STUDY PROTOCOL

REVISED Burden and risk factors for snakebite in India: protocol for a systematic review [version 2; peer review: 2 approved]

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Abstract

Introduction: Snakebite is a neglected tropical disease with a high burden in South and South-East Asia and sub-Saharan Africa. In 2019, the World Health Organization (WHO) released a roadmap which aims for a 50% reduction in death and disability due to snakebite globally by 2030. It is estimated that India has the highest number of snakebite deaths in the world.

Objective: To synthesize evidence on the burden (incidence/ prevalence, mortality, morbidity, health facility and economic), and risk factors for snakebite in India.

Methods: We will search for peer-reviewed literature and grey literature in six electronic databases (MEDLINE, EMBASE, Global Health, PsychInfo, CENTRAL, SafetyLit) and hand-search IndMed, conference abstracts, relevant websites and citation tracking. Two reviewers will screen and extract data independently with a third reviewer acting as an arbiter for any inconsistencies. Quality of the included studies will be assessed using the Joanna Briggs Institute (JBI) critical appraisal tools.

For burden, data from facility based and community-based studies will be synthesised and reported separately, except for studies conducted concurrently. We will conduct meta-analysis for community-based studies at state-level for incidence/prevalence, mortality and morbidity , if appropriate. The PROGRESS Plus lens will be used to explore equity . Analyses for each individual risk factor-outcome pair will be conducted and reported separately. If appropriate, meta-analyses will be conducted as per JBI guidelines, assessing heterogeneity using Tau-squared, Cochran's Q test and Chi-squared ($p > 0.05$) tests. We plan to conduct sub-group analyses based on pre-specific parameters. A funnel plot will be generated if there are more than nine studies included in a specific meta-analysis, to assess publication bias

When meta-analysis is not appropriate, structured tabulation of results across studies and/or by vote counting based on the direction of effect as per guidelines in the Cochrane Handbook.

Keywords

Snake Bites, Epidemiology, India, Prevalence, Incidence, risk factor, Health systems , economic costs

Open Peer Review

Reviewer Status ✓ ✓

	Invited Reviewers	
	1	**2**
version 2 (revision) 02 Apr 2020	✓ report	✓ report
version 1 16 Jan 2020	? report	? report

1 **Bert Avau**, Belgian Red Cross, Mechelen, Belgium
Cochrane Belgium, Leuven, Belgium

2 **Abul M. Faiz**, Dev Care Foundation, Dhaka, Bangladesh
Ariful Bashar, Bangabandhu Sheikh Mujib Medical University (BSSMU), Dhaka, Bangladesh

Any reports and responses or comments on the article can be found at the end of the article.

This article is included in the Snakebite collection.

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Author roles: Bhaumik S: Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Writing – Original Draft Preparation, Writing – Review & Editing; **Norton R**: Methodology, Resources, Supervision, Writing – Review & Editing; **Jagnoor J**: Conceptualization, Methodology, Resources, Supervision, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

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First published: 16 Jan 2020, **9**:25 (https://doi.org/10.12688/f1000research.21924.1)

REVISED **Amendments from Version 1**

Based on reviewer comments following major changes have been made:

1. modified the search strategy in the dataset.

2. for incidence/prevalence, mortality and morbidity we will pool data at state level and conduct meta-analysis (if appropriate) (political borders as per Surveyor General of India – May 2020) from community-based studies only. We will not pool data from health facility and economic outcomes to conduct meta-analysis.

3. More information on methods of analysis when no meta-analysis is done. This includes information on summarizing effect estimates to report range and distribution of observed values and / or by vote counting based on direction of effect (with comment on the magnitude of effect) using harvest plot and/or effect direction plot as per Cochrane Handbook guidelines

4. We have also elaborated on sub-group analysis, sensitivity analysis, heterogeneity.

5. Study scope related to risk factor restricted to risk factors of snakebite and for death due to snakebite only.

Any further responses from the reviewers can be found at the end of the article

Background

Snakebite is a neglected tropical disease, with considerable burden in South Asia, Southeast Asia, and sub-Saharan Africa[1]. They are known to affect rural, indigenous and economically disempowered communities who lack political voice[2–4]. A modelling study using data on venomous snake distribution, health-care access, and availability of snake anti-venom, estimated that globally 146.70 million people live in snakebite prone areas lacking quality health-care provisions[5]. However, broad consensus is that these numbers are underestimates as many affected by snakebite are 'out-of-reach' of the formal health systems[6,7]. Snakebite envenomation also causes long-term health effects, and is believed to have high social and economic impacts in affected communities[6,8,9]. Morbidity and socio-economic impact of snakebite is not well understood and remains under-researched globally[9,10].

In 2018, recognising the public health impact of snakebite on vulnerable communities the World Health Assembly (WHA) passed a resolution to address the burden of snakebite[4]. Earlier in 2019 the World Health Organization (WHO) released a roadmap which aims to halve by 2030 the death and disability due to snakebite globally[11]. The WHO strategy rests on four pillars of action: empowering and engaging communities; ensuring safe, effective treatment; strengthening health systems; and increasing partnerships, coordination and resource usage through collaborations[11].

More than a third of the global deaths, about 46,000 annually, are estimated to occur in India[12] with not much known about other aspects of burden[7] or risk factors in the country. Understanding the epidemiology of snakebites (in terms of incidence/prevalence of bites and envenoming, mortality, morbidity and risk factors) at the national and subnational level together with economic costs and health facility burden is critical for developing strategies, plans and programs to address the burden of snakebite. There are no systematic reviews on the burden and risk factors for snakebite in India, although evidence synthesis on burden and impact has been done for other countries or regions[13–16]. The current article provides the protocol for a systematic review on the burden and risk factors for snakebite in India.

Objectives

To synthesize evidence on the burden (incidence/prevalence, mortality, morbidity, health facility and economic), and risk factors for snakebite in India

Research questions

1. What is the burden (incidence/prevalence, mortality, morbidity, health facility, and economic) of snakebite in India nationally and sub-nationally?

2. What are the risk factors related to snakebite (bite and death) in India?

Protocol and registration

The objectives, inclusion criteria and methods of analysis for this systematic review are specified in advance and documented in this *a priori* protocol.

Eligibility criteria

The systematic review consists of two distinct evidence syntheses - burden (incidence/prevalence, mortality, morbidity, health facility and economic); and risk factors for snakebite (bite and death). Synthesis of evidence for each domain will be conducted and reported separately in alignment with recent Cochrane guidelines[17].

Eligibility criteria for evidence synthesis on the burden of snakebite in India

We will include studies that meet all the following criteria:

- **Population** – involving human participants from India, irrespective of age, gender or any other characteristics.

- **Condition** – snakebite irrespective of how it is diagnosed, measured or confirmed.

- **Setting -** facility or community-based studies; autopsy-based studies will be included for understanding aspects of burden, as relevant.

- **Burden Outcomes**- studies reporting any of the following outcomes will be included–

    - Incidence/prevalence– incidence rate of snakebite or snakebite envenoming (i.e. clinical envenoming) (population or age-specific) from community-based studies only; prevalence rate of snakebite or snakebite envenoming from community-based, autopsy-based and facility-based studies;

    - Mortality – incidence death rate (mortality rates per 100,000) due to snakebite (population or age-specific) from community-based studies only; case fatality rate due to snakebite from facility-based studies.

- Morbidity – measured using any validated disability or quality of life tools or DALYs or any other standardised measure (as defined by the authors) from community and facility-based studies.
- Health facility burden- measured in terms of proportions and/or percentages for any of the following outcomes (from facility-based studies only):
  - Visits/admissions in emergency department, clinic/out-patient department, in-patient department (for both venomous and non-venomous bites)
  - Days of inpatient admission (for both venomous and non-venomous bites)
  - Requirement of specialist consultation
  - Requirement for referral in higher facility
  - Requirement of ventilatory support / dialysis support / blood transfusion in acute setting (as defined by primary study authors)
  - Requirement of fasciotomy to manage compartment syndrome (as defined by primary study authors)
  - Requirement of long-term rehabilitation support (as defined by primary study authors)
- Economic burden- from provider perspective or client perspective (direct and/or indirect costs) – as defined and measured by primary study authors (from community-based or facility-based studies).

- **Study design –**
- cohort studies (prospective or retrospective), or
- cross-sectional studies (analytical)

- There will be no restriction by year of publication or language.

Eligibility criteria for evidence synthesis of risk factors for snakebite in India

We will include studies that meet all the following criteria:

- **Population** – involving human participants with snakebite or at-risk of snakebite from India. We will not include forensic- autopsy studies for understanding risk factors.
- **Setting:** facility or community-based studies; autopsy-based studies will be excluded as they cannot give data on risk factors.
- **Risk factors of interest and related outcomes -**No *a priori* list of risk factors is listed as the scope of the evidence synthesis is broad. We will include any risk factor related to following outcomes:
  - incidence of snakebite or death due to snakebite from community-based studies (reported in terms of relative risks (RR), odds ratios (OR), hazard ratios (HR), standardized incidence ratios (SIR) or a standardized mortality ratios (SMR); adjusted or otherwise)
  - death due to snakebite (case fatality) from facility-based studies (reported in terms of relative risks (RR), odds ratios (OR), hazard ratios (HR), standardized incidence ratios (SIR) or a standardized mortality ratios (SMR); adjusted or otherwise)
- **Study design –**We will include the following study designs:
  - cohort studies (prospective and retrospective), or
  - case-control studies, or
  - cross-sectional studies (analytical)

We will not include risk-modelling studies as they are not within the scope of the current evidence synthesis.

- There will be no restriction by year of publication or language.

Information sources and search strategy

Electronic databases

We will search the following electronic databases for eligible studies using adaptions of the MEDLINE search strategy developed for this purpose (see extended data[18]):

- MEDLINE
- EMBASE
- Global Health
- PsychInfo
- CENTRAL
- SafetyLit

Searching other resources

We will hand-search IndMed (a bibliographic database covering prominent peer reviewed Indian biomedical journals), conference abstracts (including but not limited to Indian Public Health Association Conference - IPHACON, Annual Conference of the Toxinological Society of India- TSICON, Annual National Conference of Indian Society Of Toxicology - TOXOCON: as available) and contact researchers of repute in India to identify more studies. We will also hand search vital statistics data, government reports, population surveys or white papers which have reported on the burden and/or risk factors for snakebite specifically in relevant websites. We will also hand search the reference lists of all included studies found by other methods to retrieve additional records.

Study selection

Two review authors will independently assess the eligibility of primary studies based on titles and/or abstracts in the first phase. We will then acquire the full text of all papers identified as potentially relevant by at least one review author. Two review authors will then assess these papers independently and classify them into four categories – included for burden; included for risk factors; included for both burden and risk factors; excluded. We will resolve disagreements, by discussion with a third reviewer acting as an arbiter. We will attempt to contact study authors for further information, if necessary.

Data management

We will extract data using a standardised data extraction protocol, developed by adding extra data elements to the JBI recommended minimum standards for data extraction for prevalence, incidence and risk factor systematic reviews[19,20]. This will be done by piloting the tool (independently and then reaching a consensus) on five studies (each from burden and risk factors) chosen randomly from the list of included studies. Data management will be done using the Joanna Briggs Institute- The System for the Unified Management, Assessment and Review of Information (SUMARI).

Quality of included studies

We will appraise the quality of the included studies by using the JBI quality assessment tools for cohort, analytical cross-sectional and case-control studies[19,20].

Synthesis of results

Synthesis methods for evidence synthesis on the burden of snakebite in India

Data from facility based and community-based studies will be synthesised and reported separately, except in the case of studies which have conducted both concurrently.

An equity lens will be applied to understand burden in a granular fashion. We will use the PROGRESS plus framework[21] for this purpose and extract and synthesise disaggregated data, if available on the framework parameters (PROGRESS-Plus - Place of residence; Race/tribal people; Occupation; Gender/sex; Religion; Education; Socioeconomic status; Social capital; and "Plus" to indicate other possible equity factors which might affect the outcomes of interest in relation to snakebite).

For incidence/prevalence, mortality and morbidity outcomes

Snakebite as a condition is known to be localised in nature. As such, pooling of data from heterogenous studies into one pooled national-level estimate will not reflect the variability in the burden of the condition at sub-national and local levels. The phenomenon of diluting the burden of snakebite by pooling of specific local data into national snakebite incident rate data has been previously recognised and been described as the 'tyranny of mean values'[6]. As such we will not pool data to conduct meta-analysis at the national level.

We will conduct meta-analysis by pooling data from community -based studies at the state level using current political boundaries (Political Map of India, 9th Edition, 2019, Surveyor General of India) for incidence/prevalence, mortality and morbidity. We will not pool data from any facility-based studies, as incidence/prevalence, mortality and morbidity from them will be dependent on patient, health facility and catchment area characteristics implying considerable clinical heterogeneity.

We will use the random effects model with 95% CI for incidence/prevalence, mortality and morbidity as per JBI guidelines since the assumption of one true effect for a fixed model is usually not true for prevalence and incidence data[19]. We will use a fixed-effect model with 95% CI only if we assess heterogeneity (clinical, methodological or statistical) to be significant. Statistical heterogeneity will be considered significant only if it is >40%. Heterogeneity will be assessed by Tau-squared, Cochran's Q test and Chi-squared ($p > 0.05$) tests[19].

If meta-analysis is not appropriate, we will summarise estimates using a structured tabulation of results across studies (arranged chronologically) to report range and magnitude of observed values and/or by vote counting based on the direction of effect as per guidelines in the Cochrane Handbook[22]. Results from vote counting will be reported alongside any available individual estimates study using associated visualisation like harvest plot or effect direction plot, as appropriate[22].

We plan to conduct sub-group analyses for the following, if enough studies are found:

- Sex/gender (male; female; other)
- Age groups: Children (less than 10 years), adolescent (11–19 years), young adults (20–24 years)
- Tribal / non-tribal people
- Occupation (agricultural/plantation workers or farmers, and fishermen)
- Any other PROGRESS-Plus characteristics

Sensitivity analyses will be conducted, as appropriate, and if enough studies are available, to assess robustness of results (based on assessment of different risk of bias parameters and sample size). Additional sensitivity analysis other than what is mentioned *a priori* might be conducted. We will generate a funnel plot to assess publication bias if there are more than nine studies included in a specific meta-analysis. Funnel plot asymmetry will be tested by statistical tests (Egger test, Begg test, Harbord test) as appropriate.

For health facility burden and economic burden outcomes

- We will not conduct meta-analysis for health facility burden and economic burden as the same is inappropriate because of heterogeneity across different health facilities owing to differences in characteristics of

catchment areas, the facility itself and patient characteristics. We will summarise effect estimates using a structured tabulation of results across studies (arranged state wise) to report range and magnitude of observed values as per guidelines in the Cochrane Handbook[22]. If enough studies are available we will report for different sub-groups based on: Type of health facility (government; private; non-profit)

- Level of health facility (primary health centre; community health centre; sub-divisional or district hospital)
- for economic burden - income levels (income quartiles or any other as defined by study authors) or any other PROGRESS-Plus characteristics

Synthesis methods for evidence synthesis of risk factors for snakebite in India

Analysis for each individual risk-factor outcome pair will be conducted and reported separately. We will use the random effects model with 95% CI as per JBI guidelines. We will use a fixed-effect approach only if we assess heterogeneity (clinical, methodological or statistical) to be significant. Statistical heterogeneity will be considered significant only if it is >40%. Heterogeneity will be assessed by Tau-squared, Cochran's Q test and Chi-squared ($p > 0.05$) tests[20].

If meta-analysis is not appropriate, we will summarise estimates using a structured tabulation of results across studies (arranged risk-factor wise)to report range and magnitude of observed values and/or by vote counting based on the direction of effect as per guidelines in the Cochrane Handbook[22]. Results from vote counting will be reported alongside any available individual estimates study using associated visualisation like harvest plot or effect direction plot, as appropriate[22].

We plan to conduct sub-group analyses for the following, if enough studies are found based on:

- Study design
- Setting (community based; facility based)
- Sex/gender (male; female; other)
- Age groups: Children (less than 10 years), adolescent (11–19 years), young adults (20–24 years)
- Tribal / non-tribal people
- Occupation (agricultural/plantation workers or farmers, and fishermen)
- Any other PROGRESS-Plus characteristics

Sensitivity analyses will be conducted, as appropriate, and if enough studies are available, to assess robustness of results (based on assessment of different risk of bias parameters and sample size). Additional sensitivity analysis other than what is mentioned *a priori* might be conducted. We will generate a funnel plot to assess publication bias if there are more than nine studies included in a specific meta-analysis. Funnel plot asymmetry will be tested by statistical tests (Egger test, Begg test, Harbord test) as appropriate.

Dissemination of information

We will publish the results of this review and will make the data accessible openly in re-usable format. The data will also be disseminated through evidence summaries and policy briefs to stakeholders in governments, public institutions and communities.

Study status

The search, screening and subsequent steps will be undertaken after the protocol completes peer-review.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Extended data

Figshare: Extended Data Set : Burden and risk factors for snakebite in India: protocol for a systematic review. https://doi.org/10.6084/m9.figshare.11536776.v2[18]

This project contains the following extended data:

- Prisma-P Checklist
- Study search strategy

Reporting guidelines

PRISMA-P checklist for 'Burden and risk factors for snakebite in India: protocol for a systematic review'. https://doi.org/10.6084/m9.figshare.11536776.v2[18]

References

1. Kasturiratne A, Wickremasinghe AR, de Silva N, *et al.*: **The global burden of snakebite: a literature analysis and modelling based on regional estimates of envenoming and deaths.** *PLoS Med.* 2008; **5**(11): e218.
PubMed Abstract | Publisher Full Text | Free Full Text

2. Gutiérrez JM: **Current challenges for confronting the public health problem of snakebite envenoming in Central America.** *J Venom Anim Toxins Incl Trop Dis.* 2014; **20**(1): 7.
PubMed Abstract | Publisher Full Text | Free Full Text

3. Habib AG: **Public health aspects of snakebite care in West Africa: perspectives from Nigeria.** *J Venom Anim Toxins Incl Trop Dis.* 2013; **19**(1): 27.
PubMed Abstract | Publisher Full Text | Free Full Text

4. Sachan D: **The snake in the room: snakebite's huge death toll demands a**

global response. *BMJ.* 2018; **361**: k2449.
Publisher Full Text

5. Longbottom J, Shearer FM, Devine M, *et al.*: **Vulnerability to snakebite envenoming: a global mapping of hotspots.** *Lancet.* 2018; **392**(10148): 673–84.
PubMed Abstract | Publisher Full Text | Free Full Text

6. Republic of Costa Rica: **Recommendation for the Adoption of an Additional Disease as a Neglected Tropical Disease : The Case for Snakebite Envenoming.** Geneva: WHO. 2017.
Reference Source

7. Bhaumik S: **Snakebite: a forgotten problem.** *BMJ.* 2013; **346**: f628.
PubMed Abstract | Publisher Full Text

8. Williams DJ, Faiz MA, Abela-Ridder B, *et al.*: **Strategy for a globally coordinated response to a priority neglected tropical disease: Snakebite envenoming.** *PLoS Negl Trop Dis.* 2019; **13**(2): e0007059.
PubMed Abstract | Publisher Full Text | Free Full Text

9. Harrison RA, Gutierrez JM: **Priority Actions and Progress to Substantially and Sustainably Reduce the Mortality, Morbidity and Socioeconomic Burden of Tropical Snakebite.** *Toxins (Basel).* 2016; **8**(12): pii: E351.
PubMed Abstract | Publisher Full Text | Free Full Text

10. Gutiérrez JM, Burnouf T, Harrison RA, *et al.*: **A Call for Incorporating Social Research in the Global Struggle against Snakebite.** *PLoS Negl Trop Dis.* 2015; **9**(9): e0003960.
PubMed Abstract | Publisher Full Text | Free Full Text

11. WHO: **Snakebite envenoming: A strategy for prevention and control**. Geneva: World Health Organization. 2019.
Reference Source

12. Mohapatra B, Warrell DA, Suraweera W, *et al.*: **Snakebite mortality in India: a nationally representative mortality survey.** *PLoS Negl Trop Dis.* 2011; **5**(4): e1018.
PubMed Abstract | Publisher Full Text | Free Full Text

13. Tochie JN, Temgoua MN, Njim T, *et al.*: **The neglected burden of snakebites in Cameroon: a review of the epidemiology, management and public health challenges.** *BMC Res Notes.* 2017; **10**(1): 405.
PubMed Abstract | Publisher Full Text | Free Full Text

14. Ediriweera DS, Diggle PJ, Kasturiratne A, *et al.*: **Evaluating temporal patterns of snakebite in Sri Lanka: the potential for higher snakebite burdens with climate change.** *Int J Epidemiol.* 2018; **47**(6): 2049–58.
PubMed Abstract | Publisher Full Text | Free Full Text

15. Feitosa ES, Sampaio V, Sachett J, *et al.*: **Snakebites as a largely neglected problem in the Brazilian Amazon: highlights of the epidemiological trends in the State of Amazonas.** *Rev Soc Bras Med Trop.* 2015; **48**: 34–41.
PubMed Abstract | Publisher Full Text

16. Chippaux JP: **Epidemiology of snakebites in Europe: a systematic review of the literature.** *Toxicon.* 2012; **59**(1): 86–99.
PubMed Abstract | Publisher Full Text

17. Thomas J, Kneale D, McKenzie JE, *et al.*: **Determining the scope of the review and the questions it will address.** *Cochrane Handbook for Systematic Reviews of Interventions.* 2019; 13–31.
Publisher Full Text

18. Bhaumik S, Norton R, Jagnoor J: **Extended Data Set: Burden and risk factors for snakebite in India: protocol for a systematic review.** *figshare.* Dataset. 2020.
http://www.doi.org/10.6084/m9.figshare.11536776.v2

19. Munn Z, Moola S, Lisy K, *et al.*: **Chapter 5: Systematic reviews of prevalence and incidence**. In: Aromataris E MZ, ed. Joanna Briggs Institute Reviewer's Manual: Joanna Briggs Institute. 2017.
Reference Source

20. Moola S, Munn Z, Tufanaru C, *et al.*: **Chapter 7: Systematic reviews of etiology and risk**. In: Aromataris E MZ, ed. Joanna Briggs Institute Reviewer's Manual: Joanna Briggs Institute. 2017.
Reference Source

21. O'Neill J, Tabish H, Welch V, *et al.*: **Applying an equity lens to interventions: using PROGRESS ensures consideration of socially stratifying factors to illuminate inequities in health.** *J Clin Epidemiol.* 2014; **67**(1): 56–64.
PubMed Abstract | Publisher Full Text

22. McKenzie JE, Brennan SE: **Chapter 12: Synthesizing and presenting findings using other methods.** In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions version 6.0* (updated July 2019). Cochrane, 2019.
Reference Source

Open Peer Review

Current Peer Review Status: ✔ ✔

Version 2

Reviewer Report 14 April 2020

https://doi.org/10.5256/f1000research.25296.r61923

✔ **Abul M. Faiz**
Dev Care Foundation, Dhaka, Bangladesh

The authors revised the article carefully and collected different studies using cutting edge methodology. Though, we are a bit confused for repetition of word in study design mentioned on page no-4. Same on page 6 repetition of subgroup analysis, otherwise the paper is well written and structured. However, in our opinion the paper has some shortcomings with regard to some text but it may be accepted.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 09 April 2020

https://doi.org/10.5256/f1000research.25296.r61924

✔ **Bert Avau**
[1] Centre for Evidence-Based Practice (CEBaP), Belgian Red Cross, Mechelen, Belgium
[2] Cochrane Belgium, Leuven, Belgium

No further comments.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Evidence synthesis methodology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 17 February 2020

https://doi.org/10.5256/f1000research.24174.r58690

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Abul M. Faiz
Dev Care Foundation, Dhaka, Bangladesh
Ariful Bashar
Bangabandhu Sheikh Mujib Medical University (BSSMU), Dhaka, Bangladesh

The objective related to Burden and risk factors are clumped with incidence/prevalence, mortality and morbidity and envenomation; may be provided in more elaboration specially risk factor because adverse outcome and death is not risk factor for envenomation. The authors have reported their work appropriately according to the PRISMA-P checklist.

Eligibility criteria: It should be made clear that all or part of the eligibility criteria will need to be fulfilled. Risk factor is not properly addressed here and authors has no plan for risk modelling. Risk variables are not clear too. I think more emphasis was given on burden. So more clarification and clear objective about risk factor should be mentioned.

Condition: 'irrespective of how it was diagnosed'- is it, that venomous and non venomous bites will be grouped together which will cause problem in interpretation of the results.
Dataset search strategy: It can also include venomous and antivenom as we consider economic burden .

Synthesis of result: It is not unusual to get heterogeneous result due to regional variability and low impact article. So how the authors analyse this heterogeneity should be mentioned.

Health facility burden (page 3): Usually all/most of the patients of snakebite present at the emergency department unless manifested as chronic condition. Definition/clarity is required on 'specialist', 'higher facility', 'compartmental syndrome', 'long term rehabilitation support'. How uniformity among the investigators on decision for ventilatory support, dialysis, blood transfusion will be interpreted. How the individual component of data will be collected.

Study design (page 4): It would not be wise to have a study having no restriction of 'year of publication' to see the burden and risk factors which may change over time.

Risk factors: a list may be developed. 2nd bullet is not clear- snakebite irrespective of envenomation may also be admitted, so admission does not necessarily mean envenomation.
Searching other sources: how the authors will identify 'researchers of repute'.

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Partly

Are the datasets clearly presented in a useable and accessible format?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clinician and Toxicologist

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Author Response 17 Mar 2020

Soumyadeep Bhaumik, PHFI, India

We thank the reviewer for the very useful comments and would like to clarify that we already have two separate review questions and corresponding sections. We elaborate concerns below :

- Burden is conceptualised as incidence/prevalence, mortality, morbidity, health facility and economic
- Risk factors- We agree with the concern about the risk factor and clarify and in lieu of reviewer feedback have revised to include the following two only and removed adverse outcome and envenomation as suggested:
    - Risk factor for a snakebite- this contributed to preventive aspects of bite itself
    - Risk factor for death due to snakebite

Based on the comments, we have reworded the section to provide more clarity.

Eligibility criteria: We have revised the manuscript, to provide more clarity on the eligibility criteria.

Risk factor: We have clarified the objectives for the risk factors as above. We clarify that we do not intend to or plan to do risk modelling as this is a systematic review and not a risk modelling study. Risk modelling cannot be done with summary statistics available form published literature. We have detailed methods for meta-analysis.

Condition: We thank the reviewer for the comment. We have considered this already and since we are conducting a systematic review of published studies, we must use diagnostic definitions as used by primary study authors. Hence the use of irrespective. Primary study authors would classify venomous and non-venomous and their definitions will be used.

Dataset search strategy : We have revised the search strategy to include key words related to snake anti-venom as per reviewer comments. The keywords added in search are :

“anti-venom* or antivenom* or anti-dote* or antidote* or anti-snake or antisnake”

We have not included venomous in the search strategy as it leads to decrease in the sensitivity of the search leading to retrieval of many studies on venomous animals including snake . These are not on snakebites. Any study which has looked at snakebite burden and risk factor will have the word “bite” and will be retrieved from this current search strategy.

The changes are reflected in the dataset.

Synthesis of result: We have now elaborated on this section to clarify that for the purpose of the review will be consider > 40% heterogeneity to be heterogenous

Health facility burden : We agree to the observation that most bites present at emergency department but we do not want to be exclude those who visit clinic/out-patient department, in-patient department, so as to comprehensively report on health system burden, inclusive of for disability/chronic condition resulting from snake bite.

Definition/clarity is required on ‘specialist’, ‘higher facility’, ‘compartmental syndrome’, ‘long term rehabilitation support’: We thank the reviewer but since it is a systematic review of already conducted primary studies, we are going to use the definition as per primary study authors. We cannot control how individual component of data is collected- this may or may not be uniform, but we will collect and report the different definitions /modalities of measurement along with the outcome data.

We chose to put no time restrictions, so as to report change over time.

Risk factors : We have not made an a priori list as we are looking to review all risk factors. This is also not required as this is not a primary study and out search strategy has been made broad to look for all studies on snakebite in India.

We have included admission as part of burden. We conceptualised this as health system burden since both venomous and non-venomous bites need evaluation in a health facility and is hence contributing to health system burden. As mentioned, we are collecting this data for both venomous and non-venomous bites and these will be reported separately.

Searching other sources: We will contact experts as per knowledge of the review team- this is a standard evidence synthesis approach. Detailed number of experts who contributed to identification of newer studies will be provided at full review phase.

Competing Interests: No competing interests were disclosed.

Reviewer Report 04 February 2020

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Bert Avau
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[2] Cochrane Belgium, Leuven, Belgium

The authors of this systematic review protocol aim to map the burden and risk factors for snakebite in the Indian context. To do so, they have composed two separate review questions: one on the incidence and prevalence of snakebite, the other one on the risk factors that may contribute to the burden of snakebite. A systematic review of the existing literature seems an appropriate method to reach their objectives. The authors have reported their work appropriately according to the PRISMA-P checklist. However, several suggestions for improving/clarifying the reporting of their work are made below, especially regarding synthesizing their findings.

The authors include as datasets a completed PRISMA-P checklist and a search string to search for paper in Ovid Medline. These datasets are in my opinion accessible and useable.

Specific points for consideration regarding the reporting of the methods provided:

1) Page 4 - Eligibility criteria for risk factors for snakebite in India:Can you please elaborate as to why risk modelling studies are not within scope of this systematic review? The scope of this review is as I understood broad, summarizing all the evidence on burden and risk factors for snakebite. To my understanding, risk modelling studies may contribute to the scope as set by the authors.

2) Dataset search strategy:
I would search for "envenom*" instead of "envenomation*". This will make sure you also find records that use the term "snake envenoming" instead of "snake envenomation".

3) Page 5 - Synthesis methods for evidence synthesis on the burden of snakebite in India:
Though I agree it may be misleading to pool data from different diverse regions into one national summary, it may be worthwhile to consider whether combining findings from studies from the same (or similar) regions is possible. Therefore I'm not sure whether a priori excluding the possibility of a meta-analysis for incidence/prevalence data is the best option here.

4) Page 5 - Synthesis methods for evidence synthesis of risk factors for snakebite in India:
It is generally not advisable to choose the type of meta-analysis method (fixed or random) a posteriori, based on the observed level of heterogeneity (JBI Handbook section 5.5.8.2 & Cochrane Handbook section 10.10.4.1[1]). Rather, one should consider the underlying assumptions of the two models and decide a priori which method would likely be the most appropriate in relation to the expected type of data. Please address this issue.

5) Page 5 - Synthesis of results:
In case meta-analyses are considered inappropriate, one will need to synthesize the data in another way. Please provide a method for doing this. The guidance by Campbell et al.[2] and Chapter 12 of the Cochrane Handbook[3] may provide valuable input for this.

6) Page 5 - Synthesis of results:
In case a meta-analysis can be performed, it is not unlikely that you will encounter statistically heterogeneous results. Please elaborate on how you will assess heterogeneity (i.e. what will you consider a heterogenous result?). Guidance on this can be found in Chapter 10.10 of the Cochrane Handbook[4].

7) PRISMA-P Item 12:
Although the authors state “a standardised data extraction protocol, developed by adding extra data elements to the JBI recommended minimum standards for data extraction for prevalence, incidence and risk factor systematic reviews” will be used, it is not clear which items the authors will extract. It would be transparent to add an empty copy of this data extraction sheet, to be clear about which data items will be extracted.

8) PRISMA-P Item 14:
The authors need to clarify how they will use the risk of bias assessment during data synthesis.

9) PRISMA-P Item 17:
I disagree that assessment of the body of evidence is not applicable. Several studies will contribute to outcomes, therefore it is useful to assess our overall confidence in the evidence gathered from different studies. I’m not saying the authors should definitely use the GRADE approach for this, but being transparent in how the overall strength of the body of evidence will be evaluated is necessary.

References
1. Cochrane: Fixed and random-effects estimates. 2019. Reference Source
2. Campbell M, McKenzie J, Sowden A, Katikireddi S, et al.: Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. *BMJ*. 2020. Publisher Full Text
3. Cochrane: Chapter 12: Synthesizing and presenting findings using other methods. Reference Source
4. Cochrane: What is heterogeneity?. Reference Source

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Partly

Are the datasets clearly presented in a useable and accessible format?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Evidence synthesis methodology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 17 Mar 2020

Soumyadeep Bhaumik, PHFI, India

We thank the reviewer for the comments on the scope and appropriate methods as well as the suggestions for improvement and clarification has been useful to us for revising the protocol (numbers in response correspond to numbers in query .

1. We thank the reviewer for consideration of inclusion of risk modelling studies. We have followed the guidelines of JBI (Joanna Briggs Institute) for systematic reviews of risk. The guidelines recommend study designs and we have included them : https://wiki.joannabriggs.org/display/MANUAL/7.2.1+Observational+Study+Designs . Risk modelling studies are not recommended study design for inclusion.

A risk modelling study is a statistical procedure for assigning a probability of developing a future outcome. We contend that this is not within the purview of this evidence synthesis as risk modelling studies look into prediction in contrast to cohort or case-control studies.

2. We have now modified the search strategy in the dataset.

3. Thank you for acknowledging that a national pooling might be misleading. We have had considerable discussion on the issue within the team and now looked at the issue of burden being meta-analysed more granularly and made substantial changes to reflect this in the manuscript. The summary of the new analysis for synthesising evidence is provided:
- We conceptualised burden to go beyond incidence or mortality, to mean the following which are reflected as outcomes: incidence/prevalence, mortality, morbidity, health facility and economic. Data from these come from either community based or facility based or autopsy-based studies.
- For incidence/prevalence, mortality and morbidity we will pool data at state level and conduct meta-analysis (if appropriate) in a state-wise fashion (political borders as per Surveyor General of India – May 2020) from community-based studies only. We will not pool data from any facility based studies as data from them will be dependent on patient , health facility and catchment area characteristics implying considerable clinical heterogeneity
- We will not pool data from health facility and economic outcomes and conduct meta-analysis for the same reasons as above. We have provided more information on what will be done when meta-analysis is not envisaged subsequently.

4. We have now elaborated on the section to reflect changes in alignment with suggestion. In summary, we have amended to align with the JBI recommendation of using the random effects model a priori. We will use a fixed-effect approach only if we assess heterogeneity (clinical and methodological and statistical) to be minimal.

5. We have earlier mentioned on Page 5 that we will assess patterns in the data through tabulation of results based on JBI guidelines. We have now taken note of the new Cochrane Handbook and added additional information on analysis methods where meta-analysis is not possible or not envisaged .It is revised to now include information about the structured reporting of results guidelines provided by the reviewer and following approaches will be taken as appropriate for different outcomes. A summary is provide below :

- Summarizing effect estimates to report range and distribution of observed values
- Vote counting based on direction of effect (with on comment on the magnitude of effect) using

harvest plot and/or effect direction plot.
- We will use visualisation tools, as appropriate (harvest plot, effect direction plot, etc).

We have also elaborated on sub-group analysis being done for the same as relevant for different analysis.

6. We have now elaborated on this section to clarify that for the purpose of the review will be consider > 40% heterogeneity to be a “heterogenous result” and have detailed methods used for the same

7. We have further elaborated to mention that the data extraction form will be pilot tested in the first few studies. Providing an empty data extraction form is not required as per PRISMA-P guidelines. We have now put information on the “planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators” as required in PRISMA-P. We reiterate and as noted in out transparency statement, all data will be provided with the systematic review findings.

8. We have clarified further on the use of sensitivity analysis if meta-analysis and how the use the risk of bias assessments will be used during the data synthesis process.

9. We agree that using GRADE to assess overall confidence in evidence would be useful, however GRADE is not an appropriate tool for evidence synthesis for burden and risk factors. GRADE is suitable for interventions and diagnostic test accuracy studies only and GRADECerQUAL for qualitative studies. To the best of our knowledge there are no appropriate approach available for our purpose, for which consensus tool exist.

PRISMA-P is a reporting guideline and not a methodological guidance and we have reported that overall strength of body of evidence will not be assessed in our research and rendering corresponding section in PRISMA-P not applicable.

Competing Interests: None