STUDY PROTOCOL

Burden and risk factors for snakebite in India: protocol for a systematic review [version 1; peer review: awaiting peer review]

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

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. Earlier in 2019 the World Health Organization (WHO) released a road-map which aims to halve by 2030 the death and disability due to snakebite globally. 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.

More than a third of the global deaths, about 46,000 annually, are estimated to occur in India with not much known about other aspects of burden or risk factors in the country. Understanding the epidemiology of snakebites (in terms of incidence/prevalence of bites and envenomation, 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. 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 guidelines.

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.

Burden Outcomes –
1. 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;
2. 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.
3. 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.
4. 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 adaptations of the MEDLINE search strategy developed for this purpose (see extended data):

- 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. 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.\(^6\)\(^,\)\(^2\)\(^0\).

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\(^2\)\(^1\) 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.\(^1\)\(^9\).

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’.\(^6\).

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.\(^2\)\(^0\). 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.\(^2\)\(^9\). 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

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

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