STUDY PROTOCOL

Burden and risk factors for snakebite in India: protocol for a systematic review [version 1; peer review: 2 approved with reservations]

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Abstract

Introduction: Snakebites are 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 in the case of studies conducted concurrently. We will conduct narrative analyses with the aim of understanding patterns in data through tabulation for both burden and risk factors evidence synthesis. The PROGRESS Plus lens will be used to explore equity pertaining to burden of snakebites. 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 setting, study design, sex/gender, age-groups, tribal people and occupation. A funnel plot will be generated if there are more than nine studies included in a specific meta-analysis, to assess publication bias. Asymmetry of the funnel plot will be adjudged using the Egger, Begg and Harbord tests.
Keywords
Snake Bites, Epidemiology, India, Prevalence, Incidence, risk factor, Health systems, economic costs

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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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Background
Snakebites are a neglected tropical disease, with considerable burden in South Asia, Southeast Asia, and sub-Saharan Africa1. They are known to affect rural, indigenous and economically disempowered communities who lack political voice1,2. 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 provisions3. However, broad consensus is that these numbers are underestimates as many affected by snakebite are ‘out-of-reach’ of the formal health systems4,5. Snakebite envenomation also causes long-term health effects, and is believed to have high social and economic impacts in affected communities6,7,8. Morbidity and socio-economic impact of snakebite is not well understood and remains under-researched globally9,10.

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 snakebite11. Earlier in 2019 the World Health Organization (WHO) released a roadmap which aims to halve by 2030 the death and disability due to snakebite globally12. 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 collaborations13.

More than a third of the global deaths, about 46,000 annually, are estimated to occur in India13 with not much known about other aspects of burden1,2 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 regions14,15,16. 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, envenomation, death, adverse outcomes) 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, envenomation, death, adverse outcomes). Synthesis of evidence for each domain will be conducted and reported separately in alignment with recent Cochrane guidelines17.

Eligibility criteria for evidence synthesis on the burden of snakebite in India
We will include studies that meet 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.

**Burdan Outcomes** –
- **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) community and facility-based studies.
- **Health facility burden** - measured in terms of proportions and/or percentages for the following:
  - 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.

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

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 data18):

- 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 Toxicological 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 reviews19,20. 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.\(^\text{10,20}\)

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.

We will narratively summarise the results of the study. An equity lens will be applied to understand incidence/prevalence, mortality and morbidity equity issues in a granular fashion. We will use the PROGRESS plus framework\(^\text{21}\) 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). We will assess patterns in the data through tabulation of results.

We do not intend to conduct a meta-analysis or any additional quantitative analysis and will present data as reported. In general heterogeneity between studies on prevalence and incidence is known to be common, rendering meta-analysis inappropriate\(^\text{18}\). In addition, snakebite as a condition is known to be localised in nature. As such, pooling of data from heterogenous studies into one pooled 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’\(^\text{16}\).

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

Analysis for each individual risk-factor outcome pair will be conducted separately. If appropriate, meta-analyses will be conducted as per the JBI Guidelines\(^\text{22}\). A random or fixed effects model with a 95% CI will be chosen for the meta-analysis based on the presence of heterogeneity assessed by Tau-squared, Cochran’s Q test and Chi-squared (\(p > 0.05\)) tests\(^\text{20}\). We plan to conduct sub-group analyses for the following, if enough studies are found:

- **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)**

Sensitivity analyses will be conducted, as appropriate, and if enough studies are available, to assess robustness of results but we are not specifying any *a priori* sensitivity analyses in the protocol phase. 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.v1\(^\text{14}\)

This project contains the following extended data:
- **Search strategy snakebite obj1.pdf** (Study search strategy)

Reporting guidelines


Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

References


Open Peer Review

Current Peer Review Status: ? ?

Version 1

Reviewer Report 17 February 2020

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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.

Reviewer Report 04 February 2020

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work is properly cited.

Bert Avau  
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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 10.10.4.1¹). 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 Handbook³ 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 Handbook⁴.

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

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.

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