCUSSION

* Line 246: given the study design, you cannot make the claim that children and men are "most exposed". You can only interpret that they are more common among persons that seek care. This study did not assess the characteristics of bite victims (ie exposed persons) that did not seek care.

* Line 254: this study did not assess dogs and the assumption about dog dispersion is highly speculative. The last sentence is most reasonable.

* Line 255: the study design may be biasing these findings. If the official recommendation is to discontinue vaccination if the animal is alive at the time of the 4th dose, then at least 93 people followed appropriate advice to discontinue. I highly recommend repeating this analysis with two separate populations based on the recommended PEP schedule. One analysis focused on those that were recommended to receive all 4 doses and one analysis for those that were recommended to discontinue (n = 93).

* Line 260: this may also be related to medical services available to the bite victims, which could be related to the distance from the Pasteur Institute. I highly recommend that this association be investigated in more detail.
* Line 275: this seems like a very weak excuse to not investigate the association of PEP compliance and on the status of the animal. If Pasteur Institute did NOT recommend the 4th dose, then these individuals should be analyzed separately based on their recommended course.

* Line 282 - this should have been investigated more thoroughly in the analysis. You have enough data in this study to classify a risk status to the offending dog based on presenting signs, circumstances of the bite event, vaccination history, and outcome of the animal. These are critical factors for a risk assessment made by a medical professional, as well as the bite victim when determining their perceived risk of the event. I highly suggest that the authors make an effort to ascribe a WHO-based risk classification to these biting animals and include this variable in their analysis. Based on the univariate findings and anecdotal comments in the discussion, I would expect the authors will find a strong association (particularly if the analysis is separated by the recommended 3 and 4-dose PEP schedules).

* Line 287: excellent point. Suggest to reference some of the work from Tanzania, Haiti, and Philippines that have shown that this capacity can be implemented even in low-income settings.

* Line 290: I saw no data to support the claim that RIG was not received due to cost. Please include this data in a table and the results.

* Line 300: were adverse events to ERIG also captured? Were adverse events more common among persons who received ERIG compared to those that did not?

* Conclusion: consider reviewing algorithms already published, particularly the algorithm and evaluation published by Etheart et al in 2017 in Lancet Global Health.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
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I am able to assess the statistics

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