

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Rabies mortality and morbidity associated with animal bites in Africa: A case for Integrated Rabies Diseases Surveillance, Prevention, and Control - A Scoping review
AUTHORS	Nyasulu, P; Weyer, Jacqueline; Tschopp, Rea; Mihret, Adane; Aseffa, Abraham; Nuvor, Samuel; Tamuzi, Jacques; Nyakarahuka, Like; Helegbe, Gideon; Ntinginya, Nyanda; Gebreyesus, Melaku; Dombia, Seydou; Busse, Reinhard; Drosten, Christian

VERSION 1 – REVIEW

REVIEWER	Meeyai, Aronrag University of Oxford
REVIEW RETURNED	03-Mar-2021

GENERAL COMMENTS	<p>This is a strong piece of work that in my view should be published. I have only a few comments.</p> <ol style="list-style-type: none">1) Line 85-121: the relevance of this to the review is not clear.2) Line 205-206: Is this a result from this work or from some other work? Clarification is needed. If the latter, a reference is needed.3) Tables 2 and 3 mapping morbidity and mortality: it would be useful to see the exact time period in the column “study duration” for all studies (i.e. six years 2010-2015).4) Table 5, column “Research gaps identified”: The authors refer to both research gaps and strengths identified. While the former is clear, I was confused by “strengths identified”. Is the intended meaning “Needs for strengthening research identified”? This needs to be clarified.5) In the section Strengths and limitations of this study (line 68-70), the second point highlights the key role of surveillance. I felt that the authors could have expanded on this strength by also highlighting the review’s contribution to understanding the role of other control measures.
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REVIEWER	Natal Vigilato, Marco Antonio Pan American Health Organization, PANAFTOSA
REVIEW RETURNED	10-Mar-2021

GENERAL COMMENTS	The reviewer provided a marked copy with additional comments. Please contact the publisher for full details.
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Comment: Line 85-121: the relevance of this to the review is not clear.

Response: *Thanks, this paragraph has been removed from the manuscript.*

Comment: Line 205-206: Is this a result from this work or from some other work? Clarification is needed. If the latter, a reference is needed.

Response: *Lines 189-190 (as per the current document). Thanks, a recent reference “79” has been used to clarify this conclusion. It reads “In fact, most of African countries lack a One Health approach to prevent human rabies deaths [79].*

Comment: Tables 2 and 3 mapping morbidity and mortality: it would be useful to see the exact time period in the column “study duration” for all studies (i.e. six years 2010-2015).

Response: *Pages 18, 19, 20 and 21. Thanks, the Tables 2 and 3 have been revised. The study duration has been written as suggested. However, the duration in term of month has been used for the ‘less than one year studies’.*

Comment: Table 5, column “Research gaps identified”: The authors refer to both research gaps and strengths identified. While the former is clear, I was confused by “strengths identified”. Is the intended meaning “Needs for strengthening research identified”? This needs to be clarified.

Response: *Line 531. Thanks, Table 5 has been renamed as “Mapping research gaps and strengths in Africa”.*

Comment: In the section *Strengths and limitations of this study* (line 68-70), the second point highlights the key role of surveillance. I felt that the authors could have expanded on this strength by also highlighting the review’s contribution to understanding the role of other control measures.

Response: *Lines 69-72. Thanks, the strengths of the review have been expended to other rabies control measures as highlighted in the results and discussion sections.*

Reviewer 2

Comment: Line 40: peer

Response: *Thanks, in the manuscript document on page 3 and line 40, the change has been made, it now reads “peer-reviewed....”*

Comment: Line 68: Would be interesting mention and comparing official data from the Ministries of health

Response: *Lines 69-72 Thank you for your valuable recommendation. It has been included and reads “Pulling together data from both published and grey literature from the Ministries of Health gave us an opportunity to understand the breadth of rabies epidemiology and how surveillance, prevention and control would be a critical tool in implementing effective control of rabies across Africa”*

Comment: Lines 81-100: This first paragraph is very long, recommend a summarize information about lineages and variants, because this is not the scope of this paper.

Response: *Thanks for this suggestion. This paragraph has been removed as that is not the scope of this scoping review.*

Comment: Line 135: I would recommend to move this paragraph above, to better comprehension of the magnitude of rabies in Africa.

Response: *Thanks, this paragraph has been relocated. This is now written in the main document on page 6 and lines 81 to 97. It reads “In many sub-Saharan African countries, rabies has become epizootic only in the nineteenth and twentieth centuries involved domestic dogs and free-ranging wildlife species [1-3].*

More than 59 000 people die of rabies worldwide every year [4-5], 99% of them in African and Asian countries where dog rabies is endemic [4, 6-10]. Due to the lack of laboratory confirmation, sporadic epidemiologic surveillance, and unreported clinical cases in developing countries, current mortality estimates almost certainly under-represent the true incidence of human rabies deaths [4, 8-10]. Rabies is responsible for an estimated 21,000-25,000 death annually in Africa [4, 11-12]. Figure 1 shows a map illustrating rabies distribution in thirty-two African countries considering rabies outbreaks in animals, cases and deaths in humans [13]. In 2011, a total of 33 African countries reported 1,607 outbreaks of rabies, 2,779 cases and 1,524 deaths [13]. Data shows that rabies accounts for 7.2% of all animal disease outbreaks reported making it the disease with the highest number of outbreak reports in Africa in 2011 [13]. Algeria, Namibia, Eswatini (former Swaziland), Tunisia, Uganda, Zambia and Zimbabwe reported high morbidity and mortality with 563 cases (33.9% deaths), 269 (94% deaths), 62 cases (88.7% deaths), 91 cases (90% deaths), 466 cases (40.9%), 207 cases (32.8% deaths) and 114 cases (80.7% deaths) respectively [13]”.

Comment: Line 173-175: The sentence is very long, need to be more direct to the point.

Response: *Lines 156-158. Thanks, this sentence has been revised. It now reads: In Africa, dog mass vaccination systems have demonstrated some effectiveness as proof of principle in countries such as South Africa [50-65], Tanzania [50, 66-68], Malawi [50,69] and Chad [55, 70-72].*

Comment: Lines 205-206: The sentence is very long, need to be more direct to the point.

Response: *Lines 189-190. Thanks, the sentence has been rewritten. In fact, most of African countries lack a One Health approach to prevent human rabies deaths [79].*

Comment: Line 220: in Humans? In Animals? or both?

Response: *Line 203-204. Thanks, this study objective has been clarified. It now reads: “to assess the published adverse events and complications associated with human rabies vaccination in African countries”.*

Comment: Line 222: does livestock bites? or it is a contact with an suspected animal?

Response: *Lines 206-207. Thanks, this should be a contact with a suspect animal. The study objective is now written: “to assess rabies morbidity and mortality associated with dog and contact with a suspected animal in humans”.*

Comment: Line 226: work

Response: *Line 211. Thanks, the word “work” has been included in the sentence. It now read: “This papers work used the PRISMA-ScR checklist”.*

Comment: Line 239: What were the criteria to include a European Bulletin in an African study?

Response: *Thanks for this question. Even though this is a European Bulletin, African studies are also published in there, e.g.: South Africa reports two human rabies cases within two*

months in 2021. www.who-rabies-bulletin.org/news/south-africa-reports-two-human-rabies-cases-within-two-months-in-2021

Comment: Line 239: Please correct the website. <https://www.oie.int/>

Response: *Line 224: Thanks, this website has been corrected.*

Comment; Line 314: absence of PEP? Or wound treatment?

Response: *303-304. Thanks, this sentence has been clarified as follows: “Young children are at higher risk of contracting rabies in the absence of PEP and wound care due to the location of the bites they incur”.*

Comment: Line 322: Would be interesting to quantify the number of publications that included wound wash as part of PEP.

Response: *Lines 312-313: Thanks, this section has been included. Nine studies reported wound management as part of PEP [33, 38, 41, 48, 94-97].*

Comment Line 323: It is very important and need to be clear that PEP is not treatment, so need to clarify. There is only experimental rabies treatment (e.g. Milwaukee Protocol - Recife Protocol) It is very important to change all "treatment" wording in the publication if you are meaning PEP.

Ledesma LA, Lemos ERS, Horta MA. Comparing clinical protocols for the treatment of human rabies: the Milwaukee protocol and the Brazilian protocol (Recife). Rev Soc Bras Med Trop. 2020;53: e20200352. Published 2020 Nov 6.

Response: *Thanks. The terms PEP and treatment have been reviewed throughout the document. They are used interchangeable. In the manuscript document, lines 421-458, PEP and rabies treatment have been used in their specific context.*

Comment: Line 324: Human PEP in veterinary clinics?

Response: *Line 313-314. Thanks, veterinary clinics have been removed from this sentence.*

Comment: Line 401: Mentioning the country would be interesting.

Response: *Lines 393-394. Thanks, Ethiopia and Zimbabwe have been mentioned.*

Comment: Line 475: Recommendation include a quote that Nerve tissue vaccines are not recommended by OIE and WHO

Response: *Thanks, this suggestion has been included in the text. Lines 475-477 which reads “ however, those vaccines are contraindicated by WHO because of its association with neurological adverse reactions (severe allergic encephalomyelitis), further these vaccines are inferior to modern vaccine in terms of potency and immunogenicity [108]”*

Comment: Line 478: OIE and WHO does not recommend any more for both animals and humans

Response: *Lines 482-485. Thanks, this suggestion has been taken into account. The WHO and OIE contraindicated SMBV and FBKV in both animals and humans.*

Comment: Line 623: The correct name is SIRVERA please look at <https://sirvera.panaftosa.org.br/>

Response: *Thanks, the change has been made as shown in the track change document lines 623-624. It now reads “The Database such as the New Latin American Rabies Surveillance System (SIRVERA) should be applicable in Africa”.*

Comment: Lines 624-629: In this paragraph I would like to suggest two publications that describe the mechanism of Governance of the rabies program in Americas, it is known as REDIPRA - this is a

Meeting of the rabies directors from the countries that rabies occurs since 1983.
<http://www.panaftosa.org/redipra16/>

Those two publications are:

Vigilato MAN, Molina-Flores B, Del Rio Vilas VJ, Pompei JC, Cosivi O. Canine rabies elimination: governance principles. Rev Sci Tech. 2018 Aug; 37(2):703-709. English. doi: 10.20506/rst.37.2.2859. PMID: 30747115.

Vigilato MAN, Clavijo A, Knobl T, Silva HMT, Cosivi O, Schneider MC, Leanes LF, Belotto AJ and Espinal MA 2013 Progress towards eliminating canine rabies: policies and perspectives from Latin America and the Caribbean Phil. Trans. R. Soc. B3682012014320120143
<http://doi.org/10.1098/rstb.2012.0143>

Response: *Thanks, in the revised document lines 628-632, those two publications have been included in the discussion. The sentences now read “Canine-rabies-endemic regions have formed international rabies networks based on the successful the Meeting of Rabies Program Directors of the Americas (REDIPRA) model which enables them to create a unified and directed approach towards elimination within their regions [120]. REDIPRA meetings can be considered a model for coordination and governance in the world [7, 119, 120]”*

Comment: Lines 646-647: This is a very important key, I would like to suggest describing in the text who is responsible to coordinate the activities of the canine and human rabies program in the African countries?

Response: *Thanks, this comment has been responded to in lines 656-658, it reads “In African countries, the Ministry of Health, Animal Resources, Natural Resources, Environment and Tourism are in charge of implementing the canine and human rabies programs in accordance with local, national and international bodies”.*

Comment: Lines 652-668: It is interesting the ORV. But for the canine rabies control and elimination this could be an additional tool, not really believe that ORV is the panacea. Strategy to deliver dog mass vaccinations must be improved, and also the costs of both types of vaccine should be considered.

Response: *Lines 651-656. Thanks, this paragraph has been revised according to the above suggestion, the sentence reads “New rabies control tests and technologies have been developed, such as oral rabies vaccine (ORV) may be considered as an additional tool for the canine rabies control and elimination. ORV is effective for instance in skunks, red foxes and raccoons, and lessons have been learned from recent outbreaks [125]. ORV has been demonstrated to be effective for the oral immunization of foxes, some of them being competitors for long baits year consumption. Switzerland eradicated wild rabies since 1985 [123]”*

Comment: Line 702: Here the example of REDIPRA would be great.

Response: *Thanks for the comment. We have referred to REDIPRA in lines 669-679 and it reads “However, Strategies to eliminate human rabies in Africa should adapt the REDIPRA model in African context, which emphasizes that people exposed to rabies have timely access to quality immunobiologicals, that appropriate levels of vaccination coverage in dogs in highly enzootic areas are maintained, that national rabies plans are strengthened and that systematic implementation is ensured, and that national rabies plans are strengthened and that systematic implementation is ensured, training, and the development of a laboratory quality control system, particularly in highly enzootic areas, strengthen education, communication and advocacy in enzootic areas, to ensure the continuous political support that is necessary, develop and adopt a guide that delineates the requirements for declaring countries or areas free of human dog-transmitted rabies [120].”*