Addressing the burden of snakebite: analysing policy prioritisation, evaluating health systems, and fostering research on treatments

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Addressing the burden of snakebite: analysing policy prioritisation, evaluating health systems, and fostering research on treatments

Soumyadeep Bhaumik

A thesis in fulfilment of the requirements for the degree of

Doctor of Philosophy

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Full Title:	How and why snakebite became a global health priority: a policy analysis.
Authors:	Soumyadeep Bhaumik, Anthony B. Zwi, Robyn Norton, Jagnoor Jagnoor
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The Candidate's Contribution to the Work:	I conceptualised and designed the study which this Chapter contains. During conceptualisation, I obtained feedback from my supervisors. I collected all the data for the study, conducted the analysis, validated the results, and wrote the first draft of the manuscript. I coordinated and incorporated feedback from the co-authors to prepare and submit the manuscript to the journal.
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Publication Details #2

Full Title:	Structural capacity and continuum of snakebite care in the primary health care system in India: a cross-sectional assessment
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Publication Details #3

Full Title:	Effect of COVID-19 containment measures on access to snakebite care in India
Authors:	Soumyadeep Bhaumik, Gian Luca Di Tanna, Deepti Beri, Amritendu Bhattacharya, Pratyush Kumar, Surajit Giri, Maya Gopalakrishnan, Sadanand D Raut, Amol Hartalkar, Sumanth Mallikarjuna Majgi, Jagnoor Jagnoor
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The Candidate's Contribution to the Work:	I conceptualised this study with my primary supervisor and candidate set up the data collection platform and oversaw the data collection process. I conducted the analysis, validated the results, and wrote the first draft of the manuscript. I coordinated and incorporated feedback from the co-authors to prepare and submit the manuscript to the journal.
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Publication Details #4

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Location of the work in the thesis and/or how the work is incorporated in the thesis:	Chapter 5 (Section 5.4)

Publication Details #5

Full Title:	The impact of climate change on the burden of snakebite: Evidence synthesis and implications for primary healthcare
Authors:	Soumyadeep Bhaumik, Deepti Beri, Jagnoor Jagnoor
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Date Accepted/Published:	October 2022
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Location of the work in the thesis and/or how the work is incorporated in the thesis:	Chapter 6 (Section 6.3)

Publication Details #6

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The Candidate's Contribution to the Work:	I conceptualised and designed the study which this Chapter contains, with feedback from one co-author. I developed and ran the search strategies, screened the studies, extracted the data, conducted formal analysis, validated the data, and wrote the first draft of the manuscript. A co-author did independent screening and data extraction, with disagreements resolved by consensus. I coordinated and incorporated feedback from co-authors to prepare and submit the manuscript to the journal. I drafted response and amended the manuscript based on the peer-review comments and prepared the final draft which was published.
Location of the work in the thesis and/or how the work is incorporated in the thesis:	Chapter 7 (Section 7.3)

Publication Details #7

Full Title:	Outcomes in intervention research on snakebite envenomation: a systematic review
Authors:	Soumyadeep Bhaumik,Deepti Beri, Jyoti Tyagi, Mike Clarke, Sanjib Kumar Sharma, Paula R Williamson, Jagnoor Jagnoor
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Location of the work in the thesis and/or how the work is incorporated in the thesis:	Chapter 8 (Section 8.3)

Publication Details #8

Full Title:	Core outcome set for intervention research on snakebite envenomation in South Asia
Authors:	Soumyadeep Bhaumik, Deepti Beri, Vishal Santra, Maya Gopalakrishnan, Mohammad Abul Faiz, Paula R Williamson, Mike Clarke, Sanjib Kumar Sharma, Jagnoor Jagnoor
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The Candidate's Contribution to the Work:	I conceptualised and designed the study, including design and testing of the Delphi survey and platform. I recruited panellists for the Delphi Survey, organised meetings, consultations, and workshops, conducted formal analysis, validated the data, and wrote the first draft of the manuscript.
Location of the work in the thesis and/or how the work is incorporated in the thesis:	Chapter 8 (Section 8.4)

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I confirm that where I have used a publication in lieu of a chapter, the listed publication(s) above meet(s) the requirements to be included in the thesis. I also declare that I have complied with the Thesis Examination Procedure.

Acknowledgments

Over the course of the last few years, punctured with numerous COVID-19 triggered deviations, I have repeatedly thought about how my thesis would finally look like. It is only in the last few months, that I realised it is not the outputs, but the journey, which has enriched me. I am grateful for the support of so many individuals, whose threads intertwined with mine to create a fabric. The fabric now lies bare in the form of this thesis. Like a weaver, I wonder, if the design could have been different, but unlike a weaver, I did not have absolute control of the process. To the extent that I am satisfied with the design of the fabric, I must first thank the research participants, to whom this work truly belongs, and to whom only my accountability and allegiance lies.

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Thesis abstract

Introduction

The World Health Organization (WHO) estimates 5.4 million snakebites annually. In 2019, WHO released a strategy to halve the burden of snakebite by 2030. This doctoral research aimed to generate practice and policy relevant evidence at three levels: globally, by understanding the prioritisation process in the WHO; nationally, in India, by evaluating the primary health care (PHC) system; and regionally, in South Asia, by fostering research on treatments.

Methods

To understand the global prioritisation of snakebite, I conducted a policy analysis, using interviews and documents as data sources.

To evaluate health systems in India, I analysed secondary data for the first nationwide assessment of structural capacity and continuum of snakebite care. To understand health systems resilience, I used quantitative (analysis of facility-level data) and qualitative (interviews) approaches to understand the effects of COVID-19 and conducted an evidence synthesis on the effect of climate change.

Through an overview of systematic reviews of treatments, I identified the need for a core outcome set (COS) on snakebite. I developed a COS for snakebite research in South Asia, by conducting a systematic review of outcomes and a Delphi survey.

Results

The policy analysis identified factors which enabled prioritisation of snakebite, and identified unaddressed challenges of sustaining legitimacy, and acceptance within the neglected tropical disease community.

I identified structural limitations of the PHC system and gaps in referral pathways, in India. Relevant to the context, I report, how COVID-19 accentuated existing barriers, and identified that the choice of provider is a complex process with multiple factors interplaying. Evidence synthesis indicates the need to prepare health systems for possible geographic shifts in snakebite burden due to climate change.

The overview of systematic reviews identified gaps in the evidence ecosystem. By developing a COS for future intervention research on snakebite treatments, I addressed the gap of non-standardised measurement of outcomes.

Conclusion

The findings of the thesis, provides contextually relevant evidence aligned with pillars of the WHO strategy, to practice and policy at global, national, sub-national, and program level. The policy analysis and COS work provides broader methodological insights, beyond snakebite.

Scientific publications part of the doctoral work

Published and accepted manuscripts

1. **Bhaumik S**, Tanna GLD, Beri D, Bhattacharya A, Kumar P, Giri S, et al. Effect of COVID-19 containment measures on access to snakebite care in India. Rural and Remote Health. 2023. Accepted, subject to minor revisions [Chapter 5]
2. **Bhaumik S**, Beri D, Jagnoor J. The impact of climate change on the burden of snakebite: evidence synthesis and implications for primary healthcare. J Family Med Prim Care 2022; 11:6147-58. [Chapter 6]
3. **Bhaumik S**, Beri D, Lassi ZS, Jagnoor J. Interventions for the management of snakebite envenoming: An overview of systematic reviews. PLoS Negl Trop Dis. 2020 Oct 13;14(10): e000872. [Chapter 7]
4. **Bhaumik S**, Beri D, Tyagi J, Clarke M, Sharma SK, Williamson PR, Jagnoor J. Outcomes in intervention research on snakebite envenomation: a systematic review. F1000 Res. 2022 Jun 8; 11:628. [Chapter 8]

Submitted manuscripts

1. **Bhaumik S**, Zwi AB, Norton R, Jagnoor J. How and why snakebite became a global health priority: a policy analysis. Under peer-review in BMJ Global Health. [Chapter 3]
2. **Bhaumik S**, Norton R, Jagnoor J. Structural capacity, and continuum of snakebite care in the primary health care system in India: a cross-sectional assessment. Under peer-review in BMC Primary Care. [Chapter 4]
3. **Bhaumik S**, Beri D, Zwi A, Jagnoor J. Snakebite care during the first two waves of COVID-19 in West Bengal, India: a qualitative study. This is the submitted version of the paper in Toxicon X. [Chapter 6] During the course of the

examination of the thesis, the paper was accepted and published in Toxicon X. It is available here.

4. **Bhaumik S**. Beri D, Santra V, Gopalakrishnan M, Faiz MA, Williamson PR, et al. Core outcome set for intervention research on snakebite envenomation in South Asia. Under peer-review in PLoS Neglected Tropical Diseases. [Chapter 8]

Related scientific publications during the doctoral program, but not part of thesis

1. **Bhaumik S**, Gopalakrishnan M, Kirubakaran R, Jagnoor J. Antibiotics for preventing wound infections after snakebite (Protocol). Cochrane Database of Systematic Reviews 2022;7: CD015114.
2. **Bhaumik S**, Pati S, Kadam P, Di Tanna GL, Jagnoor J. Community based interventions for bite prevention, improved care-seeking and appropriate first aid in snakebite (Protocol). Cochrane Database of Systematic Reviews 2022;9: CD015097.
3. GBD 2019 Snakebite Envenomation Collaborators (**Bhaumik S as collaborator**). Global mortality of snakebite envenoming between 1990 and 2019. Nat Commun. 2022 Oct 25;13(1):6160.
4. **Bhaumik S**, Gopalakrishnan M, Meena P. Mitigating the chronic burden of snakebite: turning the tide for survivors. Lancet. 2021 Oct 16;398(10309):1389 - 1390.
5. **Bhaumik S**, Kallakuri S, Kaur A, Devarapalli S, Daniel M. Mental health conditions after snakebite: a scoping review. BMJ Glob Health. 2020 Nov; 5(11): e004131.

Presentation, lectures, and seminars during the doctoral program

1. **Bhaumik S** [Oral presentation]. Structural capacity for snakebite care in the primary health care system in India: analysis of a nation-wide survey. 21st World Congress of the International Society on Toxinology (IST), Abu Dhabi, United Arab Emirates. October 16 - 20, 2022
2. **Bhaumik S** [Oral presentation]. Snakebite care during the two waves of COVID-19 in West Bengal, India: a qualitative study. 21st World Congress of the International Society on Toxinology (IST), Abu Dhabi, United Arab Emirates. October 16 - 20, 2022.
3. **Bhaumik S**. [Conversation Starter Oral Presentation] Core outcome set for intervention research on snakebite in South Asia. 14th World Conference on Injury Prevention and Safety Promotion. Adelaide, Australia. November 27-30, 2022
4. **Bhaumik S** [Oral Presentation] Policies, legislations, issues, and structural capacity to address snakebite in India. Virtual Pre-Conference Global Injury Prevention Showcase. March 22-26, 2021
5. **Bhaumik S** [Invited Lecture] Snakebite: a public health challenge makings its way to ICUs. It is Common in the Tropics" State of the Art Session. The Intensive Care Society, United Kingdom. 2021
6. **Bhaumik S** [Seminar]. Snakebite and climate change: preparedness for the imminent crisis. Within Seminar on the Need for transdisciplinary systems thinking to address snakebite. The George Institute for Global Health India. 2021

7. **Bhaumik S** [Panel Discussion]. National Snakebite Awareness Summit, Integrated Health and Wellbeing Council, New Delhi. September 2021
8. **Bhaumik S** [Invited Seminar]. Snakebite: a neglected global health challenge. The School of Public Health and Community Medicine, UNSW Sydney. 24th June 2020.

List of courses, workshops, and training attended

1. UNSW (PHCM 9381) Policy Studies: Term 2 2019 (Grade 88/100).
2. UNSW (PHCM 9331) Ethics and Law in Public Health: Term 3 2020 (Grade 83/100).
3. Leadership Foundations Program, UNSW, Australian Higher Education Graduation Statement recognized non-credit program: July 2022.
4. Research Making Impact Program, UNSW, non-credit course: 2022 .
5. Negotiation Strategies for Researchers, UNSW, non-credit course: August 2022.
6. Cochrane Review Author Training [Online] on “Beginning a Systematic Review Protocol” and “Methods Section of the Protocol,” Cochrane UK: November 2021.
7. Cochrane Review Author Training [Online] on “Analysis Methods for Systematic Reviews” and “Advanced Topics in the Analysis and Reporting of Systematic Reviews,” Cochrane UK: November 2021.
8. Ecology: Ecosystem Dynamics and Conservation. American Museum of Natural History, Howard Hughes Medical Institute and offered through Coursera: June 2021.
9. Application of Health Equity Research Methods for Practice and Policy an online non-credit course authorized by Johns Hopkins University and offered through Coursera: June 2020.
10. Introduction to Philosophy an online non-credit course authorized by The University of Edinburgh and offered through Coursera: June 2020.
11. 2nd Annual Implementation Science Research Training School by Global Alliance for Chronic Diseases, Bangkok, Thailand: November 2019.

List of abbreviations

Abbreviations, when used, has been presented in full the first time it has been used in each chapter. Common abbreviations used in multiple chapters are listed:

- COS: Core Outcome Set
- GHN: Global Health Network
- HAI - Health Action International
- ICD: International Classification of Diseases
- MSF- Médecins Sans Frontières
- NTD: Neglected Tropical Disease
- SDG: Sustainable Development Goals
- SR: Systematic Review
- STAG-NTD: Strategic and Technical Advisory Group for Neglected Tropical Diseases
- WHA: World Health Assembly
- WHO: World Health Organization

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1. Introduction

1.1. Background

The Rod of Asclepius (⚕), the most common symbol of medicine, has a single snake intertwined on the staff of Asclepius, the Greco-Roman God of Medicine. [1] The symbol adorns the logo of thousands of medical and health care organisations, including the World Health Organization (WHO) and the World Medical Association. Snakes, as living beings, have been held in awe, fascination, fear, and even loathing, by humans for as long as culture can be traced. Anthropologists have hypothesised that the evolutionary ability to detect and avoid venomous snakes might have played a role in the development of primate brains. [2]

One might think that the problem of snakebite, which has existed from times immemorial, and whose symbolism is so closely related to medicine and healthcare, would by the 22nd century, have ceased to be a public health issue. But that is not the case; snakebite co-exists along with the other omnipresent problem of human society- poverty.

1.2. Snakes and snakebite

Snakes are almost ubiquitous. Except for the polar regions, very high altitude and a few islands, snakes are found everywhere in this planet. There are 3971 species of snakes globally [3] of which around 500 are venomous. These snakes synthesise and secrete highly toxic venoms. [4] The habitat of many venomous snake species is in remote areas where interactions with humans are minimal, if at all. Only 200-250 snake species are

responsible for any deaths or permanent disabilities in humans. [5] [6] Venomous snakes mostly belong to the *Viperidae*, and *Elapidae* family, although some species of *Lamprophiidae* and *Atractraspidae* family are also known to cause envenoming. [4] [7] Only a few snakes in the *Colubridae* family are venomous, particularly those in the genus *Boiga*.

Snakebite envenoming is the clinical condition resulting from the injection of venom from a venomous snake into a human (can also be due to venom being sprayed into the eye by a few species of snakes, which can spit venom). Venomous snakes which commonly cause envenoming are considered to be of highest medical importance by the WHO and categorised as Category 1 snakes. [8] Other venomous snakes, which can cause envenoming, but are less implicated in envenoming, or for which exact data is not available (because of their apparent non commonality), are classified by WHO as having secondary medical importance. [8] A detailed list of medically important snakes, together with distribution maps and crowd-sourced photographs is maintained by the WHO in an online platform(https://snbdatainfo.who.int/). However, not all bites by medically important snakes lead to envenoming. A venomous snake might bite without injecting venom, a phenomenon called "dry bite" (i.e., a snakebite without envenoming). [9] The proportion of "dry bites" varies from species to species, but the pattern is also dependent on several other factors, including but not limited to age, infection of the venom gland, or trauma experienced by the snake. [9] [10]

Snakes deliver their venom through a specialised apparatus which consists [7] of:

- venom gland: which secretes the venom,

- group of compressor muscles (temporalis, digastric, pterygoid, and the anterior temporalis muscle): which control the venom gland,
- venom duct: which connects the venom gland to the fangs, and
- fangs: through which the venom is injected to the tissue of the bitten individual.

Snake venoms are complex compounds- they have varying toxicological and biochemical profiles contributing to a diverse range of clinical manifestations. [7] Toxins within a snake venom provoke systemic and/or local manifestations. [11-17] The spectrum of systemic manifestations, [4 7] which might be seen due to snakebite envenomation include, but are not limited to:

- neurotoxic manifestations (leading to respiratory paralysis),
- nephrological manifestations (kidney injury),
- haematological manifestations (bleeding or thrombosis),
- cardiovascular manifestations (heart rhythm or blood pressure disturbances),
- myotoxic manifestations (generalised breakdown of muscle fibres, called rhabdomyolysis),
- endocrine manifestations (anterior pituitary insufficiency).

In addition, bites may have local manifestations (oedema, pain, necrosis, and compartment syndrome),and in some cases permanent physical sequalae, including but not limited to amputations and chronic wound infections. [18]

While there are tremendous variations, in general, bites from snakes in the family *Viperidae* predominantly induce local effects, haematological manifestations and cardiovascular manifestations, whereas those from the family *Elapidae* predominantly induce neurotoxic manifestations. [4 7] Some species produce unique symptoms. As for

example, envenoming by *Dispholidus typus*, *Thelotornis* spp., *Rhabdophis* spp., *Philodryas* spp. (called non-front fanged *Colubroid* snakes), is characterised by a slow evolution of ecchymosis, haematological manifestations, and acute kidney injury with minimal local manifestations. [4 7]

1.3. Problem statement

Snakebite is a public health problem in many countries. The Global Burden of Disease study estimates, that 63,400 people (95% CI 38,900-78,600), died due to snakebite in 2019, most of them in South Asia. [19] Snakebite envenoming also causes morbidity - both physical (contractures, amputations, chronic infections, malignant ulcers, and blindness) and mental (depression and post-traumatic stress disorder).[20-22] Snakebite primarily affects communities who are underserved and socio-economically disadvantaged: agricultural workers, indigenous people, and those living in rural areas and forests. [7 23 24] These communities often have poor housing conditions, and have limited access to education, health, and social services. Snakebite not only affects socio-economically disadvantaged people, but also pushes people to poverty on account of high treatment costs leading to out-of-pocket expenditure, loss of income and death of primary earners in the family .[18] There is widespread acknowledgement, including by the WHO, that information on mortality , morbidity and socio-economic impacts of snakebite is incomplete and inadequate, thus leading to underestimates. [21 25] There is also a need for the development of a minimum data set and consensus definitions for epidemiological parameters related to snakebite. [25]

In 2017, the WHO designated snakebite envenoming as a neglected tropical disease (NTD),[26] thus providing recognition that action to address the burden of snakebite burden is not commensurate to the suffering it causes. Subsequently in 2019, and

backed by a mandate for member states through a 2018 World Health Assembly resolution, the WHO released a prevention and control strategy to halve the mortality and morbidity due to snakebite by 2030. [25]

The prioritisation of snakebite envenomation within the WHO, a norm-setting organisation in public health, has changed the landscape, with increasing attention and resourcing, for strategies, policies, and programs to address its burden. [7] At the global level, the WHO 2019 strategy [25] identifies four broad pillars of action:

- empowering and engaging communities,
- ensuring safe, effective treatments,
- strengthening health systems, and,
- increasing partnership, coordination, and resources.

Like other NTDs inadequate policy attention, and lack of profitable markets has meant limited investment for snakebite research. The strategy [25] recognises the need for research to address the burden of snakebite, and integrates, research within the pillars of action. In effect, the strategy sets priorities for policy and practice relevant research.

In the pillar for "empowering and engaging communities", [25] the WHO strategy earmarks, the need for qualitative research (to better understand community perceptions on snakes, snakebites and snakebite envenoming), implementation research (to develop and test context-appropriate targeted community-based programs for prevention and risk-reduction, care-seeking), health economics studies (to understand the socio-economic burden of snakebite envenoming in humans, livestock and domestic animals) and snake ecology (to understand the snake-human interface better).

For “ensuring safe effective treatment,” [25] the WHO recognises the need for developing better snake anti-venoms, the only therapeutic agent currently known to prevent deaths and act against systemic manifestations. In recognition, that the broad process for manufacturing snake anti-venom has not changed for decades, the WHO calls for investment in “new and emerging technologies, (that) may revolutionize the treatment of snakebite envenoming…to deliver ‘next generation’ treatments”. [25] Thus, pre-clinical and intervention research (clinical trials) on therapeutics of various aspects of snakebite is a key area of work. Such research should focus not only on acute management of snakebite, but also on management and rehabilitation of chronic sequalae of snakebite.

For “strengthening health systems” the WHO strategy [25] identifies the need for costing studies, economic modelling studies on policy choices, and geographic information services (GIS) enabled studies to inform localisation of health facilities. The strategy also lays down its plan to support research to ensure sustainability of snake anti-venom markets, strengthen logistics-supply chains, and inform development of robust clinical practice guidelines. In addition, it notes the need to foster research on “ecology, epidemiology, clinical outcomes and therapeutics of snakebite envenoming”. [25]

As such, there is a necessity and demand for policy and practice relevant research, across all pillars to support implementation of the WHO strategy and development of policies, strategies, and programs at global, regional, national, and sub-national levels.

1.4. Aim, goals, and objectives of the thesis

1.4.1. Aim

To generate practice and policy relevant evidence, which contributes to reducing the snakebite burden.

1.4.2. Goals and objectives

A. Goal: To map and understand the prioritisation of snakebite in the global health agenda

- A.1. Objective: To understand how and why snakebite became a global health priority leading to the first World Health Assembly on snakebite, followed by the WHO strategy for its prevention and control.

B. Goal: To evaluate health systems in India for provision of snakebite care

- B.1. Objective: To assess structural capacity and district-level adequacy of critical elements for the provision of continuum of snakebite care in the primary healthcare system of India.
- B.2. Objective: To understand the effect of COVID-19 on snakebite care in India.
- B.3. Objective: To understand potential implications of climate change for health systems, through an evaluation of scientific evidence on the impact of climate change on burden of snakebite.

C. Goal: To foster research on safe and effective treatments for snakebite envenomation

- C.1. Objective: To identify gaps in the evidence ecosystems on interventions for management of snakebite envenomation.

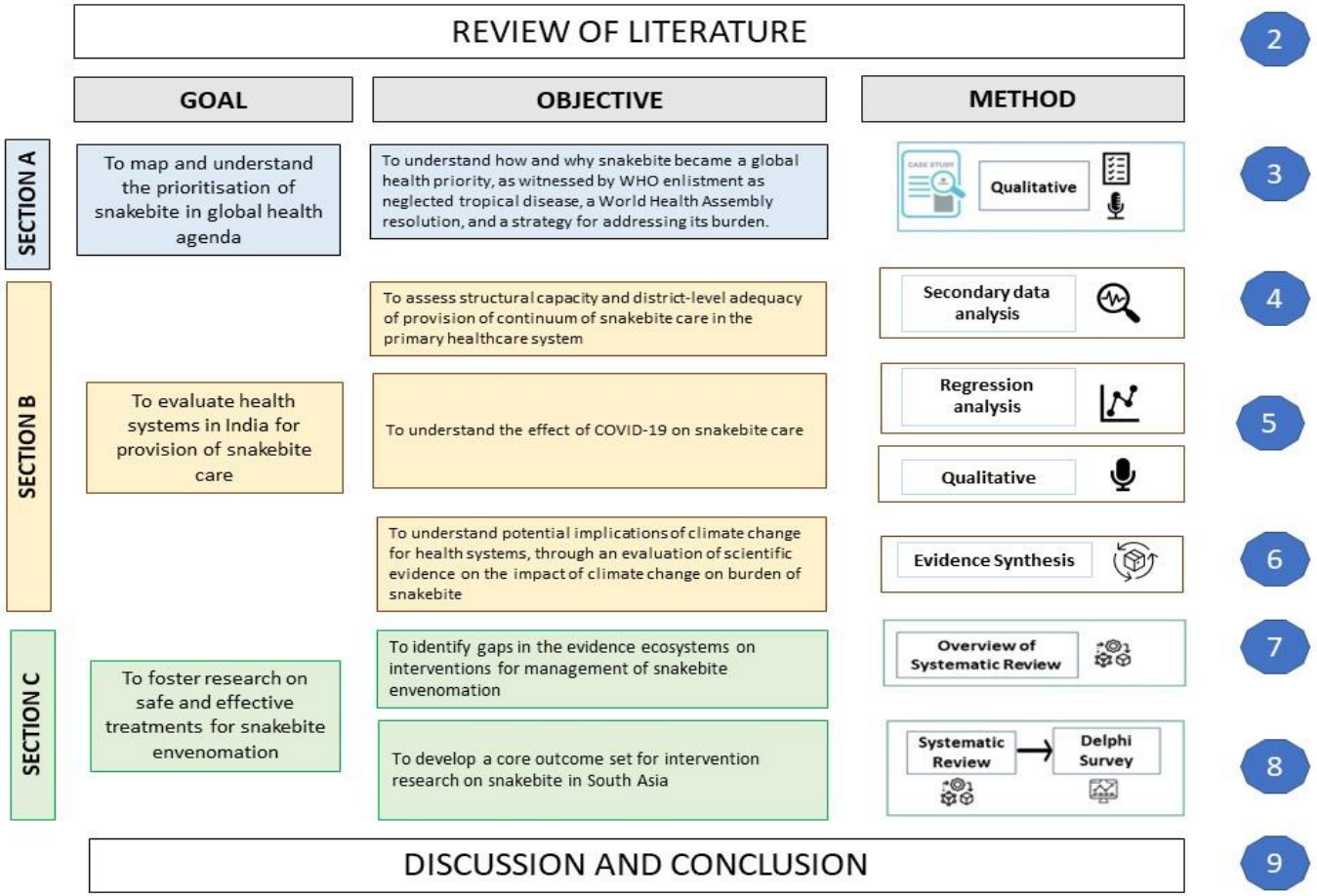
- C.2. Objective: To develop a core outcome set for intervention research on snakebite in South Asia.

1.5. Structure, method, and context of the thesis

My overall aim was to generate evidence to enable strategies, policies, and programs for addressing the burden of snakebite. The research studies are organised into three sections, each representing a thematic stream and corresponding to a specific goal. Within each section are chapter(s), with specific objectives. Each chapter contributes to the one aspect of the goal of the corresponding section and consists of one or multiple manuscripts which have been published or accepted or are under peer review (submitted) in an academic journal.

The thesis, thus, comprises of: a chapter reviewing the literature; 8 manuscripts (4 already published or accepted and 4 submitted), organised within 6 chapters in the 3 sections; and a discussion and conclusion chapter. The formatting and referencing style of different manuscripts is in accordance with the journal in which it is published, accepted, or submitted. The thesis structure is presented diagrammatically in Figure 1 below.

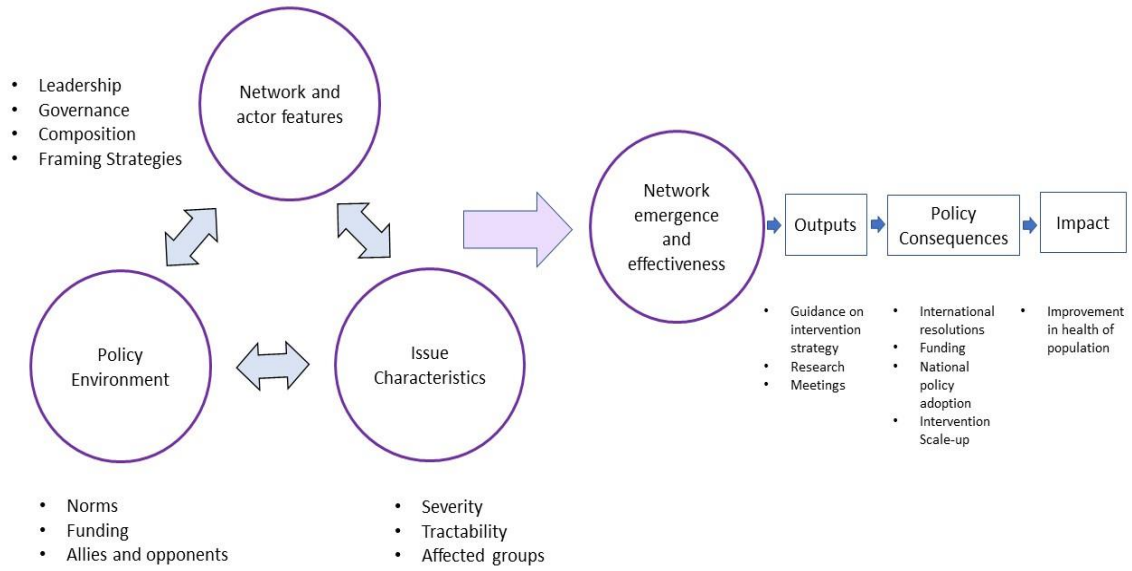
Figure 1: Overview of thesis structure: goals, objectives, methods, and chapters



The review of literature chapter (Chapter 2) provides an overview of the burden and approaches for addressing the burden of snakebite.

In the section A, I aimed to understand how and why snakebite found space in the global health agenda (Chapter 3). This was a good fit for the work as I started my doctoral journey in the backdrop of the Seventy-first World Health Assembly, in 2018, which saw a resolution on snakebite being adopted. In this section, I was guided by work done by Shiffman *et al* [27], on the emergence and effectiveness of global health networks (GHN) in agenda setting. The framework by Shiffman (Figure 2) defines GHN as "cross-national webs of individuals and organizations linked by a shared concern to address a particular health problem that affects or potentially affects a sizeable proportion of the world's population". [27]

Figure 2: Shiffman's framework on the emergence and effectiveness of global health network



(Image developed based on previous work [27] with permission from Jeremy Shiffman)

In the GHN framework, Shiffman [27] intertwines methods from three disciplines - political science, international relations, and health policy, and the framework has its roots based on data from a series of case studies. [28-33] Understanding the political prioritisation of snakebite in the global health agenda, would not only contribute to the emerging body of scholarly work on global health governance, but would also enable navigation of "path dependency" for addressing snakebite. Path dependency is a system thinking concept which refers to processes or decisions in the past, constraints events or decisions later. [34-36] Section A, would contribute to the last pillar of the WHO strategy by providing insights towards "increasing partnership, coordination, and resources" [25] at a global level.

While understanding the priority setting process, enables understanding of policy environment, it is also essential to focus on the approaches for addressing the burden of snakebite, in a contextually relevant manner. For the rest of the thesis, I thus focussed on two pillars of the WHO strategy [25] to reduce mortality and disability due to snakebite by 50% by 2030:

- strengthening health systems, and
- ensuring safe effective treatments.

In Section B, I focussed on "strengthening health systems" for provision of snakebite care in India. I situated this work in India, because it has the greatest number of deaths due to snakebite, and the second highest age-standardised mortality rate globally. [19] The area of strengthening health systems for snakebite has largely been neglected prior to the WHO strategy, with research focus on snakebite being largely clinical. I used

secondary data from a nation-wide facility level to analyse the structural capacity and continuity of care within the public primary health system (Chapter 4). The analysis helps develop a baseline understanding of key issues and gaps with respect to snakebite care across different states of India. I had also planned to develop a health system strengthening intervention, focussing on snakebite, for *Adivasis* (Indigenous people) of Odisha through a research grant that I was awarded in 2020. At that point, such an approach had not been taken for snakebite, anywhere in the world, and I was pleased to get support from the national funder so early in my career. However, with the sudden emergence of COVID-19, the granting agency initially withheld and subsequently withdrew the funding, ostensibly because of changed priorities of the health system (and, perhaps rightly so). While this was a challenge, albeit an unexpected one, it offered me the opportunity to explore more contemporary policy relevant questions, within the constraints of resource available. I chose to better understand health systems resilience for snakebite care. Health system resilience has been defined as the ability to prepare for, manage, and learn, from shocks (sudden, unexpected, and extreme change which impacts health system) and stress (gradual changes which strain health systems).[37-41] Shocks and strain might be due to several factors – disease outbreaks, extreme weather events, economic effects of climate change, human migration and conflict.

I focussed on exploring how COVID-19 and consequent containment measures affected provision of snakebite care through quantitative (exploratory regression analysis of facility-level data), and qualitative approaches (in-depth interviews) (Chapter 5). To understand how health systems need to prepare for climate change, I evaluated the

available scientific evidence on the potential impact of climate change on the burden of snakebite (Chapter 6).

The changed focus of the thesis also opened space for expanding my doctoral work to another pillar of the WHO strategy, thus leading to the work in Section C, which contributes to the "ensuring safe, effective treatment" [25] pillar of the WHO strategy. For this section, I chose to contribute towards conducting research which can foster future research on the domain, an area highlighted in the WHO strategy. Prior to my enrolment in the doctoral program, I evaluated [42] the existing WHO guidelines on treatment of snakebite - by the South East Asian Regional Office (WHO-SEARO) and the African Regional Office (WHO-AFRO). The evaluation [42] found that the guidelines were of low quality, and not aligned with the WHO's own standards for guideline development [43] - specifically the recommendations were not backed by any systematic reviews of evidence. To understand the evidence ecosystem better, I conducted an overview of systematic reviews (systematic review of systematic reviews) on interventions for management of snakebite (Chapter 7). Through this work, I identified several gaps. One of these, was a fundamental problem around non-standardisation and heterogeneity in outcomes, resulting in the inability to compare different interventions for management of snakebite. I filled this gap by developing a core outcome set for intervention research on snakebite in South Asia, the region with majority of snakebite deaths. [19] A core outcome set (COS) is a consensus-derived minimal set of clinical endpoints which are consistently measured by researchers and practitioners for a particular health condition. [44] I used standard methods developed by the Core Outcome Measures in Effectiveness Trials (COMET) Initiative(www.comet-initiative.org). Research conducted to develop the COS for intervention research in South Asia is presented in Chapter 8.

Overall, the three sections are situated at three levels. Section A pertains to policy prioritisation of snakebite is global in nature. Section B, which is on health systems, is situated in India, the country with the highest burden of snakebite. The results of the studies in this section are more pertinent for informing policies, strategies, and programs at national and sub-national level. The findings might be relevant to other settings with similar context. Section C pertains to the global evidence ecosystem, but the flagship work focusses on South Asia (Bangladesh, Bhutan, India, Nepal, Pakistan, and Sri Lanka). Situating the work in a high burden geographic region was essential to not only consider context, but also account for the heterogenous nature of snakebite as a condition. The context in which the primary studies are conducted has been discussed within individual chapters, as relevant.

The concluding chapter (Chapter 9) brings together the work presented across chapters, considering the overall aim and section goals.

1.6. Statement on epistemic reflexivity

Reflexivity is an important part for any research. I have accounted for researcher positionality, and how I mitigated against it in individual chapters, where relevant, thus addressing the issue of critical reflexivity- now a standard practice in qualitative research. [45 46] However, equally, if not of greater importance, is epistemic reflexivity: how a researcher's worldview and values, influence the choice of research question, methods, and the consequent assumptions which come along with it. Being explicit about epistemic reflexivity, is not a standard practice, but, I believe, this is essential, more so when discussing a body of work, as my thesis does. Many researchers perhaps shy away from epistemic reflexivity, to align with the normative of "objectivity" in the

academic community. I seek to be transparent, such that knowledge users can interpret it based on their own world views, and values.

I grew up in rural Bengal, living almost all my childhood within the residential campus of a primary health centre level hospital of a public sector company in India. This meant growing up observing and experiencing the health system and its actors in close range - patients, caregivers, healthcare workers, healthcare managers, trade-union leaders, and the public. Where I grew up snakes and snakebites were a part of life. I heard about countless deaths due to snakebite because people were "late" to reach the military hospital, more than 50 kilometres away, due to "poor awareness". This was what I normalised, the need for community awareness and education to address snakebite. This continued through medical school, and I had then advocated for the legal recognition of the right to health information. [47] My belief then was that a rights-based approach will make the government accountable for increasing awareness. Later in life, as I learnt about health promotion theories and gained wider life experiences through community and policy-oriented work, out of hospitals, I understood that awareness without supportive and enabling structural and environmental changes did not improve health outcomes. In fact, even well-intentioned efforts to increase awareness might lead to unintended harmful consequences and contribute to making healthcare more inequitable. [48] Thus, my initial plan of research in the doctoral program involved developing a health system strengthening intervention for addressing the burden of snakebite. Since things did not work out on those lines, and with the advent of COVID-19, I had to set out to answer other feasible research questions. The change in scope of the doctoral work, however benefitted me, as I became more aware and diligent about reflexivity.

I consider myself as having a pragmatist worldview [49]. My research and its method focus on what is needed to understand and solve a public health problem. I not only choose to answer questions of practical relevance, but also aim to analyse and present data in a manner which potentially increases its value for knowledge users and the public. This worldview has influenced the broad thesis aim of generating evidence, relevant to strategies, policies, and programs for addressing the burden of snakebite as well as specific goals, objectives, and the nature of analysis.

As a start, I wanted to better understand existing practice and policy framings through my research. For this purpose, I needed to understand how and why snakebite was prioritised in the global health agenda. Agenda setting by a norm-setting organisation like WHO has downstream consequences, which as a pragmatist was important for me to uncover. This led to the conceptualisation of Section A of the thesis.

For the other two sections, I used the WHO strategy [25] to inform my choice of research questions. My preference is towards generating practice and policy relevant knowledge, over investigator-driven pursuit of knowledge, supposedly egalitarian in nature. The use of the WHO strategy, as a focal point for identifying research priorities, also offered me the benefit of being able to hold multiple studies into two thematic streams (section B and section C). It also enabled easier communication with a diverse group of collaborators and stakeholders.

In section B, which is on health systems for snakebite care, there is little work done globally. I chose to do work which can provide understanding of the core health systems issues by assessing structural capacity and gaps in continuum of snakebite care (Chapter 4) and then seeking to understand health systems resilience [40 50] by exploring the effect of COVID-19 containment measures (Chapter 5) and climate change (Chapter

6). The most recent nation-wide dataset that is available, is not specifically designed for snakebite, but had the critical parameter of availability of snake anti-venom. This meant I could provide empirical data to ascertain or refute the dominant framing of availability of snake anti-venom as the critical issue in the health system in India. The dataset also predates larger health reforms in primary healthcare system in India, which started from 2019. But a baseline assessment, means there is guiding information for policy makers to rely on, instead of being solely reliant on expert opinion. As a pragmatist, the choice, between not doing the analysis or making of making best use of available data to answer a relevant question, was easy for me.

In 2020, COVID-19 led to lockdowns across India. In my home state (West Bengal, India), there were concurrent extreme weather events: Cyclone *Amphan* in May 2020, and Cyclone *Yaas* in May 2021. The need to focus on health systems resilience was evident. Future health systems need to account for and be prepared for infectious disease outbreaks and climate change. [40 50] But what does that mean for snakebite? This led me to work on the effect of COVID-19 (Chapter 5) and climate change (Chapter 6). My intention, while conducting the analysis in Section B, was always to present data on visual formats, which practice, and policy stakeholders would engage with.

In section C which is on fostering research for "ensuring safe, effective treatments" [25], I started with an evaluation of the empirical evidence base through an overview of systematic reviews (Chapter 7). When I identified the inadequate quality of the systematic reviews on snakebite as an important issue in the knowledge translation pathway, I chose to focus on the issue of outcomes (Chapter 8) in intervention research. It was a fundamental gap in building the evidence base for better treatment of snakebite

envenoming and was achievable within the constraints of resources of the doctoral program.

Overall, COVID-19 triggered the transformation of my doctoral journey from a specific health system focussed project, to exploring ideas across multiple streams, held together with the common purpose of generating research evidence for reducing the burden of snakebite. I believe, though not without pain, that this transformation lends the research presented in the thesis, towards greater impact and contribution of knowledge, than a single health system focussed project, would have perhaps achieved. Additionally, and because a doctoral program, in its essence, is a training pathway, I feel that the transformation, posits me better for practice and policy focussed public health research. As a pragmatist, I see it as developing competencies, for contributing to useable and relevant knowledge, and for collaborating with transdisciplinary teams.

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2. Review of literature

2.1. Chapter overview

The chapter provides an overview of the epidemiology of snakebite, and existing strategies to address its burden of snakebite. It also describes challenges in understanding the true burden of snakebite. Overall, this chapter guided the thesis, including identifying research gaps that were pursued.

This chapter has not been submitted or published.

2.2. Burden of snakebite

2.2.1. Global burden of snakebite

Snakebite is a public health problem in many countries, but as with many other neglected tropical diseases (NTD), burden estimates for snakebite is scarce.

There have been four serious attempts [1-4] to estimate the global burden of snakebite, mostly focussing on bites, envenoming and mortality. These estimates have been summarised in Table 1 and discussed subsequently.

Table 1: Global estimates of the snakebite burden

Studies / Burden Parameters	Bites per year	Envenomation per year	Deaths per year	Permanent sequalae per year	Years of life lost (YLL) per year
Swaroop *et al* 1954[1]	500,000	-	30,000 -	-	-

			40,000		
Chippaux 1998 [2]	5,400,000	2,682,500	124,345	~100,000	-
Kasturiratne *et al* 2008 [3]	1,200,000 - 5,400,000	420,549 - 1,841,158	19,886 - 93,945	-	-
Global burden of Disease Study 2019 [4]	-	-	63,400 (38,900 – 78,600)	-	2.94 million (1.79–3.74 million)

It is important to note that the World Health Organisation (WHO) 2019 strategy document [5] cites the burden of snakebite as: 5.4 million bites, 1.8 - 2.7 million envenomings and 81,000 - 138,000 deaths. The WHO strategy cites a 2017 review, [6] which in turn cites the Chippaux 1998 [2] and Kasturiratne *et al* 2008 [3] papers. While the bites and envenomation numbers review uses the upper limits (and rounds off) for bites and envenomation, for deaths it mentions that they "combined upper estimates of mortality ranging from 81,410 to 137,880 deaths". [6] It is not clear how the numbers for death were arrived at, but it is these estimate that the WHO uses, including in its website.

The first attempt to understand the global burden of snakebite was undertaken by Swaroop *et al* from the then Statistical Studies Section of the WHO, and published in 1954.[1] At that time, the 5th International List of Causes of Death (rechristened now as International Statistical Classification of Diseases and Related Health Problems, and is in its 11th edition), did not have a specific provision for noting snakebite deaths and snakebite deaths were coded within two code categories - 175 (deaths from agricultural and forestry accidents) and 194 (attack by venomous animals) along with "deaths caused by other venomous animals". Although there was no segregated data available

from the ICD (International Classification of Diseases) reporting, many countries in which snakebite was a public health problem officially reported associated bites and deaths due to snakebite. Swaroop *et al* [1] reported continental and national data on snakebite, totalling around 500,000 bites and 30,000 - 40,000 annual deaths globally.

The next serious attempt to assess the global burden of snakebite came more than 50 years later by Dr Chippaux from Niger. [2] The study reported that every year there were about 5,400,000 snakebites, 2,682,500 envenoming and 124,345 deaths, with another 100,000 people suffering from severe sequelae. [7] Majority of the burden was found to be in South and South-east Asia, Africa, and South America, but there was extensive disparity in the epidemiological data between countries. The study however brought to attention the fact that the burden of snakebite was many times higher than what Swaroop *et al* [1] had first reported.

The third global estimate [3] came from researchers in Sri Lanka in 2008, who used data from the WHO mortality database (ICD-10 code X20-deaths due to venomous snakes and lizards), and additional data acquired from Ministries of Health, National Poison Centres, and from grey literature. They estimated 1,200,000 - 5,400,000 bites, 421,000 - 1,841,000 envenoming and 20,000 - 94,000 deaths, due to snakebite, every year. [3] Unlike the previous attempts to estimate the burden of snakebite, the study by Sri Lankan researchers provided methodological details on how they arrived at burden estimate- making the study a landmark.

The latest global estimate on the burden of snakebite is from Global Burden of Disease 2019 (GBD-2019), which estimates 38,900 - 78,600 deaths and 1.79 million - 3.74 million years of life lost (YLL) due to snakebite globally every year. It reports country level information on deaths, age-standardised mortality rate and YLL, and notes that in

terms of absolute terms, India (95% CI 29,600 - 64,100), Pakistan (95% CI 1470 - 2950) and Nigeria (95% CI 977 - 2640) were estimated to have the greatest number of deaths.

Aside from global estimates, data on burden of snakebite are also available at the regional level in sub-Saharan Africa and the Americas from meta-analysis. [8 9] The meta-analysis of studies from sub-Saharan Africa from 1970 - 2010 found 314,078 [95% CI 251,513 - 377,462] envenoming and 7,331 [95% CI 5,148 - 9,568] deaths and 5,908 - 14,614 amputations per year in the region. [9] Out of these about 95% envenoming and 97% deaths occurred in rural areas. In the Americas, meta-analysis by Chippaux found 57,500 snakebites, resulting in about 370 deaths every year. [8] Both the meta-analyses noted wide variation across and within countries.

2.2.2. Burden of snakebite in South Asian countries

Overall, and across all global estimates, there is consistency that South Asia (with India being the highest) has majority of the snakebite burden. This sub-section presents key national level estimations from community-based surveys in South Asia (Table 2). The thesis relates to South Asia, except for Section A, which has a global policy focus. There are sub-national surveys in South Asian countries (such as in Bangladesh, India and in Nepal [10-12]), country-level estimates from the GBD-2019 estimate, [4] and many studies based on hospital data, but they have not been described for brevity. Data from national-level community-based surveys have been summarised and discussed subsequently. There are no nationally representative community-based surveys in Bhutan, Nepal, and Pakistan (last searched December 2022). Overall, there is scarcity of national-level data in South Asian countries.

Table 2: Burden data from national-level community-based surveys in South Asian countries *

Countries / Burden Parameters	Bites per year	Envenomation per year	Deaths per year	Permanent sequalae per year	Years of life lost (YLL) per year
Bangladesh [13] (2007-2008:rural)	589,919	-	6041	-	-
Bhutan	-	-	-	-	-
India [14] (2000-2014 data extrapolated to 2019)	1.11 -1.77 million	0.77 - 1.24 million	58,000	-	-
Nepal	-	-	-	-	-
Pakistan	-	-	-	-	-
Sri Lanka [15] (2012-2013)	80,000	30,000	400	-	-

**Most recent shown when multiple data sources are available.*

In Bangladesh, two large population-based surveys have provided burden estimates on snakebite. A 2003 survey [16] in Bangladesh reported 10.98/100,000 (95% CI 8.88 - 13.44) bites and 1.22/100,000 (95% CI 0.6199 - 2.175) deaths due to snakebite annually. Another study which used data from 2008-2009 reported 623.4 / 100,000 (95% CI 513.4 - 789.2 /100,000) bites annually [13] in rural Bangladesh. Overall, this translates to 589,919 people bitten and 6041 people dying due to snakebite in rural Bangladesh. [13]

In India, two studies [14 17] provide nationally representative estimations of snakebite mortality. The data from these studies arise from the Million Death Study (MDS), in which death was recorded 2.4 million nationally representative households (total of 14

million people) of India between 1998 - 2014.[18] The first iteration of MDS study (estimates based on 2001-2003 data) on snakebite in India reported an age-standardised mortality rate of 4.1/100,000 (99% CI 3.6 - 4.5) nationally. [17] The second iteration of MDS study (estimated based on 2000 - 2014 data, extrapolated to 2019) reported an age-standardised mortality rate of 4.8/100,000 (99% CI 4.4 - 5.0).[14] This corresponds to 1.11 - 1.77 million bites, about 70% of which lead to envenomation, and 58,000 deaths. There were variations in between states, but overall mortality rates due to snakebite had fallen for children (0 - 14 years) and young adults (15 - 29 years), but not for those who are middle aged (30 - 69 years).[14] The Indian Council of Medical Research is currently conducting a survey in 13 states to estimate the burden of snakebite as part of a national task force on snakebite. [19]

In Sri Lanka, a nationwide community-based survey was conducted in 2012-2013.[15] The overall incidence of snakebite found was 398 (95% CI: 356 - 441) / 100,000, envenoming was 151 (95% CI 130 - 173) / 100,000 and deaths due to snakebite was 2.3 (95% CI: 0.2- 4.4) / 100,000.[15] Subsequent analysis of the data from this survey, demonstrated spatiotemporal patterns wherein in certain regions hotspots persisted throughout the year, but in other regions changes in hotspot were seasonal in nature. [20]

Although there are no national level estimates, it is worthwhile to note that the most comprehensive assessment of the burden of snakebite in South Asia is available from the Terai region of Nepal. These studies conceptualise snakebite using a One-Health lens, thus providing estimates for both humans, domestic animals, and livestock. The Terai region study, [21] with a sister site in Cameroon, [22 23] aimed to assess the burden of snakebite in a transdisciplinary manner quantifying and geospatially mapping impact of snakebite on human health, livelihood, and animal health with the intent to develop

predictive models for medical, ecological, and economic indicators as well as geographical accessibility to healthcare. Studies published [24-26] so far show:

- burden of snakebite in humans: 251.1/100,000 bites (95% CI 201.7 - 312.6) and 22.4 / 10, 000 deaths due to snakebite. This extrapolates to 26,749 - 37,661 bites and 2386 - 3225 deaths due to snakebite, annually.
- burden of snakebite in animals: 42 to 202 / 100,000 bites with a morality of 79 - 100% mortality. About 92% of the bites took place inside or around the house or farm in Nepal.

2.2.3. Challenges in understanding the burden of snakebite

Data on snakebite burden (particularly bites and deaths) might be available from various sources, both within and outside the health sector (Table 3), but they do not provide population-level estimates. A key problem of acquiring population-based data on the burden of snakebite is that robust surveys need large sample size, making them costly to conduct. Where population-level estimates are available, it shows that data on bites and deaths, due to snakebite, are significantly underreported in official data. [11 22 27 28] A key reason behind the inadequacy of within health sector data is the preference of traditional healthcare providers over formal health systems. Studies report that traditional health care providers are the first point of care for 86% in Bangladesh, [29] 49.7% in Mali [30], 56% in Nepal [12], 66% in India, [11] and 68% in Kenya [31]. The reasons for preference of traditional health care providers have been studied through qualitative research in Cameroon, Eswatini, Myanmar and South Africa. [32-36] Data sources outside the health sector also have significant limitations. In nations and areas, where snakebite is common, civil registration systems are often weak. For children, adolescents and young

adults, whose death is not linked to inheritance of property, finances or other civil matters, registration of death is poor. Similarly in jurisdictions where snakebite deaths are legally needed to be reported to the police, it acts counter-productively by acting as a barrier to accessing formal health services. Compensation and insurance claim data has many deficiencies, many of them not specific to snakebite. However, there is no research conducted around compensation claims data on snakebite and there exists a knowledge gap.

Table 3 : Sources of data on burden of snakebite (non population-based)

Within the health sector	Outside the health sector
• health information management systems, • health facility admission and discharge data, • health facility death records • ambulance/ emergency services and pre-hospital care data • data from poison control centres or snakebite (or animal bite) helplines.	• government data around vital registration systems, • data from disaster response/ management departments • police data, • records held by forest officials • workplace injury / bite data including worker compensation • government compensations claim • insurance company claims

Apart from deaths, those with snakebite also develop chronic morbidity and disability, including, but not limited to amputation, contractures, chronic ulcers, chronic renal failure, musculoskeletal disorders, and post-traumatic stress disorder. [37-39] Notably, most data sources capture snakebites deaths, and not morbidity or disability. Snakebite usually happens in areas with weak health systems where resource constraints imply

provision of care being accorded higher priority. As such capturing data on types and severity of non-fatal health outcomes, socio-economic effects and disability is not a priority. This is more so if there are high case fatality rates. In India, an ongoing population-based study aims to estimate the community-derived disability weights due to snakebite, [40] which would lay the foundation for more robust morbidity estimations in the future.

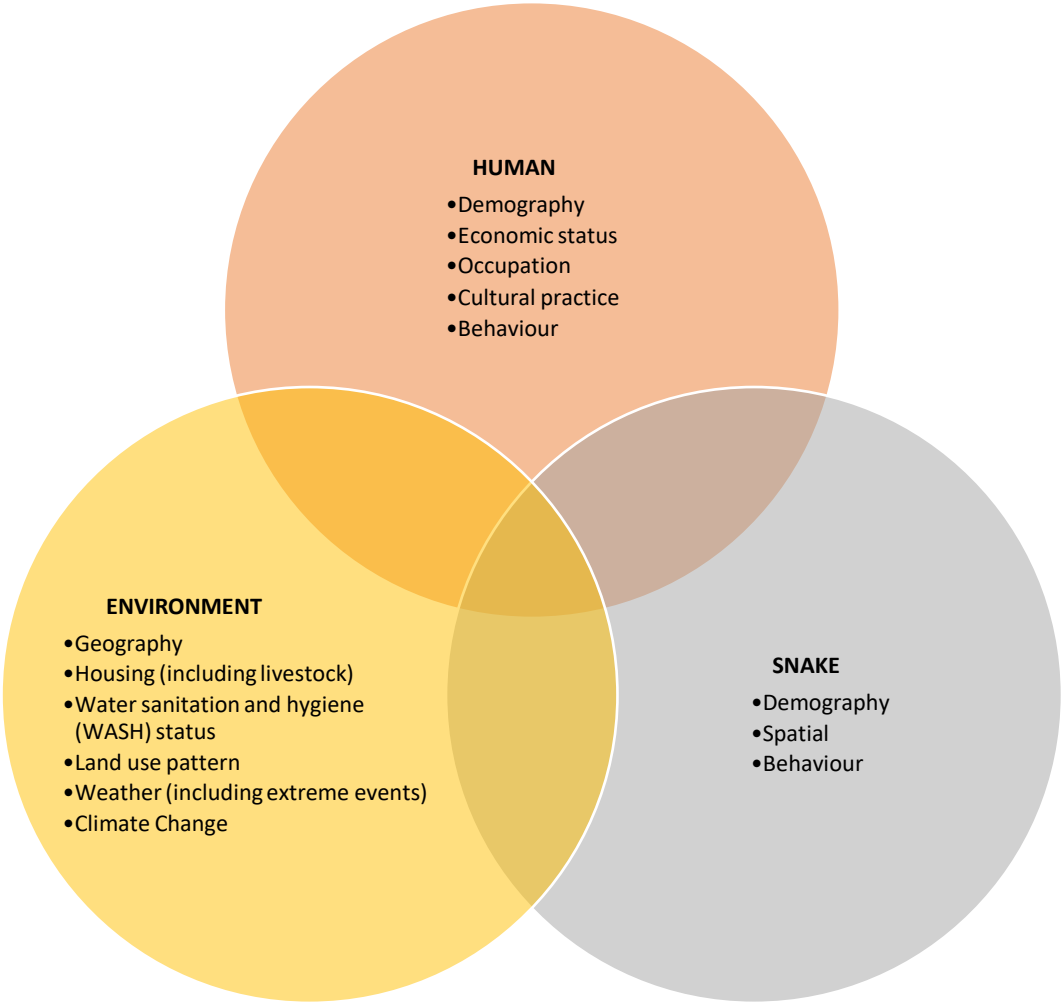
The burden of snakebite is not restricted to humans alone. Although overlooked, the available scant evidence demonstrates not only high incidence but also high fatality rates due to snakebite in domestic animals including livestock. [41] Death of livestock causes mental and economic distress to families, but this has not been quantified. Ongoing attempts in Nepal and Cameroon aim to understand the burden of snakebite comprehensively in humans and animals using a One Health Approach. [24 26]

In summary, there is a need for more robust population level estimates of incidence, mortality, morbidity, and disability due to snakebite in humans, domestic animals, and livestock. Epidemiological work on snakebite was not the primary intent of the thesis, but I contribute to the understanding of how the burden of snakebite might change due to climate change (Chapter 6). Outside of the thesis, I contributed, as a collaborator, on the paper estimating the mortality of snakebite by using data from the GBD-2019 study, which was published in 2022. [4] I also worked on a low-cost method (community knowledge approach) for estimating the burden of drowning. [42] The method, once validated for snakebite, can enable notable change in acquiring robust population-level estimates on incidence, and mortality due to snakebite.

2.2.4. Risk factors for snakebite

For a long time, risk factors for snakebite have been described only in terms of those related to humans. However, there is growing recognition that bites due to snakes are a function of human-snake-environment conflict; snakebite is increasingly being conceptualised in a One Health lens. [26 43 44] The risk for snakebite, is thus a dynamic and complex interaction of several human, snake, and environmental factors (Figure 1). Given the multiple factors in each of domains, the transdisciplinary nature of it, [21 45 46] and because interaction between these elements is context-dependent, [43] the risk for snakebite is not completely understood.

Figure 1: Risk for snakebite: a complex and dynamic interaction of human, snake, and environmental factors



Among the three domains (human, snake, and environment), human factors for snakebites are most studied. Snakebites disproportionately affect people from the lower economic strata of the society. [31 47-53] Children and young adults are known to be at elevated risk of snakebite too. [28 54] It affects agricultural workers - rice paddy farmers,

tea-pickers, fishers[i] (particularly those using hand nets in warmer tropical seas), rubber tappers, cocoa, and sugarcane workers. [12 23 31 55-58] Many occupational deaths due to snakebite, occur in sole income earners. [10 29 31 47 59] Furthermore, in many countries, where out of pocket expenses for accessing formal health services is the norm, acute medical emergencies, like snakebite contribute to sudden family poverty. One community-based study from India reported that 40% of people with snakebite took informal loans to pay for treatment of snakebite; repayment required 17.8% to sell stored crops, 14% jewellery, 9.3% cattle, 5.4% vehicles, 3.9% family land or property, and 3.1% had to remove children from education. [10] As such, snakebite potentially has inter-generational socio-economic effects pushing people to poverty because of loss of income, high treatment cost, and unavoidable loans and debt. A recent review has summarised the vicious cycle of poverty and snakebite. [37] Snakebite is an important cause of death in Indigenous, pastoral, hunter-gatherer, firewood collector, and gypsy (*Romany*) communities. [6 60] The cultural practice around menstrual huts (*Chhaupadi*) in Nepal, has also been associated with snakebite in adolescent girls. [61] Some protective behavioural risk factors for snakebite, documented in the literature or mentioned in guidelines, are appropriate use of protective gear by agricultural workers, cleanliness near house and animal sheds, use of mosquito nets, and not sleeping on the ground. [43 62]

The snake-related factors which influence bite are related to demography (age/sex/ diversity of species in a geographic area), spatial ecology (habitat choice of species, seasonal activity pattern, prey availability) and behaviour of snakes. Detailed description about these factors is beyond the disciplinary scope of the thesis. Snake-

[i] Gender neutral term for fishermen, which is more commonly understood.

related risk factors for snakebite, been comprehensively reviewed, in 2021, by Malhotra *et al.* [43]

Snakes are almost ubiquitous, but bites are most common in South Asia, central and west Africa, and South America where the human-snake interaction is high on account of a shared habitat. However, the risk of snakebite in humans, is not solely dependent on the concurrent sharing of habitat with snakes. Living in housing with poor condition, lack of access to proper water, sanitation, and hygiene (WASH) facilities (both related to poverty), and lack of maintenance of proper standards and cleanliness in livestock shelters are risk factors for snakebite. [28 63] Change in land use patterns, such as agricultural intensification, urbanisation and deforestation are also known to modify the risk of snakebites. Activity patterns of snakes and humans are influenced by seasonal patterns, weather fluctuations, and El Nino, [20 48 64] thus changing the human-snake-environment interface. Because snakes are ectothermic, the risk of snakebite is also expected to be affected by climate change, and consequent extreme weather events. [65] Surge of snakebite cases has been reported immediately after floods, seasonal storm surges and tidal bores. [28] They dynamicity of the human-snake-environment conflict has been described in Malhotra *et al.* [43]

Overall, there remains key gaps in understanding the risk of bites. There is a need for not only more herpetological and ecological research, but also greater transdisciplinary work to better understand the human-snake-environment conflict. Such research can inform mitigation strategies and snakebite prevention programs.

2.3. Approaches for addressing the burden of snakebite

The major approaches for addressing the burden of snakebite, as identified by the 2019 WHO strategy for prevention and control of snakebite [5] are:

- empowering and engaging communities,
- strengthening health systems,
- ensuring safe, effective treatments, and
- increasing partnership, coordination, and resourcing.

Various actions to address the burden of snakebite, under these four approaches, as mentioned in the WHO document [5] is summarised in Table 4, which I further categorised into policy and practice priorities, and research priorities.

Table 4 : Strategies envisaged by the WHO [5] for addressing the snakebite burden

WHO pillars / Priority categories	**Policy and practice priorities**	**Research priorities**
Empowering and engaging communities	• Enhancing community awareness • Engaging communities for burden estimation • Ensuring effective first aid, ambulance transport and pre-hospital care • Improving care-seeking behaviour	• Qualitative research on knowledge, attitudes, practice, perceptions, Socio-cultural, spiritual aspects of snakes, snakebite, and snakebite envenoming • Implementation research on prevention, risk reduction and improvement of care-seeking pathway • Ecological research on human-snakebite interface

Ensuring safe, effective treatments	• Increasing availability, accessibility, and affordability of treatments for snakebite • Improving control and regulation of snake anti-venom (SAV). • Introducing pre-qualification program for SAV • Integrating training packages on snakebite in health worker education and training program • Improving clinical decision-making, treatment, recovery, and rehabilitation • Encouraging investment in innovative research on new therapeutics	• Research on "next-generation" treatments • Research on therapeutics for long-term sequalae • Research to identify clear clinical endpoints for treatment effectiveness • Research to improve accuracy and reliability of diagnostics

Strengthening health systems.	• Strengthening community health services
	• Improving health facilities and service delivery.
	• Including snakebite in national and sub-national health plans.
	• Enhancing monitoring and surveillance mechanisms, including advocating for snakebite being made a notifiable disease
		• Development of
		  ○ minimum data set for assessing burden
		  ○ standardised tools, applications, and software packages, for collection and analysis of data on snakebite envenoming
		  ○ minimum data set, definitions for of common

	• Investing for improving access to snakebite care • Improving capacity of public agencies for better regulation of snake antivenoms • Improving supply chains logistics to ensure antivenom accessibility	epidemiological parameter by WHO and advocacy around its usage. ○ Health economics studies around costing, models for financing and economic modelling to support strategic options for governments • Foster research on the ecology, epidemiology, clinical outcomes, and therapeutics of snakebite envenoming. ** ○ Ecological research on snake-human interactions ○ Geographic Information Services (GIS) studies to develop better understanding of spatial and temporal epidemiology of snakebite ○ Operational research on modalities for a sustainable snake anti-venom market

Increasing partnership, coordination, and resources	• Supporting governance and leadership for snakebite action • Promoting advocacy on snakebite • Enhancing integration, coordination, and cooperation with other public health program • Building strong regional partnerships and alliances • Developing a strong, sustainable investment case for snakebite program • Coordinating data management and analysis.	• Cost benefit and cost-effectiveness studies
**WHO categorises this activity within strengthening health systems, but it is cross-cutting. It does not pertain to health system nor requires a health systems approach.		

2.3.1. Empowering and engaging communities

Prevention of snakebite involves mitigating human-snake-environment conflict. As such, community-based interventions to increase awareness, and promote items (as for example, boots or bed nets) which prevent bites play a key role. Another key challenge is that many communities, there is a preference for traditional healers over formal health systems, for snakebite treatment. [28 32-35 66] Implementation and evaluation of community-based interventions requires consideration of substantial complexity, which practitioners (often with nimble means, supported by small charities with the sole intent of community education, not research) and many researchers do not recognise. Not only

are community-based interventions multi-sectoral, [67] they often have multiple components, which interact with each other, and with behaviours of those delivering or receiving those interventions. To that effect, and outside of the thesis work, I lead the development of a typology and logic model of community-based interventions [62] for snakebite by reviewing key documents and with inputs from researchers, and a practitioner. Community-based interventions for snakebite [62] (detailed in Table 5) might be of several types depending on their primary intent (often multiple). They might aim for:

- preventing snakebite or mitigating snake-human conflict through awareness or education,
- bringing physical changes in home environment to decrease the risk of snakebite or snake-human conflict,
- promoting the use of items which can prevent snakebite,
- improving access to snakebite care for formal health systems (i.e., improving care seeking behaviour), and
- improving community by-stander research and/or first aid for snakebite.

Table 5: Types of community-based interventions for addressing snakebite*

Types of community-based interventions for snakebite	**Definitions**
1. Interventions to prevent snakebite or decrease snake-human conflict, or both	Interventions usually aims to impart knowledge on behavioural change, physical changes in the environment, behaviour of the snake or its prey, the nature of snake-human conflict, its mitigation, and

	the importance of the snake in the environment. This includes but is not limited to health education and awareness campaigns, mass media, social media, or policy changes.
2. Physical changes in the home environment to decrease snakebite or decrease snake-human conflict, or both	Interventions aimed at physical modification of the environment in or around the home and community that can decrease snakebite or snake-human conflict, or both. This includes but is not limited to the following. • Netting of doors and windows by wire mesh or Velcro and in drainage pipes through vent caps. • Trimming of trees, grasses, branches, creepers. • Plastering or filling up of holes, gaps, crevices in dwelling. • Moving cattle, poultry sheds away from main dwelling. • Removal of piles of rubble, cow dung, stacked wood, and building materials. • Use of tight-lid rubbish bins (rodent control). • Maintaining a clear area around house or cattle or poultry shed.
3. Promotion of the use of items that decrease snakebite	Interventions that ensure that people and communities have physical access to items that decrease snakebite (bed nets, shoes, high boots, elevated platform, or beds for sleeping, etc.)

4. Interventions emphasising the use of formal health systems	Interventions that aim to promote the use of formal health systems providing modern medicine services over traditional medicine or spiritual healers when the latter is known to be associated with poorer outcomes.
5. Bystander first aid or community first response	Interventions (like guidelines, training, and education) for community first responders to develop first-aid and basic and life support until medical assistance is ensured.
*used with permission: Bhaumik S et al 2022. [62] All rights reserved John Wiley and Sons.	

Understanding "what" community-based interventions works, in "which" settings, and "why" would also need accounting for other parameters of complexity: the non-linear nature of pathways linking interventions with outcomes, presence of feedback loops, synergies, and phase changes, and evident tailoring and adaptation during intervention implementation. [68-70] Community-based programs on snakebite are not based on health promotion theories, either (Bhaumik S, unpublished results of Cochrane systematic review). [62] Development of community-based intervention needs substantial formative research, followed by co-development of interventions, and subsequent evaluation using implementation research framework. [68 70] There is research aiming to understand knowledge, attitudes and perspectives on snakes and snakebite, in many populations, [27 32 66 71-73] but they are not usually tied to development or evaluation of community-based programs.

It is worthwhile adding that some community-based interventions for snakebite can be integrated with existing NTD programs, because of the potential for shared gains. As for

example, the use of bed-nets, for prevention of malaria, dengue and other vector borne diseases, also provides protection from snakebites. [74] Similarly, improvement in WASH conditions, and interventions to enhance the acceptability and use of formal health systems is expected to provide even wider cross-cutting benefits, across diseases.

In summary, while community-based programs for snakebite are common, there exists knowledge gap (desired research findings do not exist) and population gap (lack of prior research on priority population groups) on perceptions on various aspects related to community-based interventions. There is also a theoretical gap (poor application of theory to generate solutions) in research on development and evaluation of community-based interventions for snakebite.

Outside of this thesis, but conducted concurrent to the doctoral program, I contributed towards addressing the theoretical gap , through development of a typology and logic model for community-based interventions for snakebite. [62] These will also be useful for practitioners and researchers interested in development and evaluation of community-based interventions for snakebite. The thesis did not explicitly aim to conduct research relevant to "empowering and engaging communities" though one qualitative study, which is part of the thesis, (Chapter 5), contributes to contextually relevant understanding of the use of formal health systems in communities.

2.3.2. Strengthening health systems

Once a snakebite, has taken place it is an acute medical emergency- requiring a strong health system capable of providing timely, affordable, quality, and equitable provision of acute, chronic, and rehabilitative snakebite care services. [5 28 75] The health-system response for snakebite begins at the first point of care (ambulance or emergency

services, or health facility, usually primary health centres) and continues thereafter. Health system strengthening for snakebite care would thus focus on the following aspects of continuum of care:

- effective transport to health facility and/or pre-hospital care,
- effective management in health facility, including resuscitation, if required,
- referral to higher centres of care, for management of complications, if any,
- management of complications of envenoming in higher centres, and
- follow-up and rehabilitation.

The only definite treatment for systemic effects of snakebite envenomation, is the snake anti-venom. Snake anti-venom needs to be administered in the first few hours of the bite for achieving optimal outcomes. [76] It is well known that delays in reaching formal health systems, is a major contributor to the mortality and morbidity of snakebite. [77-79] Delayed presentation to health facilities leads to development of complications, including long term sequalae, thus increasing costs and burden to those affected by the snakebite and the systems alike. [10 28] Studies from many high burden countries have documented delays in reaching formal health systems. [22 28 36 80-84] In some contexts, [85 86] those bitten with snakes present on time to health facilities, but there are delay in instituting appropriate treatment – indicating the need for operational research, quality improvement initiatives, and health facility assessments to improve service delivery. A before-after study, conducted in Nepal found that motorcycle- based transport of victims by volunteers to a specialised snakebite treatment centres together with community health education decreased case fatality from 10.5% to 0.5% and bites from 502 bites/100,000 to 315 bites/100,000 population. [87] However, there is not much empirical research on effectiveness of similar initiatives.

Challenge related to human resources for health has also been documented – lack of, or poor availability of health workers, and poor capacity for snakebite management. [28 80 88 89] Tailored training for snakebite management in healthcare workers has been described as critical to address the burden of snakebite. [80 89-91] A small randomised controlled trial found that implementation of a standard operating procedure (SOP) together with a checklist improved some aspects of first aid for snakebite in Chinese military doctors. [92] Empirical evaluation on effectiveness of training programs, using robust study designs is almost absent.

There is a wealth of research around clinical epidemiology of snakebite, including outcomes related to complications, but research evaluating health systems capacity, assessing models of care delivery, quality improvement initiatives is missing. Health facility assessments are one of the key tools for evaluating the status of the health system and strengthening health systems. [93-96] But no assessment of capacity of health systems for delivery of snakebite care exists globally. There are no facility standards or checklists with respect to snakebite care either. National level assessment of capacity of health systems using health facility assessments can empirically prove, or disprove, the dominant proposition that snake anti-venom is the critical gap in snakebite care. Similarly, there is research documenting the need for development of rehabilitation services in areas with high burden of snakebite, [72 97 98] but no research on models of care for delivery of rehabilitation services for snakebite.

In summary, the understanding that snakebite is common in underserved populations, who live in geographic areas with weak health systems. Health systems challenges, include access, coverage, quality, social and financial risk protection, for snakebite care

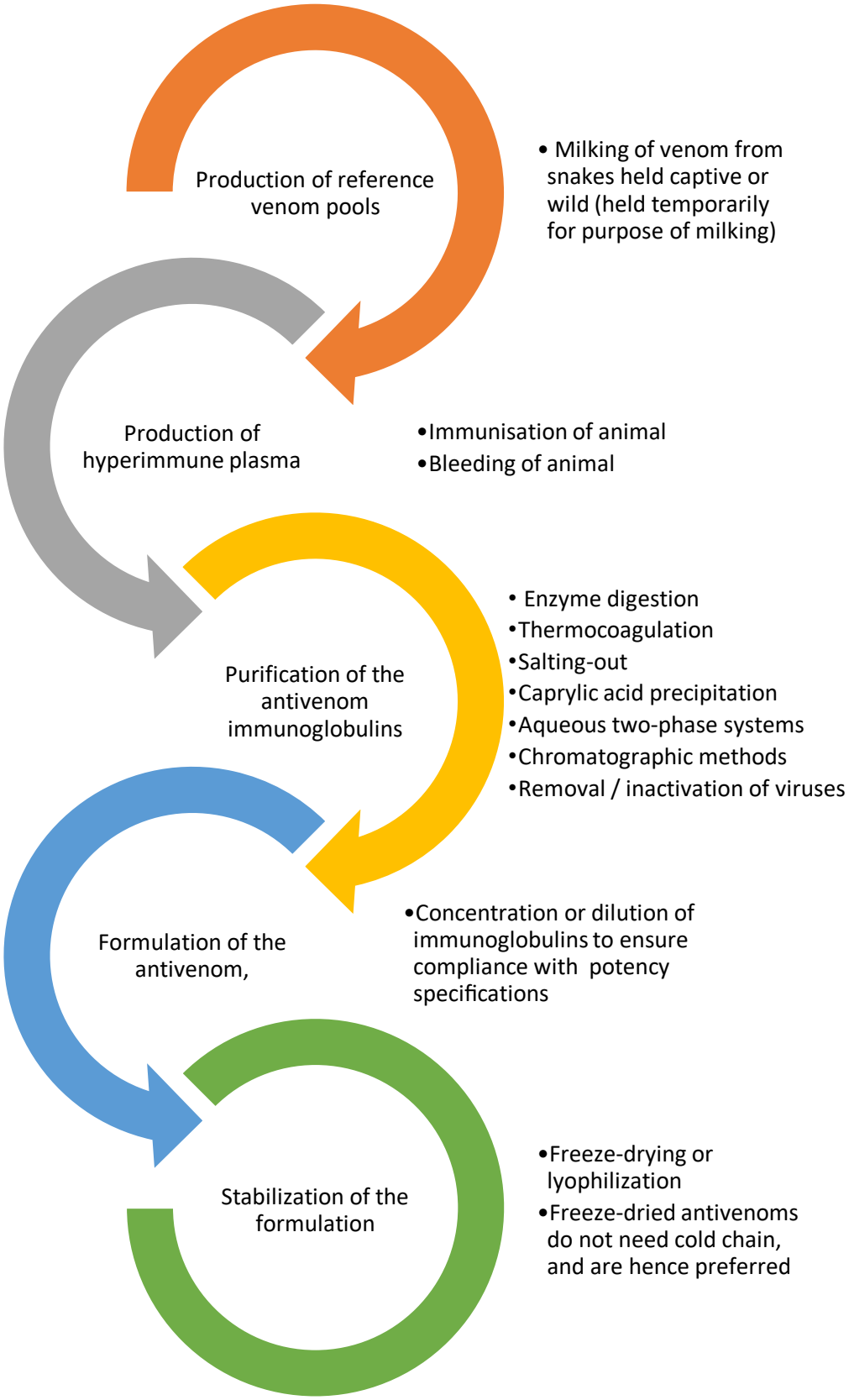
is well recognised, but empirical evidence on several aspects related to health systems is scarce.

In relation to "strengthening health systems" for snakebite care, I conducted a national level assessment of structural capacity and continuum of snakebite care (Chapter 4), and through multiple studies (Chapter 5 and Chapter 6), explored the domain of health systems resilience.

2.3.3. Ensuring safe, effective treatments

The WHO recognises the availability and access for good quality snake anti-venom as a critical component for successful treatment of snakebite envenoming. [99] Snake anti-venom comprises of concentrated immunoglobulins of large, domesticated animals (usually horse, sheep, or camels) who have been hyper-immunized with snake venom over period of months to year. [6] Snake anti-venom is the only antidote to systemic effects of snakebite envenoming. It is manufactured by milking venom from the snake, injecting it a large, domesticated animal (usually horse, sheep, or camels), drawing blood from the animal to separate plasma and subsequent harvesting to separate the immunoglobulin. A detailed review of existing process of industrial manufacturing of snake antivenom is beyond the scope of the thesis but is available elsewhere. [100] The process has been summarised in Figure 2.

Figure 2: Steps for industrial production of snake anti-venom



Apart from resource constraint key issues, which impede access to snake anti-venom, has its roots in aspects related to the manufacturing process:

- **Resource and compliance intensive**: The general scheme and principles for production of snake anti-venom (involving domesticated animals, bloodletting, and purification to extract the anti-venom) remains unchanged for about a century. The process requires monitoring of health of snakes, investing resources for upkeep of their health for compliance with animal welfare laws (for horses or other animals on whom blood is injected). In most jurisdictions, keeping snake captive, and milking venom, need additional permissions and compliance (specific to snakes) under animal conservation and forest laws, to prevent illegal trade around snakes and enable conservation. The resource and compliance intensive nature of production, acts as a market barrier for new manufacturers and for existing manufacturers to scale-up production. [5]
- **Ensuring suitability of reference venom pool**: Unless the reference venom pool which is used for manufacturing the snake-venom is relevant to the geographic area in which it is being marketed, the effectiveness and safety of snake antivenom is compromised. In many countries in Africa, the government buys the antivenom, developed from venom of snake species which are not present in the region, [99 101] i.e., the reference venom pool is foreign. Apart from snake species, it is known there is intra-species geographic variation too. These issues mar countries like India, with huge manufacturing capabilities, but the entire reference venom is sourced from a single snake park in South India, resulting in sub-optimal effectiveness of the snake anti-venom in other parts of India. [102-105] There are gaps in understanding of intra-species variation of venoms, and their impact on clinical practice and outcomes in

many high-burden nations (population gap i.e., lack of research on priority population groups).

- **Quality control:** The complex process implies that there is a need for regulators to enforce compliance with appropriate Good Manufacturing Process (GMP). However, in many countries with high snakebite burden, capacity of regulatory and enforcement agencies for quality control of snake antivenoms is limited. [99]

The challenge around overcoming the resource and compliance intensive nature of the current production process of snake anti-venom is research dependent. There are newer technologies available, which can potentially contribute to solving the problem. The WHO strategy [5] thus calls for investment in research on "next-generation" treatments (addressing theoretical gaps in research). Pre-clinical research on the use of "small molecules" for treatment of snakebite envenoming [106-109] also shows promise. Research to develop therapeutics for long-term sequelae of snakebite envenomation, is also an area of neglect.

Suitability of reference venom pool and quality control can be addressed by policy levers, which the WHO, has by 2022 already made substantial progress on:

- Development of Target Product Profiles (TPP) to function as reference standards for manufacturing. TPP are minimum specifications for antivenom products, manufactured for a well-defined geographic area and purpose (e.g., a standard for an antivenom with broad-spectrum coverage against a range of snake species).[99] Capacity building for regulatory and enforcement agencies in high-burden nations on the use of TPPs is also necessitated.

- Initiation of WHO pre-qualification program for snake antivenom. Such a process would enable purchasers, donors, and end-users be confident that a product they are buying, is suitable, safe, and effective in the intended context of use.

The WHO strategy for addressing the burden of snakebite, earmarks the need for fostering research on "clinical outcomes, and therapeutics of snakebite envenoming", within the pillar of "strengthening health systems." [5] However, it is a better fit in the "ensuring safe, effective treatment" domain. Research on clinical outcomes and therapeutics neither pertain to health systems, nor do they require the use of health systems approach. Pre-clinical research, and clinical research around existing diagnostics and therapeutics is also limited. There is also need for research to improve clinical decision-making, treatment, recovery, and rehabilitation.

Overall, research gaps for ensuring safe, effective treatment for snakebite are: use of next generation technologies to develop snake anti-venom (theoretical gap), development of newer therapeutics and diagnostics (knowledge gap), research on existing diagnostics and therapeutics (knowledge gap and population gap), and research to improve clinical decision-making and to improve outcomes (for treatment, recover and rehabilitation) for those affected by snakebite.

In the thesis, I focus on conducting studies which contribute to fostering research on snakebite treatments (Section C). The genesis of the work done in this section was a pre-doctoral work, where I evaluated the WHO guidelines on snakebite, to find that recommendations within the guideline were not supported by evidence from systematic reviews. [110] To get insights for what research can contribute to address fundamental

gaps in the evidence ecosystem for snakebite, I conducted an overview of systematic reviews on interventions (Chapter 7). Subsequently, I filled one of the identified gaps of non-standardised measurement of outcomes (Chapter 8).

2.3.4. Increasing partnership, coordination, and resources.

The objective around increasing partnerships, coordination, and resources in the WHO strategy [5] is an enabling objective to support the successful integration and implementation of other approaches for addressing the burden of snakebite. The inclusion of this as a separate pillar, indicates understanding of the need for focussed strategic work for greater visibility and recognition of snakebite envenoming, a disease which has only recently come in the global health agenda. Broadly, the strategy aims to support governance and leadership to integrate snakebite envenoming within universal health coverage and SDG agenda. The WHO strategy [5] identifies the need for cost-effectiveness and cost-benefit research for developing investment case for snakebite programs.

While the strategy does not so, but health policy research can contribute significantly for development of strategies to enhance partnership, co-ordination, and resource sharing. The global policy analysis (Chapter 3) provides insights on how partnership and co-ordination for the cause of those affected by snakebite can be enabled. Health economics studies were not under the purview of the thesis.

2.4. Conclusion

Overall, practice and policy relevant research pertaining to the different approaches for reducing the burden of snakebite, is scant. Most research so far has primarily

contributed to identifying and defining the problem but significant knowledge gap, and population gap, mapping to all the four approaches to address the burden of snakebite remain. There is empirical gap (gap in empirical evaluation of propositions) in knowledge which maps to research relevant for "health systems strengthening" [5] and "ensuring safe, effective treatment," [5] and theoretical gaps (poor application of theory to generate solutions) in knowledge on approaches to "empowering and engaging communities." [5] Economics and policy research to increase partnership, co-ordination and resource sharing is also a significant research gap.

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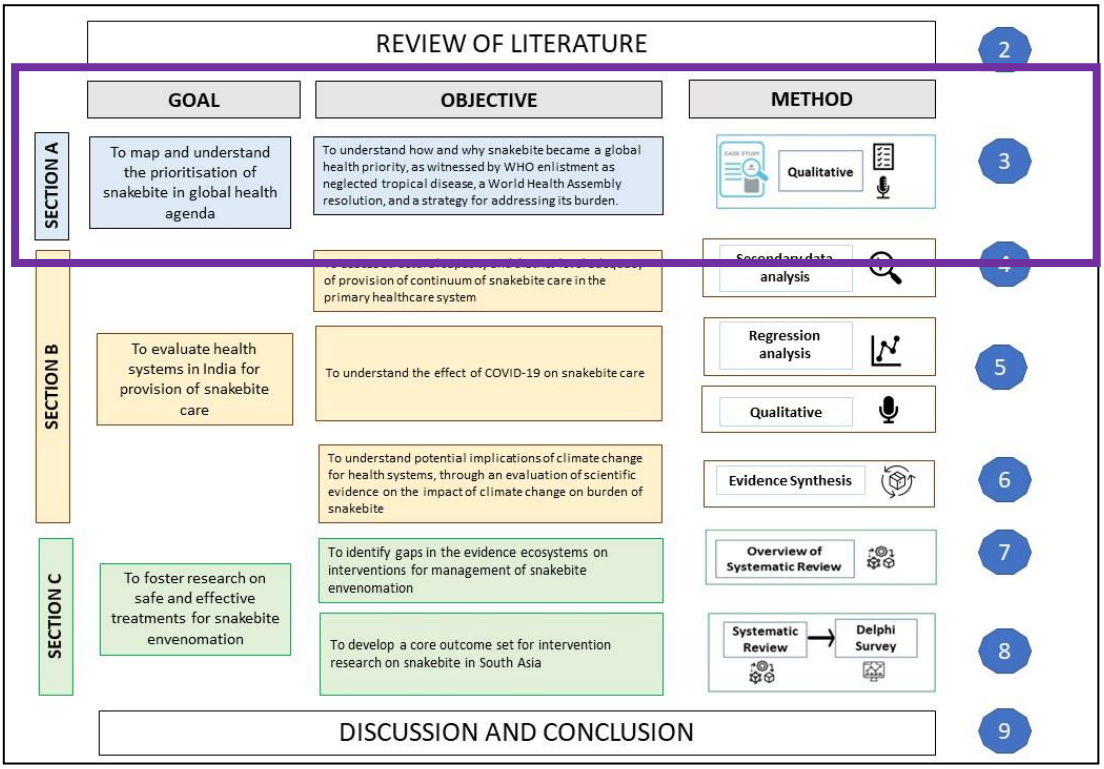
Section A: The prioritisation of snakebite in global health agenda

"Propaganda is a soft weapon: hold it in your hands too long, and it will move about like a snake, and strike the other way"

~Jean Anouilh, French dramatist (The Lark)

In this section, I attempt to get clarity on the agenda setting of snakebite in the global health space, with a view of unpacking the "soft weapon."



3. Understanding how and why snakebite became a global health priority

3.1. Chapter overview

In this chapter, I present a policy case study to understand the process of prioritisation of snakebite in the global health agenda. The policy analysis makes a valuable contribution to the larger aim of the thesis, of generating practice and policy relevant work on snakebite. Understanding the global policy framing and process around WHO, a norm setting organisation in global health, is crucial for future work on snakebite. On a broader scale, and beyond snakebite, it adds to emerging literature on global health governance around agenda setting.

This chapter is the **submitted** version of the article

- **Bhaumik S**, Zwi AB, Norton R, Jagnoor J. How and why snakebite became a global health priority: a policy analysis. [Under peer-review in BMJ Global Health]

3.2. Candidate's contribution to the work

I conceptualised and designed the study which this Chapter contains. During conceptualisation, I obtained feedback from my supervisors. I collected all the data for the study, conducted the analysis, validated the results, and wrote the first draft of the manuscript. I coordinated and incorporated feedback from the co-authors to prepare and submit the manuscript to the journal.

3.3. Submitted manuscript

How and why snakebite became a global health priority: a policy analysis

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Abstract

Background

In 2018, the World Health Assembly passed the first resolution [WHA 71.5] on snakebite, subsequently leading to an explicit global target being set for reducing its burden. We aimed to understand how and why snakebite became a global health priority, with a view to identifying the barriers to sustaining its prioritisation.

Methods

We conducted a policy case study, using in-depth interviews, and document as data sources. We drew on Shiffman et al' s framework on the emergence and effectiveness of global health networks to guide the analysis.

Results

We conducted 20 interviews and examined 91 documents. We found that policy prioritisation of snakebite occurred in four phases: pre-crescendo, crescendo, de-crescendo, and re-crescendo. The core of the snakebite network consisted of an academic epistemic community, but the network expanded during the re-crescendo phase to include civil society organisations and state actors. The involvement of diverse stakeholders led to better understanding of World Health Organization (WHO) processes, wherein funding and state actor support is crucial. The use of intersecting and layered framing of the issue, and framing solutions around snake anti-venoms, in a background of cross-cultural fascination and fear of snakebite further enabled prioritisation in the re-crescendo phase. Ebbs and flows in establishing legitimacy of the snakebite network, and reluctant acceptance of snakebite within the neglected tropical diseases community are unaddressed challenges.

Conclusion

Our analysis implies a fragile placement of snakebite on the global policy agenda and identifies two ongoing challenges. It also indicates the need for revisiting the WHO criteria for designation as a neglected tropical disease, which reinforces biomedical discourse on diseases. We suggest that future analysis of prioritisation consider discerning temporal patterns (like the four crescendos, in our case), and incorporate three intersecting but distinct dimensions of legitimacy.

Summary box

What is already known on this topic

- Snakebite has attracted attention in the World Health Organization (WHO): in 2018 the World Health Assembly resolution on snakebite [WHA 71.5] led to a global strategy in 2019 an explicit global target to reduce the snakebite burden by 50%.

What this study adds

- We document and analyse the fluctuating priority accorded to snakebite in WHO over time and describe the pre-crescendo, crescendo, de-crescendo, and re-crescendo pattern of prioritisation
- We identify ebbs and flows in establishing legitimacy of the snakebite network, and reluctant acceptance of snakebite within the neglected tropical diseases (NTD) community as unaddressed challenges.

How this study might affect research, practice, or policy

- Inclusion of wider base of proponents, with leadership from endemic nations, and re-orienting investments towards community-based programs and health systems strengthening, might enhance the legitimacy of network and promote acceptance of snakebite within the NTD community.
- There is a need for revisiting the WHO criteria for designating a NTD, which reinforces existing biomedical discourse on conditions.
- Future policy analysis on global health priority analysis, should explicitly consider discerning temporal patterns (like the four crescendos, in our case), and incorporating the three intersecting but distinct (issue, actors, network) aspects of legitimacy.

Background

Snakebite is a global public health problem with heightened incidence in several countries. The World Health Organization (WHO) estimates 125,000 global deaths are due to snakebite, annually. [1] Most deaths occur in South Asia and Africa. [2-4] In 2017, the WHO added snakebite to its list of neglected tropical diseases (NTD), thus recognising its public health impact. [5 6] This was followed by the 2018, 71st World Health Assembly (WHA) resolution [WHA 71.5] on snakebite, and the subsequent launch, in 2019, of the associated WHO strategy to halve its burden by 2030. [2 7-9]

This study aims to understand how and why snakebite became a global health priority, as witnessed by WHO enlistment as NTD, a resolution, and a strategy for addressing its burden. Understanding the process of prioritisation is important because WHO sets the normative boundaries within which global health actors act, and influences issue conceptualisation. [10 11] We conducted this study with a view of understanding the enablers and barriers for sustained placement of snakebite on the global health agenda. The study is also of relevance to advocates of other neglected and emerging public health problems, seeking to find a place in the contested global health space.

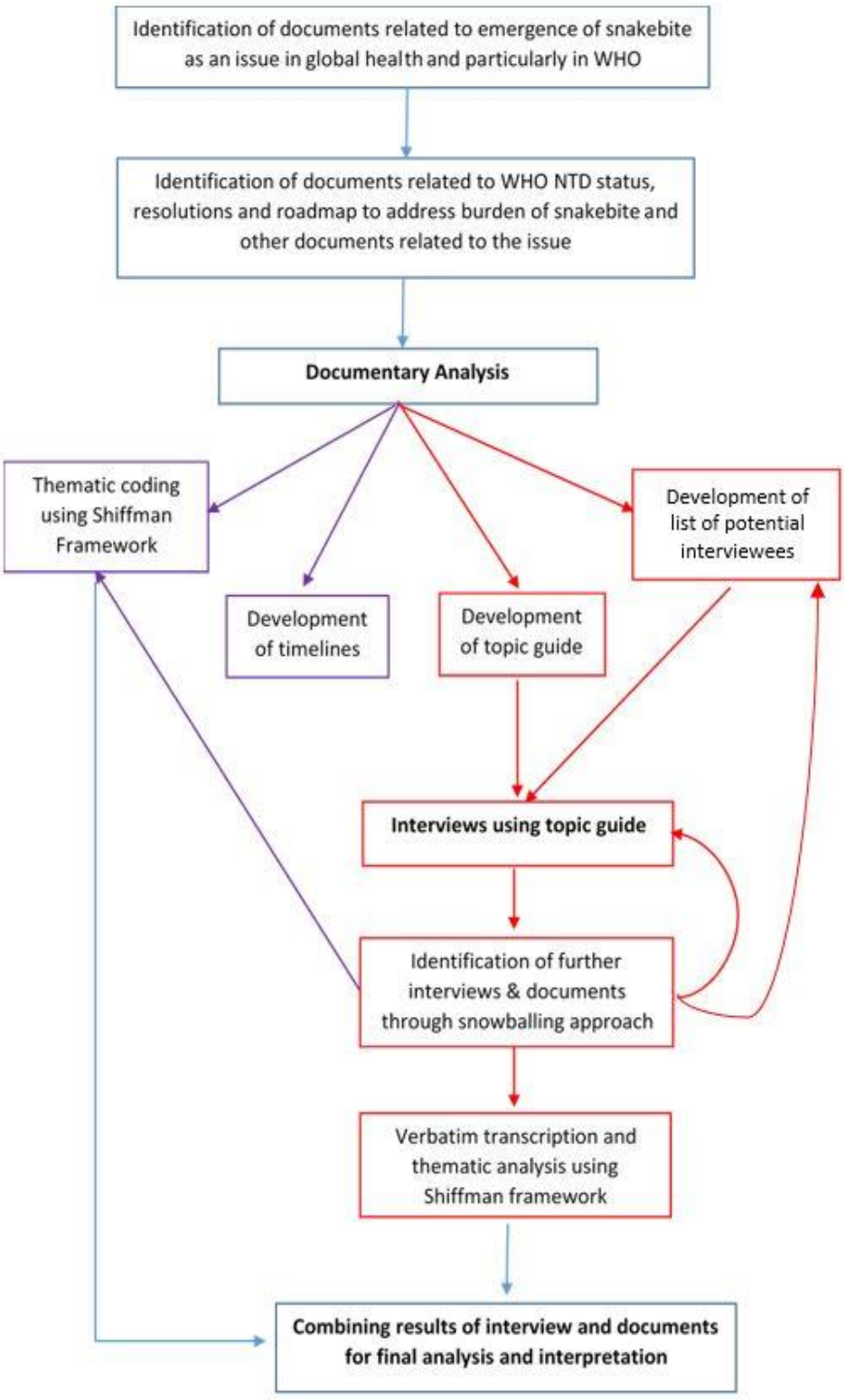
Methods

Study design and approach

We conducted a policy case-study [12] and employed the process-tracing (outcome-explaining) methodology. [13] Outcome-explaining process tracing is a case-centric approach which aims to craft sufficient explanation of a historical process. [13] Broadly,

we qualitatively analysed data from in-depth interviews of stakeholders and documents (summarised in Figure 1).

Figure 1: Schematic diagram showing the methodological approach and study design



We used Shiffman et al' s framework on the emergence and effectiveness of global health networks (GHN)[14] for this purpose. The framework defines a GHN as a "web of individuals and organisations linked by a shared concern to address a sizeable portion of the world's population." [14] It identifies three categories of factors (issue characteristics; network and actor features; policy environment) which influence the emergence and effectiveness of GHNs. We drew on Shiffman' s GHN framework, [14] based on our *a priori* knowledge that subsequent to the removal of snakebite from the WHO-NTD list (2015), a network of non-state actors was advocating for snakebite during 2015-2019, resulting in a WHA side-event, a WHA resolution, and a WHO strategy on snakebite (2019). [2 9] We set a temporal boundary of 2015-2019 but were flexible to accommodate earlier events and activities of relevance to our period of interest.

Data sources

We examined relevant documents and conducted in-depth interviews.

Document analysis

We searched for documents (reports, meeting notes, press releases, opinion pieces, academic articles, newsletters), which were issued/authored by WHO (headquarters, committees, or divisions), governments, non-state actors and global health funders, related to the prioritisation of snakebite, and/ or were related to emergence or effectiveness of the network.

We searched electronic databases (PubMed and WHO-IRIS), and hand searched websites of organisations identified as playing a role in the WHO prioritisation process. Details of the search strategy and websites searched is presented in **Appendix 1**.

Additional, documents referred to, or provided by participants were also included in the analysis.

In-depth interviews

We conducted in-depth interviews with people who met any one of the following criteria:

- WHO staff, representatives of member states, ministries who participated in sponsoring WHO/ WHA events or resolutions, in any capacity.
- Non-state actors involved in the WHO process, in any capacity.

We employed a purposive sampling strategy. All interviews were conducted online in English by the lead investigator (SB) using a topic guide which consisted of mapping questions, broad open-ended questions, and specific probes. An iterative and inductive approach was adopted with the initial topic guide modified, as additional aspects and issues emerged. We drew on the evolving understanding of the issue from documents and other in-depth interviews, to add, remove or modify probes, thus customising questions for a particular participant. No fixed order of questioning was followed. We did not aim to resolve disagreements among different participants, but rather attempted to understand the diversity of views and the rationale for these differences.

Analysis

All interviews were transcribed. Where relevant, we asked for clarifications by e-mail, post-interview. We sought to minimise bias by triangulating across multiple data sources and informants. For large documents or documents where snakebite was only mentioned in a segment, we coded the relevant section or the executive summary. An

iterative modality was used, with the lead researcher (SB) initially coding data based on Shiffman et al' s 2016 framework [14], pausing, reflecting, discussing with other authors, and making reflective notes, to ensure consistency and prevent bias. We also took particular care to identify codes, and aspects which did not fit into the framework.

Ethics

The study was approved by the institutional ethics committee of UNSW, Australia (HC 210040) and informed consent was obtained.

Research team reflexivity

Our multi-national, research team comprises of outsiders to the process studied. The disciplinary background of team members includes medicine, international public health, social science, global development, and injury research. All researchers have experience in qualitative research, including policy research and practice.

Patient and public involvement

Patients and members of the public were not involved in any aspect of the study.

Results

Documents and in-depth interviews

We initially retrieved 924 documents, of which 91 were included in the final analysis (flowchart showing selection of articles and full list of documents included is available in **Appendix 2**). We also coded the documentary screened at the WHA side-event. [15]

We conducted in-depth interviews with 20 people, for an average duration of 65 minutes (36-104 minutes). One other informant did not give an interview but provided multiple documents. Summary characteristics of the participants are presented in Table 1.

Table 1: Summary characteristics of study participants

Country	• Snakebite endemic :7
	  ○ Asia: 4
	  ○ South America: 1
	  ○ Africa: 1
	  ○ Oceania: 1
	• Snakebite non-endemic: 13
	  ○ United Kingdom and Europe: 9
	  ○ North America: 4

Gender	• Male :14 • Female: 6
Constituency	• Academics: 11 • Non-academics: 9
Affiliations	• NTD and other WHO departments [names redacted to prevent deductive disclosure]: 3 # • Funders: 2 • *University / Academic Institutes [names redacted to prevent deductive disclosure] in Australia, Bangladesh, Costa Rica, France, India, Sri Lanka, USA, UK :11 # • *Non-profits [names redacted to prevent deductive disclosure]: 2 • *Health Action International: 2 • *Medicine Sans Frontiers: 2 #Some persons moved between organisations.

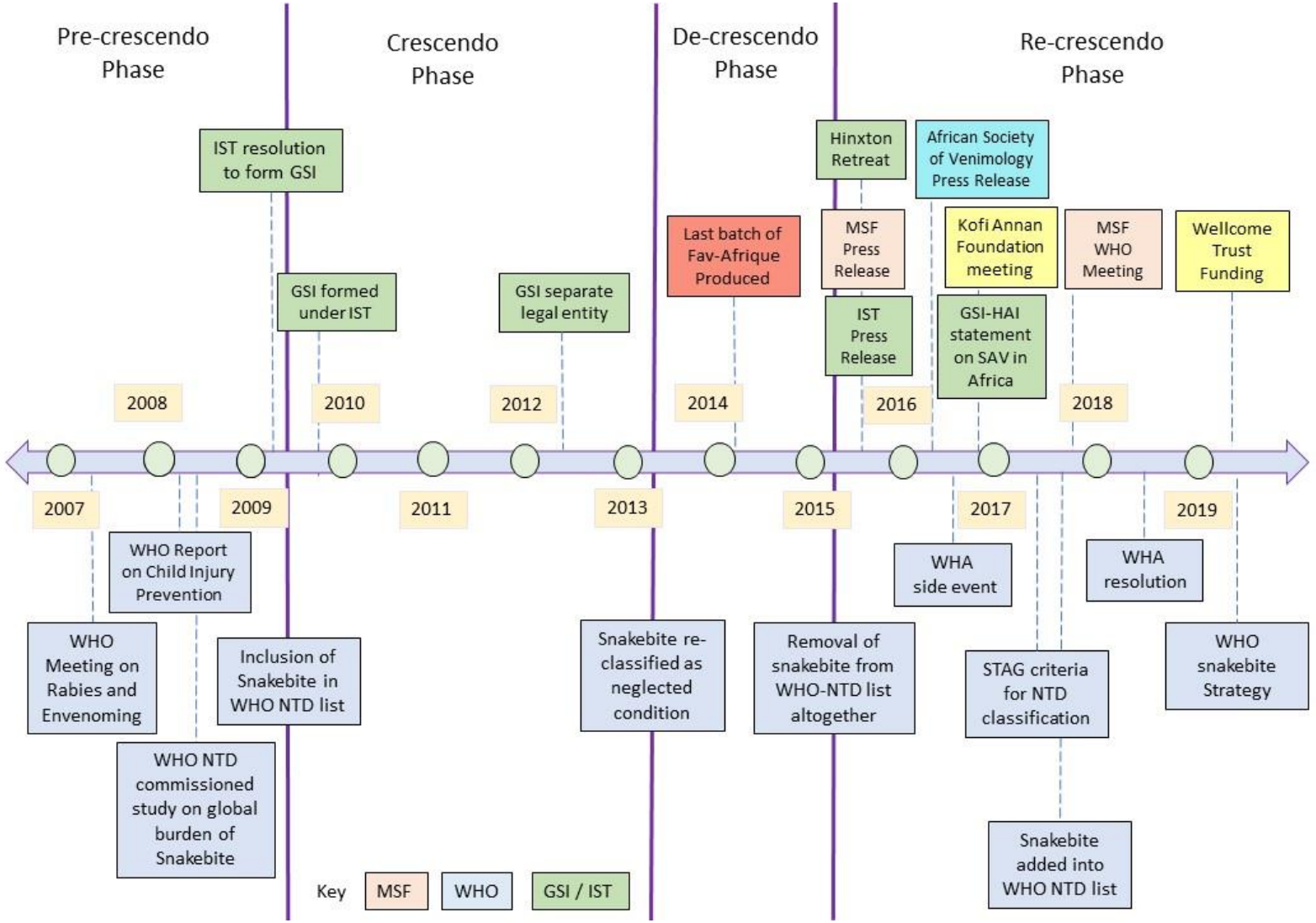
	* Participated in key events, formally engaged held positions at Global Snakebite Initiative representative and/or played key role in WHO process (development of technical dossiers for WHO, WHA resolution, WHO strategy) or advocacy on the issue).

Key findings: timeline of events

Though our study emphasis was on 2015-2019, we constructed a timeline of key events (Figure 2) over a longer period to understand earlier events that may have influenced or affected those in our period of interest. A more detailed timeline of events is available in an online dashboard (link). We divide the entire process into four heuristic phases, based on policy consequences in the WHO. We label these phases as "four crescendos," which are:

- **Pre-crescendo phase** (prior to April 2009): events prior to snakebite being added as a NTD in the WHO list. [6 16]
- **Crescendo phase** (April 2009 – 2013): from April 2009 to the "demotion" of snakebite as a "neglected condition" in 2013. [6 17]
- **De-crescendo phase** (2013 to mid-2015): From 2013 to being removed altogether from the WHO-NTD list. [6 17]
- **Re-crescendo phase** (mid 2015 – May 2019): From mid-2015 to the WHO releasing the snakebite strategy. Key events in this phase were:
    - World Health Assembly (WHA) side event: May 2016.[18 19]
    - Snakebite added to WHO-NTD list as a Category A NTD: June 2017. [6 20]
    - Adoption of WHA resolution: May 2018. [9]
    - Release of WHO strategy on snakebite: May 2019.[2]

Figure 2: Key events in prioritisation of snakebite across four crescendos



Key findings: the how and why of prioritisation

The findings, drawing on the GHN framework [14], within the four crescendos is summarised in Table 2 and is detailed subsequently.

Table 2: Summary of study results mapped in the four crescendos

DOMAINS		**Pre-crescendo** (prior to April 2009)	**Crescendo** (April 2009 to 2013)	**De-crescendo** (2013 to mid-2015)	**Re-crescendo** (mid-2015 to May 2019**)**
ISSUE CHARACTERISTICS	**Affected Groups**	Implicit understanding that snakebite affects those with poor socio-economic status, including children			
	Severity of snakebite	Global burden estimates	No new global estimate		Burden data used consistently with acknowledgment of data gaps
	Unique issue characteristic	Cross-cultural fascination and fear of snakes			
	Tractability	Multi-faceted solution			Framing solutions primarily around research, production, and logistics of snake anti-venom
NETWORK AND ACTOR FEATURES	**Leadership and Governance**	Academics			Academics and leadership of MSF and HAI *
	Network Composition	Academics under aegis of International Society of Toxinology	Academics under aegis of International Society of Toxinology and Global Snakebite Initiative		Academics under IST and GSI, with civil society actors and state actors

	Framing Strategies	-	Technification		Intersecting and layered framing (moralisation, securitisation and technification)
POLICY ENVIRONMENT	**Acceptance within neglected tropical disease community**	-	Concerned	Denied	Reluctant
	Legitimacy	Legitimacy of individual actors. Issue seen as legitimate.			Ebbs and flows in legitimacy of network intersecting with legitimacy of individual actors and legitimacy of issue.
	Funding	WHO-NTD Division	Commonwealth Serum Laboratory, and Norton Rose, Australia (pro-bono legal aid)	None	Wellcome Trust, Lillian Lincoln Foundation, Dutch Government, Hennecke Family Foundation and Kofi Annan Foundation.
*MSF- Médecins Sans Frontières; HAI - Health Action International					

Issue characteristics

Affected groups

Snakebite primarily affects the rural poor and agricultural workers. [4 18 20-25] Most snakebite deaths occur in South Asia and Africa. [4 26 27] Snakebite is also common in

Indigenous people (including in some high income nations) , and has been described as a condition which has" long been oppressive for indigenous people". [28] Snakebite was also recognised as an important cause of death in children. [29] Broadly, across all crescendo phases, there was an implicit understanding among stakeholders of the condition affecting those with poor socio-economic status and an importance cause of death in children.

Severity of snakebite

In the pre-crescendo phase, researchers in Sri Lanka (commissioned by the WHO-NTD department) provided a global estimate of the burden of snakebite. [26] Participants believed that the evidence from this paper, provided justification for addition of snakebite as an NTD in 2009.

"…at the time, the person who led the NTD program, I believe, identified that the burden (of snakebite) is needed to be better understood… pretty soon after the Kasturiratne paper came out, snakebite was included on the WHO NTD priority list…." – IDI 017

Around the same time, the WHO Child Injury Report [29] noted 100,000 - 200,000 deaths and 400,000 amputations each year due to snakebite. The report used the relative, instead of the absolute burden in children. Data from this report were used by many actors in further advocacy.

There were no new global estimates available in the crescendo, de-crescendo or re-crescendo phases. The lack of availability of new burden data might have contributed to the decrescendo. This was overcome in the re-crescendo phase, by the members of

snakebite network demonstrating consistency in the use of data on bites and deaths, with simultaneously acknowledgment of data gaps, including for disability and socio-economic burden, due to the occurrence of snakebite in areas with weak health systems.

Fascination and fear of snakes

Multiple respondents highlighted that the cross-cultural association of snakes, be it fear or fascination, led to inherent recognition of the issue by stakeholders, media, and the public alike. This was one key factor that remained constant across time.

"...in every culture, it has this sort of sexual kind of you know, superpower…everybody understands the snake...So that was one of the best things about it is that you did not have to explain what is the snake? … a lot of NTDs, like Mycetoma, no one had ever heard of it. Nobody knew what it was!"- IDI 019

Participants who spearheaded media and advocacy efforts acknowledged the strategic use of the visual nature of snakes, to create a "media-friendly campaign."

Complexities in defining tractability

The multifaceted and complex nature of strategies required to address snakebite, and divergent viewpoints on it, led to challenges in defining tractability (quality of being easily dealt with). The recognition among stakeholders of the burden being primarily driven by social determinants, and the problems being common in areas with weak health systems, meant the need for multi-sectoral solutions, adding to snakebite being seen as not tractable.

"…living in remote, rural areas and the shortage of health staff, and the fact of health worker crisis in Africa; the fact that we have poor transport and communication systems, and, in some places, roads are impossible in rains. – IDI 011

In the re-crescendo phase, the network identified addressing issues around research, production, and logistics of snake anti-venom (referred to only as anti-venom in subsequent text) and improved clinical management as priority domains of action. Participants recognised that because snakebite affected those who had little ability to pay, there was no market incentive for investments in research or production of anti-venoms. The issue is further complicated due to the fragmented nature of the anti-venom market (it is relevant to only a specific geography), which restricts market size. Multiple participants identified that framing tractability around anti-venom, in the re-crescendo phase, as a factor which helped push snakebite in the global agenda.

"Pushing the antivenom side, managed to get it onto the agenda at the WHO… was clearly the correct strategy to push it up higher, there were people that could push snakebite, uh, from the treatment side rather than from the prevention side." – IDI 012

Network and actor features

Leadership group, governance structures and clarity of roles

In the crescendo phase, a small group of academics, took the lead in forming the Global Snakebite Initiative (GSI), as a special project under the aegis of the International

Society of Toxinology (IST). During this time, the leadership engaged in deliberative communication through the IST newsletter (including on legal advice sought and funding considerations). Subsequently GSI became a separate legal entity from 2012 to gain more financial and operational autonomy.

As soon as snakebite was dropped from the WHO NTD list, it was the GSI and IST networks (same group of individuals) which sprang into action. The core inner group of this network comprised academics from Australia, Costa Rica, and UK. In the re-crescendo phase this expanded to include the leadership of Médecins Sans Frontières (MSF) and Health Action International (HAI), two well respected international civil society organisations. Internally, there was clarity in roles: MSF leading media and public advocacy efforts, HAI leading policy advocacy with WHO, and academics offering technical insights and evidence. The Permanent Delegation to the United Nations of Costa Rica functioned as focal point for engaging with other state actors. This relationship with the Costa Rican government was fostered by a Costa Rican academic through the then Minister of Health of Costa Rica.

"The role of the diplomatic mission of Costa Rica was very important because they know how to present a document like that for an organization like the United Nations, because this it's not like a technical or scientific document. It is a diplomatic document...they invited representative of different embassies to attend a meeting where this document is presented, is discussed, and is modified."- IDI 006

Multiple participants identified a WHO-NTD division staffer, as an effective leader who championed snakebite within WHO.

> *"WHO does [have) a lot of people … I do not find very good managers and administrators, but it means that when you do find one who is, they stand out from the crowd. XXX [name redacted] is absolutely one of them … Every large organization you need the external facing people, but you will also need the champions behind the scenes who make it work." IDI 020*

Network composition

In the crescendo and de-crescendo phases, the GSI-IST network evolved, but it was restricted primarily to academics and clinicians. When snakebite was removed from the WHO NTD list, the need for coalition-building, by engaging with a more diverse set of actors, was recognised by the core inner group of the network. A UK and Costa Rican academic organised, the Hinxton Retreat [18] in 2015, to develop a strategy for a "more globally coordinated, multi-faceted approach" for snakebite. [18] Prominent organisations who participated include MSF, HAI, different WHO departments, The Lancet and the Wellcome Trust (which funded the meeting).

Academics in the snakebite network, had the ability to advocate in high-impact journals, [5 18 30-32] but with coalition- building during the re-crescendo phase they could overcome their limitation of "almost no understanding of how the WHO works" (IDI 007). Involvement of HAI and MSF, led to an understanding of the processes and motivations

of WHO (recognition of state power, and funding needs of WHO) and the consequent need for media and advocacy efforts.

"We do what our states would like us to do. We do not just, you know, out of the blue sky just take out something and put on our work plan. It must come from our countries supported by other partners. "- IDI 008

"Snakebite before was NTD, but it was, removed from its status… this time there was really, an appetite to see a wider net of stakeholders, including civil society(organizations)" – IDI 004

"HAI came aboard, and they took a lot of the policy work, … achieving the right steps in policy at WHO"- IDI 009

During the re-crescendo phase, there was more engagement with state actors, and national level actors, but the core inner group remained constant. Involvement of countries in supporting WHO related activities in the re-crescendo phase is detailed in **Appendix 3**.

Use of intersecting and layered framing strategies

Framing refers to the process by which proponents (and detractors) create and portray issues – reflecting the politics of assigning meaning and significance to public issue through social interactions. [33] Prior to the re-crescendo phase, the snakebite network predominantly used a technification frame. During the re-crescendo phase, a dynamically evolving, intersecting, and layered framing strategy was used. Soon after

snakebite was dropped from the WHO list in 2015, GSI-IST used a predominant moralisation frame: addressing snakebite as an ethical imperative. Fresh from the de-crescendo, the network's primary source of power was normative. Those affected by snakebite were framed as "politically voiceless." [2 34] GSI-IST claimed moral authority to counter social injustice, arising from their technical understanding and long-standing commitment on the issue as academics. The moralisation frame was supported by evidence on the burden of snakebite, relative to other NTDs, and was enabled through cross-cultural fear and fascination about snakes.

"We humans and our primate cousins have an innate fear of snakes and other venomous animals – so our instinct is to run away. Unfortunately, this revulsion for snakes has clouded the judgement of Ministers, donors and WHO leadership to the point where they are ashamed to admit and do anything about the public health burden of snakebite." Said Prof David Warrell. President of IST][35]

The powerlessness of those affected, also meant that support from state actors for the WHO resolutions was comparatively easier. Snakebite was seen as a non-political issue, unlike other global issues, which were often tied to interest group motivations.

MSF supplemented the framing of moralisation by intersecting it with a securitisation frame. MSF put a timeline for action by highlighting that the manufacturing of Fav-Afrique, "the only antivenom that has been proven safe and effective to treat envenoming from different types of snakes across Sub-Saharan Africa" [36] has stopped , with the last batch due to expire in June 2016. The source of power for MSF was due to its reputation as a humanitarian organisation with global media and advocacy

capabilities; the power , at that time, further enhanced through its important role in addressing Ebola and in critiquing WHO and advocating for a more strenuous response to Ebola outbreaks. [37]

The "Minutes to Die" [38] documentary played a pivotal role in framing snakebite in moralisation and securitisation frames, to garner traction. A shorter version of the documentary [15] was shown in the WHA side event (2016), which had attendance from senior WHO leaders. The documentary used strong imagery and narratives to highlight the "helpless" condition of people and communities affected by snakebite. During the re-crescendo phase, it was screened 114 times, mostly in universities and conferences attended by policy makers. One participant who attended the WHA side event was not overly positive about the documentary but still acknowledged its contribution to gaining traction.

"… to be honest, it is, it is a bit of, um, development porn. It is, it is, you know, it is about, oh, these poor people being bitten, and then they have not got anywhere to go… the film was, was dangerously exploitative…" IDI 001, while talking about the value of advocacy and the role of the movie in it.

Post the WHA side event, the network enhanced the use of technification. This was driven by the need to demonstrate the alignment of snakebite with the formal criteria of NTD, which the WHO STAG-NTD committee set for the first time in 2016, and to recognise solutions which were perceived to be feasible by more diverse stakeholders.

The moralisation narrative was inter-weaved with the technification one, by mentioning that the broad process by which an anti-venom is manufactured (involving injecting venom to a horse, 'bleeding' to acquire serum and develop anti-venom) had not changed over time, despite progress in biotechnology.

Policy environment

Ebbs and flows in legitimacy

Legitimacy (by what authority does one exert power) is known to be a challenge for GHNs. [39] We identified three distinct but intersecting dimensions of legitimacy: legitimacy of the issue, legitimacy of individual actors, and legitimacy of the network.

In general, and throughout all phases, there was inherent recognition of snakebite as a legitimate public health problem due to its issue characteristics. Early documents of IST during the pre-crescendo phase (2009) mention that the formation of GSI was based on positive and informal discussions with key individuals from the medical toxinology field, primarily from non-endemic nations. This formed the inner core group of the snakebite network. There was universal recognition that individuals in the inner core, were accomplished researchers who contributed their professional lives to the cause of snakebite. The individual credibility and the efforts and action they undertook, translated to the legitimacy of the snakebite network, and strengthened legitimacy of snakebite as an issue. However, in the re-crescendo phase and as snakebite gained traction in the global agenda, there was an ebb in the legitimacy of the power which network exerted. The leadership of the snakebite network was perceived by some to be lacking legitimate actors from high-burden nations, particularly from Africa. The moralisation and securitisation frame meant Africa was the focal point for advocacy, but

stakeholders from this region were not engaged optimally. In May 2016, prior to the WHA side event, the African Society of Venimology (ASV) issued a press release titled "African Experts, Ignored Again on Snakebite, Move Forward Alone". [40] The ASV was established in 2012, after a pan-African survey revealing its need, [28] making them legitimate actors with whom the WHO should have engaged extensively .

"Once again, with the notable exception of the 4th Conference in Dakar, in which the World Health Organization (WHO) was represented, international agencies, albeit invited, did not attend." - minutes of 6th International Conference on Envenomation by Snakebites and Scorpion Stings in Africa organised by ASV [41]

The GSI in the IST newsletter mentioned the issue as disappointing and called it an attempt to "create controversy" which "did not prevent the success". [42] As a remedy they mentioned they would be "engaging directly with all of the ASV members as we move forward". [42] The ebb in legitimacy was overcome by such engagement and the parallel involvement of Kofi Annan (former secretary-general of the United Nations, and a Nobel Laureate from Ghana). The involvement of Kofi Annan enhanced legitimacy of snakebite as a global health issue and ensured support from state actors, particularly from Africa. Kofi Annan's interest on snakebite was based on its impact in Ghana, an issue brought to his personal attention by Akshay Rath, [34] a UN physician from India.

Despite the success of the network in getting snakebite in the global health agenda, multiple participants expressed concerns about the legitimacy of the power which

snakebite network exerted by framing solutions and consequent resourcing around anti-venoms.

> *"Global Snakebite Initiative, scientists…its brilliant science, but these scientists and they are all men - just to say that again. They want to go to Africa and start injecting people with 'their antivenom.' So, they become service delivery and they know how to deliver their own antivenom and many are medical doctors, but they, they sort of in a very white saviour kind of way, they go striding into rural Kenya to deliver antivenom to the poor." IDI 001*

Participants also mentioned that the WHA resolutions and strategy left out issues of concern to LMICs, like intellectual property. Research interests of non-endemic nations were mentioned to be primarily driving the agenda of the WHO strategy on snakebite.

> *"Many of the participants or associated researchers (were) from UK and other European countries had the focus little bit tilted towards Sub-Saharan Africa and Africa in general…there was no recognition that most of the burden is in South Asia "- IDI 002*

Acceptance within the NTD community

In the pre-crescendo phase, there were two key WHO initiatives outside the NTD division:

- Meeting on "Rabies and envenoming: a neglected public health issue" [43] in 2007 by the WHO Quality Assurance and Safety Cluster leading to the first WHO guidelines on quality control of anti-venom. [44]
- Release of the "World report on child injury prevention" in 2008 by the WHO Injury and Violence Prevention Department with a section on snakebite. [29]

Multiple participants believed that in 2009, the then head of the WHO-NTD department, was instrumental in the inclusion of snakebite in the WHO NTD list. However other than the 2008 meeting minutes of the Strategic and Technical Advisory Group for NTD (STAG-NTD)[i], which mentions the need for understanding direct and indirect costs of "NTDs including snake bites", there is no documented discussion on snakebite in the STAG-NTD in the crescendo or decrescendo phase. Participants believed that the "demotion" and subsequent removal of snakebite from the WHO-NTD list was because snakebite was not a "disease" nor was it amenable to elimination or eradication, unlike other diseases in the WHO-NTD list. To align with and enhance acceptance within the NTD community, the formal technical dossier [4] (submitted by member states to the STAG-NTD) for inclusion in the WHO-NTD list, was for snakebite envenoming (the clinical condition due to "venoms of toxins in the bite of a venomous snake") rather than for snakebite. [4] Participants involved in the process believed that the application process was aided by the availability of a criterion for a condition to be designated as an NTD, which the STAG-NTD developed that year. [45] However, despite the framing around snakebite envenoming, the STAG-NTD expressed concerns about its listing as an NTD. The STAG-NTD finally recommended that:

[i] The STAG-NTD is the principal advisory group with respect to NTDs on WHO, with the mandate to advise on policies and strategies, which reports directly to the WHO Director General.

"It is unsure that the programmatic aspects of this (snakebite envenoming) would be best handled by the NTD Department. It was decided therefore to defer this decision to WHO's senior management… STAG also notes the following caveat: that any additional responsibilities associated with snakebite being included in the NTD portfolio should come with additional resources."

The then Director General, WHO, endorsed snakebite envenoming as a Category A NTD, [i] leading to its inclusion in WHO-NTD list in June 2017. One participant believed, this might have been an act of ensuring legacy, but this could not be triangulated with other data.

The acceptance of snakebite envenoming within the NTD community (WHO and beyond) however, continues to be a challenge. Even in the 2019 STAG-NTD meeting concerns were expressed about how the inclusion of snakebite envenoming "opened the NTD categories to non-infectious diseases". [46]

Funding

Participants who were part of the inner core of the network, mentioned that in the crescendo phase, they operated with an impression that the WHO-NTD status would ensure funding. In re-crescendo, the understanding of funding needs of WHO, led them to engage actively with funders and wider group of stakeholders. Support from

[i] A disease classified as category A NTD meets all four criteria set by NTD-STAG: i) disproportionately affects the poor causing significant morbidity and mortality; ii) endemic in tropical and sub-tropical areas; iii), amenable to broad control elimination or eradication, and iv) research on it is relatively neglected. The categorisation implies commitment for large scale program by WHO-NTD department. A category B NTD meets any 3 of the four criteria and does not come with any explicit program commitment from WHO-NTD department.

Wellcome Trust, was key to the success, and the relationship was fostered vide professional relationships with UK based researchers in the inner core. Multiple participants stated that major funders for NTDs continue to be unconvinced of snakebite envenoming as an NTD despite the WHO categorisation.

"Gates Foundation has a huge portfolio in NTDs. Most of the NTDs that they have been focusing on are the ones… with an elimination / eradication target…new NTD like snakebite …it is potentially a bit less appealing, "- IDI 015

A summary of the key funders in different crescendo phases is integrated within Table 2.

Discussion

The prioritisation of snakebite occurred in a crescendo, de-crescendo, re-crescendo manner. In the re-crescendo phase, it was enabled by a diverse network composition, better understanding of the processes and funding needs of WHO, recognition of the need for engaging the media, and the use of intersecting and layered framing strategies. Involvement of Costa Rica and Kofi Annan were important to overcome ebbs in establishing legitimacy, and to garner support from state actors. Reluctant acceptance of snakebite within the NTD community is a barrier to its sustained placement on the global health agenda.

The fluctuating pattern of prioritisation implies a fragile placement of snakebite in the global health agenda. Despite the successes of integrating snakebite in the agenda, the network faces a challenge in sustaining its legitimacy, particularly in endemic nations.

This might be due to several factors. Recent calls for decolonising global health, have increased awareness and recognition of the "foreign gaze," epistemic injustice, power asymmetries in global health initiatives and the need for structural reforms in the global health ecosystem. [47-52] Data from the snakebite envenoming medicines database, shows that 11 of the 13 projects funded by Wellcome Trust, a key global health funder for anti-venom research, were awarded to research institutions in non-endemic nations (UK, Europe, and USA). [53] Disproportionate allocation of material resources, reinforces perceptions around legitimacy.

The other issue of reluctant acceptance of snakebite within the NTD community has its roots, in what might be described as epistemic injustice, [52 54 55] meted out by the normative WHO establishes through its criteria for classifying a condition as an NTD. [45] Third in the list of the four mandatory criteria for a Category A listing (which implies "large scale action in the portfolio of the NTD Department") is that a disease should be "immediately amenable to broad control, elimination or eradication". [45] This reinforces the existing biomedical discourse on snakebite, [56] with the necessity of defining tractability narrowly around anti-venoms. The bigger issue around NTD definition, which arises from our analysis, merits establishment of an independent commission with adequate disciplinary and "tropical" (i.e., endemic, or high burden) country representation to revisit the existing criteria for NTD designation. Such a move will ensure justice for people affected by NTDs, like snakebite. There is also lack of internal consistency in the definition owing to the need for identified tools for control, eradication, elimination, or broad control, as well as research on it being neglected.

While larger ecosystem changes in global health governance are complex and might be beyond the purview of the snakebite network, several strategic changes are possible to

improve legitimacy in endemic nations and promote acceptance within the NTD community. This is particularly relevant as the WHO strategy enters the implementation phase [57] for which national-level plans will need to be developed and implemented. Action towards ensuring ownership of intellectual property rights for newer anti-venoms and diagnostics to public agencies in endemic nations is an area of work for WHO, GSI, IST, HAI, and MSF to consider. Global funders might consider funding research institutions in countries with highest burden of snakebite directly, to enable long term structural changes. [48] Focusing and prioritising investment on strengthening health systems and empowering communities for prevention and improved care-seeking aspects of the WHO strategy, [57] and ensuring that actor from endemic nations are leading snakebite initiatives, might enhance legitimacy and enable inclusion of wider base of proponents. The use of One Health as a framework for understanding and addressing snakebite, should also be considered: it has successfully attracted large multi-country collaborative funding. [58 59] The joint action plan of WHO, Food and Agriculture Organization of the United Nations, World Organisation for Animal Health and United Nations Environment Program identifies snakebite as an area of work in 2022-2026.[60] The WHO, and other proponents of snakebite might commission focussed policy analysis to identify entry points for snakebite within the NTD and One Health community. The WHO might also consider developing regional status reports, as has been done in drowning, another condition recently prioritised globally. [61 62] Such reports not only stimulate action, and allow for monitoring, but also creates space for dialogue.

One aspect of snakebite prioritisation was the successful use of a documentary to frame and garner traction on the issue in WHA, and beyond. However, the pitfalls of such sensitisation were also noted in our study. Similar strategies might be used for agenda

setting, but they should adhere to recent guidelines on the use of imagery in global health (which were not available during that time) to ensure respect for affected people, and avoid content that is insensitive, misrepresentative or leading to stigmatisation, and stereotyping. [63]

Though we did not aim to develop theory, our study identifies some areas which might be explored in future policy analysis studies, and theory-driven work on GHNs. While dynamicity is key to any policy analysis, and it is understood to be part of any policy analysis, temporal variations should be more formally integrated in the GHN framework to enable more robust, rather than intuitive analysis. Discerning patterns of temporality, such as the "four crescendos" we detected in our study, should be explicitly considered in future studies, and integrated within analytical frameworks. Theory driven work to revise the GHN framework, might consider explicitly integrating legitimacy within the policy environment domain. It is recognised that global health actors use cultural, social, financial, and symbolic capital(legitimacy) to not only advance ideas, but also secure power. [64-66] With the recognition that global health being a field of power relations, [64] legitimacy is an important aspect to analyse, and perhaps more broad and useful than allies and opponents in the current framework. Contributions of our study to knowledge gaps with respect to research questions, earlier identified by Shiffman *et al* is summarised in Table 3.[67]

Table 3: Summary of contributions of the study to knowledge gaps on global health networks

Domains of future research questions on GHN	Contribution of the current study
Global agenda setting	Our study demonstrates network effectiveness in the absence of objective robust data on burden and tractability through effective use of framing strategies, good leadership, clarity in actor roles and involvement of states. As such it adds to the growing literature that the role of GHNs extends beyond producing knowledge (evidence), but also linking knowledge with normative claims, particularly by adding a moral element.
National efforts	Our study identified that owing to the structure of WHO, state actors, continue to hold considerable power in global agenda setting. However, GHNs can influence states. Our study, however, could not discern if this were on account of principled stand (because of moral principles that snakebite as a neglected disease should be addressed) by state actors, or because material imperative (because of the perception that snakebite is a non-political issue and it enhances diplomatic relations with other states, which can be suitably used for pursuing other material objectives.

Framework generalisability	In our study the categories from the GHN framework were broadly useful. However, we suggest conduct of theory driven work to further enhance generalisability of the GHN framework, and consider: • integrating discerning of temporality patterns, (such as "four crescendos" in our case) explicitly in the analytical framework, • integrating legitimacy in policy environment domain of framework, and • adding unique issue characteristic, related to characteristics and/or cultural aspects of organism involved in disease condition (and/or its interaction with humans and the environment).
Legitimacy	Our study notes three dimensions of legitimacy – legitimacy of individual actors, legitimacy of the power which the network and legitimacy of the issue. The three, though distinct, intersect with each other. Perceptions on legitimacy of power were related to not only network composition and leadership but also effects framing strategies and tractability narratives.

Our study strength lies in the use of in-depth interviews and the vast amount of documentary data. While we did not get interviews from many people we invited, our extensive documentary analysis (together with information from other interviews) means we could understand the prioritisation process comprehensively, except for two aspects. We acknowledge them as limitations. The gaps pertain to understanding the motivation of state actors, and information pertaining to events in the pre-crescendo and

de-crescendo phase. We acknowledge them as limitations. We could not, access documents or get interviews from any state actors. One key informant thought that the motivation for Costa Rica to lead a WHA resolution, was to enhance its diplomatic stature globally, while another thought it was driven primarily by commercial interest (public universities in Costa Rica are involved in SAV manufacturing)- neither of which, we could triangulate. Similarly, the motivations for the Dutch government to fund advocacy for a disease not endemic in their own nation is not clear. We do not know why states supported or dropped out from different WHA related activities (**Appendix 3**). We acknowledge that the lack of information on state actors and how international relation between different member states, affected agenda setting, is a weakness. Such a scenario is common in similar case studies. [62] We also acknowledge gaps in the understanding of the inner machinations of WHO during the initial listing, demotion, and removal of snakebite in the NTD list. This was because of no documentation about it in the NTD-STAG meetings (we do not know if it was not discussed at all or not documented in minutes) and because we did not get enough interviews from people involved in the pre-crescendo, crescendo and decrescendo phase.

The research team, being outsiders in the process, have no positionality bias. However, we cannot rule out social desirability bias from participants. Many participants were pleased to be part of the study which looked at the process "historically." The desire to be part of history, might have led participants to overstate their own role and contributions. We mitigated against this by triangulating data from multiple sources.

Conclusion

Our analysis implies a fragile placement of the issue of snakebite on the global policy agenda. Implementation of the WHO strategy to achieve 2030 targets, would be dependent on how successfully the snakebite network enhances legitimacy, and promotes its acceptance within the NTD community. The study also merits the WHO criteria for designation as a neglected tropical disease, which reinforces biomedical discourse on diseases. We suggest that future analysis of prioritisation consider discerning temporal patterns (like the four crescendos, in our case), and incorporate three intersecting but distinct dimensions of legitimacy.

Competing interests

SB has advised WHO-SEARO for its regional plan for snakebite envenoming. No other competing interests to declare.

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Underlying data

The data underlying the results presented in the study, cannot be made publicly available or shared externally to prevent deductive disclosure of the participants of the study.

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Appendix 1: Details of search for documents

PubMed Search Strategy

("Snake Bites"[MeSH Terms] OR snakebite*) AND (WHO OR "World Health Organization " OR WHA OR "World Health Assembly"): Restricted to 1999-2019

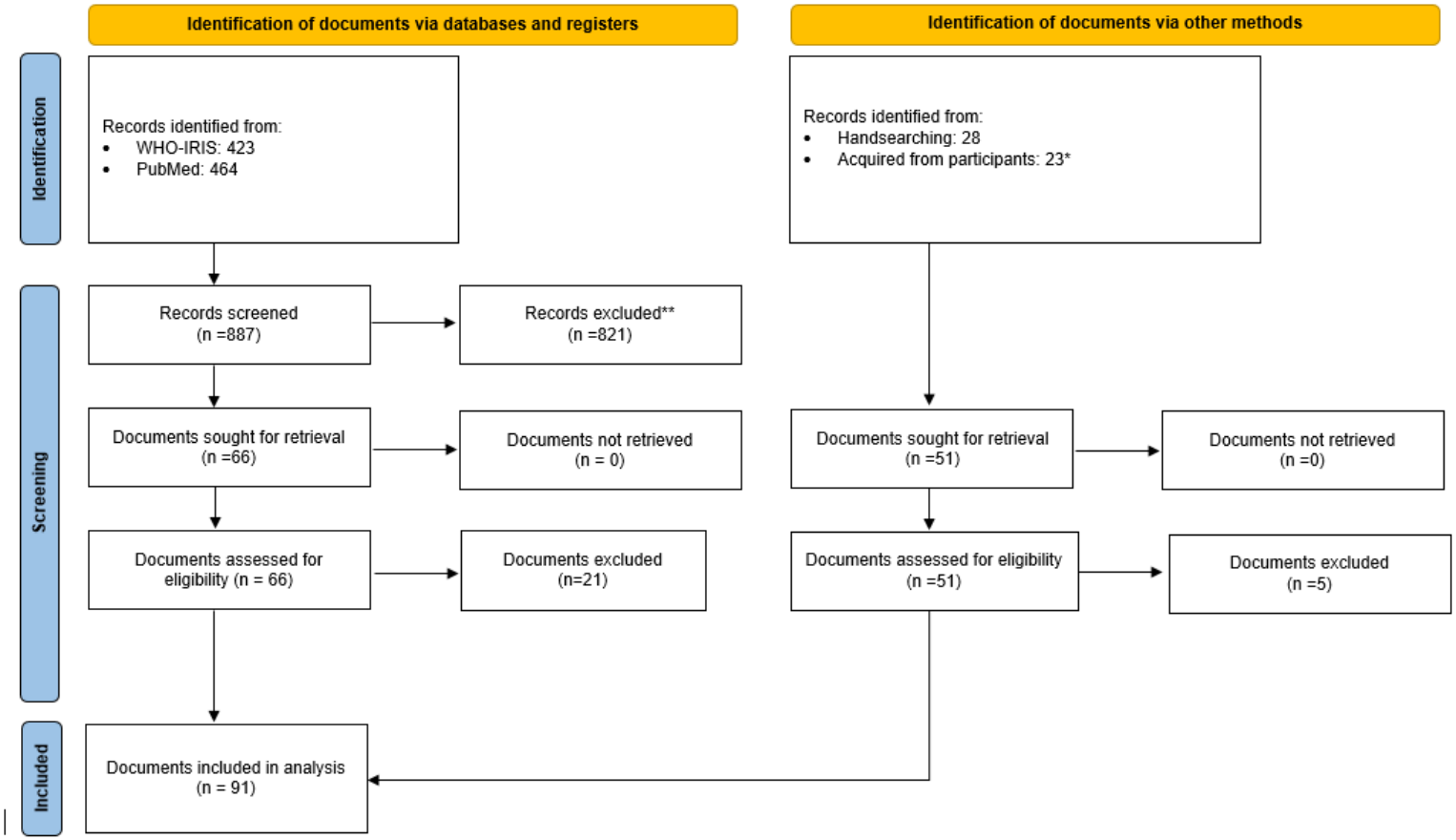
WHO-IRIS search strategy

Snakebite: restricted till 2019

List of websites hand searched

1. World Health Organization (only section on snakebite) https://www.who.int/
2. Kofi Annan Foundation https://www.kofiannanfoundation.org/
3. Health Action International https://haiweb.org/
4. Minutes to Die Movie https://minutestodie.com/
5. Medicines Sans Frontiers https://www.msf.org/
6. Global Snakebite Initiative https://www.snakebiteinitiative.org/
7. International Society of Toxinology https://www.toxinology.org/
8. Amref Health Africa https://amref.org/
9. Wellcome Trust https://wellcome.org/
10. Lillian Lincoln Foundationhttps://lillianlincolnfoundation.org/

Appendix 2a: Flowchart of articles included



Appendix 2b: Documents included in final analysis

Official WHO documents

1. Costa Rica. Recommendation for the Adoption of an Additional Disease as a Neglected Tropical Disease: The Case for Snakebite Envenoming Geneva2017 [Available from: https://cdn.who.int/media/docs/default-source/ntds/snakebite-envenoming/recommendation-for-snakebite-envenoming-for-adoption-of-additional-ntd.pdf?sfvrsn=c5c37234_4] Accessed on 25 December 2022.
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Appendix 3: List of countries related to different WHO related activities

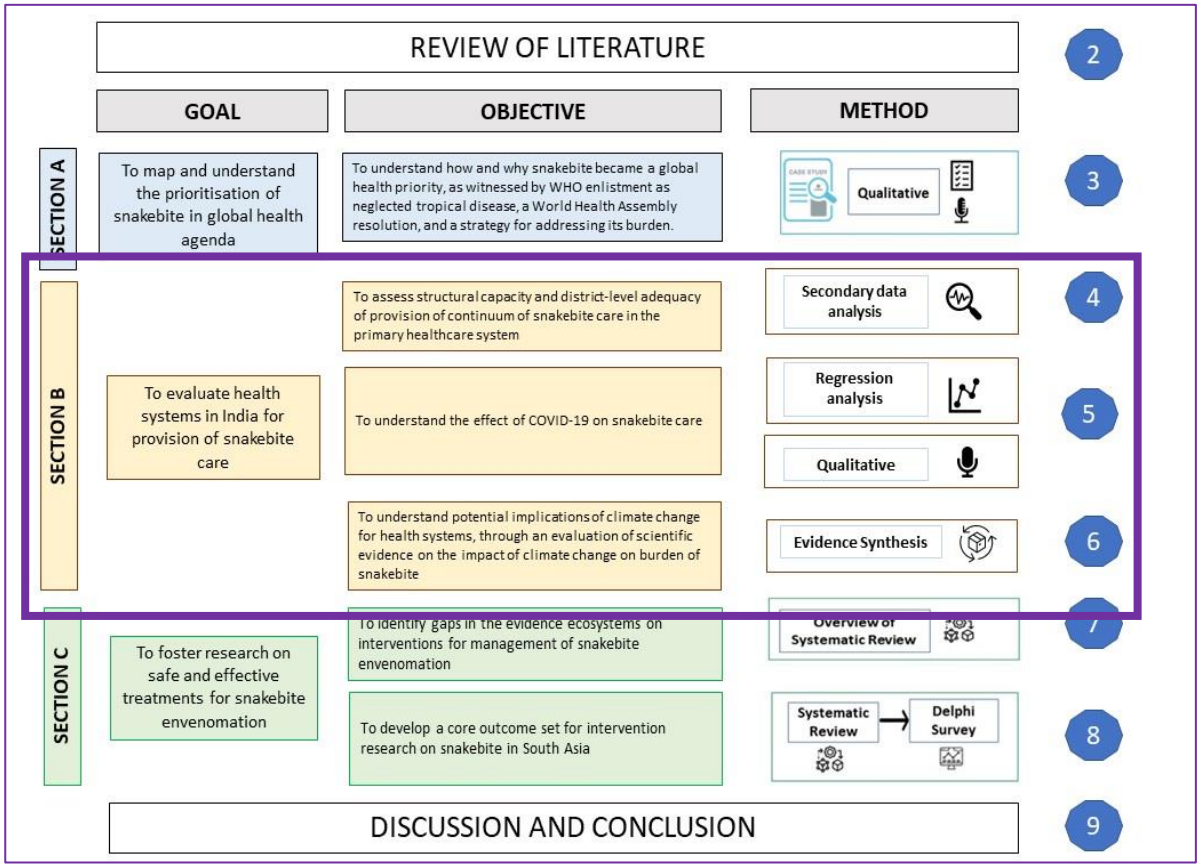
WHA side event sponsor	Countries recommending addition of snakebite to WHO-NTD list	Sponsor of WHA resolution to address burden of snakebite
1. Afghanistan, 2. Angola, 3. Bangladesh 4. Benin 5. Burkina Faso 6. Cameroon, 7. Chad, 8. Costa Rica 9. Gabon, 10. Guinea, 11. Kenya, 12. Namibia, 13. Nepal, 14. Nigeria, 15. Pakistan, 16. Papua New Guinea, 17. Philippines, 18. Senegal 19. Uganda	1. Angola 2. Benin 3. Brazil 4. Cameroon 5. Chad 6. Colombia 7. Costa Rica 8. Ecuador 9. Honduras 10. Guatemala 11. Mexico 12. Namibia 13. Netherlands 14. Pakistan 15. Panama 16. Philippines 17. Peru 18. Uganda	1. Angola, 2. Australia, 3. Benin, 4. Brazil, 5. Burkina Faso, 6. Colombia, 7. Costa Rica, 8. Ecuador, 9. France, 10. Gabon, 11. Guatemala, 12. Honduras, 13. India, 14. Jamaica, 15. Kenya, 16. Mexico, 17. Netherlands, 18. Nigeria, 19. Pakistan, 20. Panama, 21. Philippines, 22. Peru, 23. Senegal, 24. Thailand, 25. Zambia. 26. Geneva

Section B: Evaluation of health systems in India

"I am the jungle's eyes. I can see the past, and the future. It is I, Kaa, who witnessed the coming of man. And the jungle trying to survive. I saw chaos and darkness come to our lands."

~ Kaa, Snake character in Mowgli: Legend of The Jungle. 2018

In this section, like Kaa, I attempt to see the health systems status (structural capacity, continuum of care) and acquire insights for the future (health systems resilience) for snakebite care in India.



4. Structural capacity and continuum of snakebite care in the primary health care system in India

4.1. Chapter overview

In this chapter, I analyse national level data from a health facility survey to assess structural capacity and continuum of snakebite care in India. While health systems issues for snakebite are acknowledged, and the need for addressing them well recognised, there is scarce empirical evidence around it. The analysis, the first of its kind globally, provides insight on priority areas of focus for comprehensive health systems strengthening and establishes a baseline for monitoring progress. The study is relevant to the current policy context in India, wherein the Union Government has identified building capacity of health workers as a priority area of action to address the burden of snakebite (September 2022).

This chapter is the **submitted** version of the article currently in peer-review.

- **Bhaumik S,** Norton R, Jagnoor J. Structural capacity, and continuum of snakebite care in the primary health care system in India: a cross-sectional assessment [Submitted in BMC Primary Care]

4.2. Candidate's contribution to the work

I conceptualised and designed the study which this Chapter contains. I obtained the data, developed the protocol, and statistical analysis plan. I conducted the analysis, validated the results, and wrote the first draft of the manuscript. I coordinated and

incorporated feedback from the co-authors to prepare and submit the manuscript to the journal.

4.3. Submitted manuscript

Structural capacity and continuum of snakebite care in the primary health care system in India: a cross-sectional assessment

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Abstract

Background

In 2019, the World Health Organization, set a target to halve the burden of snakebite, by 2030, and identified ‘health systems strengthening’ as a key pillar of action. In India, the country with most snakebite deaths, the Union Government identified (in September 2022) training of health workers as a priority action area. In this policy context, we provide empirical evidence by analysing the most recent nationwide survey data

(District Level Household and Facility Survey - 4), to assess structural capacity and continuum of snakebite care in primary health care system in India.

Methodology

We evaluated structural capacity for snakebite care under six domains: medicines, equipment, infrastructure, human resources, governance and finance, and health management information systems (HMIS). We categorised states (aspirant, performer, front-runner, achiever) based on the proportion of primary health centres (PHC) and community health centres (CHC), attaining highest possible domain score. We assessed continuum of snakebite care, district-wise, under five domains (connectivity to PHC, structural capacity of PHC, referral from PHC to higher facility, structural capacity of CHC, referral from CHC to higher facility) as adequate or not.

Results

No state was front-runner or achiever in all six domains of structural capacity in PHCs or CHCs. Broader domains (physical infrastructure, human resources for health, HMIS) for structural capacity were found to be weaker than the specific domain of medicines for snakebite care in almost all states, both at PHC and CHC level. Availability of human resources and equipment were of greater concern in CHC than at PHC in many states.

No district had adequate continuum of snakebite care in all domains. Other than the domain of transport availability from CHC to higher facility (48% districts adequate,) and transport availability from PHC to higher facility (11% districts adequate), for all other domains, less than 2% districts were adequate.

Conclusion

Comprehensive strengthening of primary health care, across all domains, and throughout the continuum of care, instead of a piece-meal approach towards health systems strengthening, is necessitated to reduce snakebite burden in India, and possibly other high-burden nations with weak health systems. Health facility surveys are necessitated for this purpose.

Background

Snakebite is a neglected tropical disease (NTD) which primarily affects rural communities in South Asia and sub-Saharan Africa. [1 2] It is estimated that globally up to 78,600 people died due to snakebite in 2019.[3] In addition to death, snakebites cause considerable long-term physical disability, has mental health manifestations, and adds to the socio-economic problems, of already deprived communities. [2 4-8] According to estimates, 65.25% of those who are at risk of being bitten by a snake reside in areas with the lowest access decile to high-quality healthcare, highlighting how unequal access to healthcare and a potential lack of high-quality care can increase vulnerability to severe snakebite envenoming outcomes. [9]

In 2019, the World Health Organization (WHO) released a strategy to reduce snakebite related death and disability by 50% by 2030. [10] One of the four objectives of the WHO strategy is strengthening health systems – with a focus on ensuring time-critical service delivery in primary health care. [10 11] Snakebite is a medical emergency, and hence care provisioning at the primary healthcare level, which is closer to the geographical site of bite incidents, is essential for reducing mortality and morbidity due to snakebite. [1 10-12] Snakebite is endemic in rural areas of low- and middle-income countries, where health

systems are typically weak. It is acknowledged that health system gaps in terms of availability, access, affordability, and quality are a major barrier in reducing snakebite related death and disability, [10 12-17] but empirical evidence is lacking. The focus of the current study is India which has the highest number of deaths due to snakebite , and the second highest age-standardised mortality rate globally, next to Somalia. [3] In the current study, we aimed to establish a nation-wide baseline status of health system India, to monitor progress and to identify priority domains for strengthening by:

1. assessing structural capacity for snakebite care in the primary health care facilities in the different states of India, and
2. analysing district-level adequacy of critical elements for provision of continuum of snakebite care in the primary healthcare system (from village to primary health centre (PHC) and to linked community health centre (CHC)) in India.

For this purpose, we used the District Level Household and Facility Survey (DLHS-4, 2012-2013), the most recent nationwide publicly available dataset which has facility survey data. Despite recent focus on strengthening primary health care in India there is no recent nation-wide facility assessment available (for snakebite or otherwise). [18] With more than 80% of the global deaths due to snakebite reported in India, the WHO target for 50% reduction in the burden of snakebite by 2030 cannot be attained without reducing the burden in India. [3] Establishing a baseline for health facility capacity for snakebite care, is of current policy relevance in India. The Mission Steering Group, the apex decision making body for strategy and implementation of the National Health Mission, in its 7th meeting held in September 2022 identified inadequate capacity of health workers as a gap and has allocated funding for their training. [19] Our study is conducted under this backdrop, and with a pragmatic stance, with the intention to

inform policy formulation through empirical evidence, based on best available data source.

Methods and analysis

Context

The primary healthcare systems in India. [20] consists of sub-centres (SCs) with linked primary health centres (PHCs). The SCs at the village level focus primarily on preventive and promotive care. A PHC is the first point of medical contact in the public healthcare system, where a medical doctor is available. The PHCs are linked to community health centres (CHCs) which serve as referral points for the PHCs, which in turn are linked to district hospitals (DH) and medical colleges. Overall, a district serves as a self-sufficient unit of the health system wherein all except advanced sub-speciality care is available.

Data Source

The DLHS-4 is a population-linked facility survey conducted by the Ministry of Health and Family Welfare, Government of India and primarily aimed to collect district level information on maternal, reproductive and child health and assess progress of related national programs. It is a multi-stage, stratified, probability proportional to size sample with replacement design, cross-sectional, nationally representative survey. In DLHS-4, the primary sampling unit (PSU) in rural areas are villages (as defined by the Census of India 2001 sampling frame) and the PSU for urban areas, Urban Frame Survey (UFS) blocks as per the National Sample Survey Office. The facility component of the survey involved survey of all levels of public health facilities (SC, PHC, CHC, DH) linked to

the PSU. The facility survey collected data on infrastructure, staffing, services, and other components related to organisational structure. The data was collected by trained personnel and involved interview of relevant facility personnel, physical observation, and inspection of registers. Further detailed descriptions of the sample methodology and survey process are available in the DLHS website (http://rchiips.org/index.html).

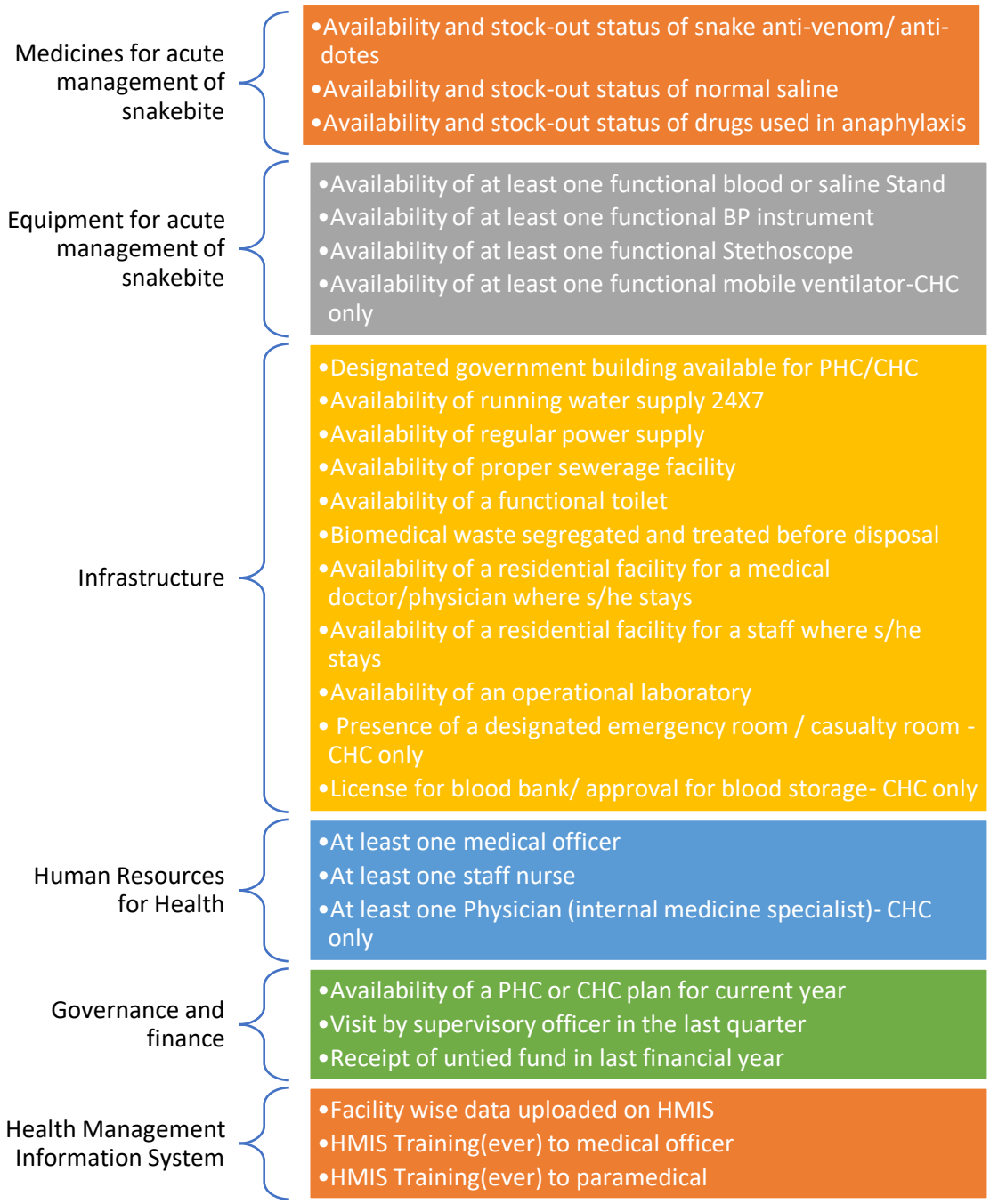
For this study on snakebite, we use data from the PHC and CHC facility component of DLHS-4 only. We excluded DH from the analysis because the DLHS facility data on district hospitals did not collect information on availability of snake anti-venom (SAV), a critical drug in the management of snakebite without which assessment of structural capacity or continuum of care is not meaningful. We excluded SCs from the analysis because of the structural design of the public primary health care system, wherein a SC does not have any medical doctor, and thus not a point of contact for snakebite. The training manual for community health workers, who are placed at SC also recommends immediate referral to nearest health facility (PHC or CHC).[21]

Assessment of structural capacity for acute management of snakebite

Assessing public health system performance is a complex exercise but has its roots in the Donabedian framework which links structures, processes, outputs, and outcomes to understand aspects of quality of care. [22] Turnock and Handler at the Centres for Disease Control and Prevention (CDC (Centres for Disease Control)), USA [23] first proposed the use of a conceptual framework similar to the Donabedian framework for assessing performance of public health systems. The framework consists of four components (mission, structural capacity, processes, and outcomes) operating in a macro context. We conceptualised structural capacity for snakebite care under six domains (Figure 1) – two domains specific to snakebite care (medicines for acute management of snakebite,

equipment for acute management of snakebite) and four broader ones pertaining to health systems (infrastructure, human resources for health, governance and finance, and health management information systems).

Figure 1: Structural capacity for management of acute snakebite care: domains and indicators



The steps for assessing structural capacity involved:

- **Identification of Indicators:** The DLHS-4 survey is not specifically designed to assess any aspect of snakebite care as the focus is primarily on maternal, reproductive and child healthcare. In the absence of any other facility level data on snakebite (at national or state level), the nationally representative DLHS-4 data acts as the best available data source for the purpose. For identifying indicators for the domains of structural capacity specific to snakebite care we mapped the variable in the facility component of DLHS-4 to the national snakebite treatment guidelines. [24] For identifying indicators for the four broader domains of structural capacity, we identified indicators for each of the essential elements of that domain based on the Indian Public Health Standards, [25] and availability of indicators in DLHS-4. Overall, for the six domains, we had 23 indicators for PHC and 27 indicators for CHC. This includes some 5 composite indicators for PHC (at least one medical doctor, and at least one staff nurse, availability of snake antivenom, availability of normal saline and availability of anaphylaxis drug) and 6 composite indicators for CHC (at least one physician, at least one general duty medical officer, at least one staff nurse, availability of snake antivenom, availability of normal saline and availability of anaphylaxis drug), which we derived from the data. Other indicators were directly available in DLHS-4. Detailed descriptions of all the indicators in the six domains for PHC and CHC are available in the **Supplementary Appendix 1** and a summary pictorial description is provided in Figure 1.
- **Normalisation:** We rescaled each indicator as 1 if the structural capacity criterion was positive (for example, if the snake anti-venom was available on the

day of the survey and there was no stock-out for more than 10 days during the 30 days preceding the survey it was awarded a score of 1), otherwise we scored it as 0.

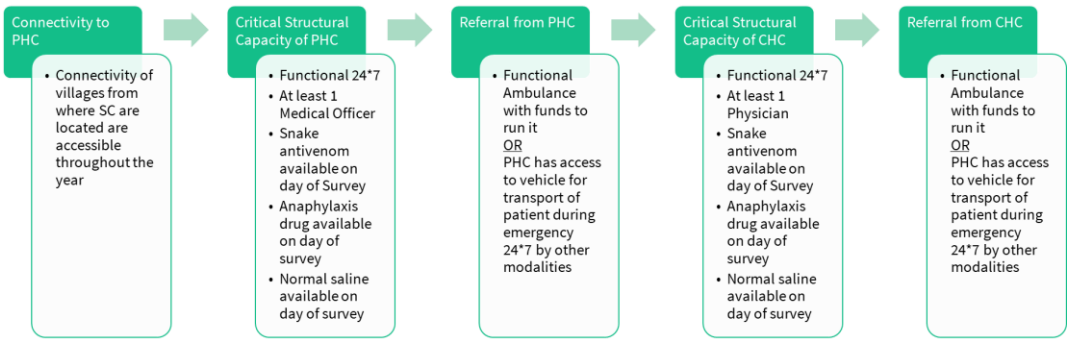
- **Weightage:** For each domain, equal weightage was given to each indicator in alignment with the United Nations Sustainable Development Solutions Network methodology. [26] We calculated domain scores for PHC and CHC separately by summing the scores for individual structural capacity element scores in that domain. We did not calculate an overall (or composite) score for structural capacity, but instead present domain-wise scores as overall scores mask domains of strength and weakness, especially in a setting where individual domain scores vary significantly (as is the case in our study).
- **State domain scores:** We benchmarked the adequacy of structural capacity for domains (separately for CHC and PHC) using cut-off levels, set *a priori*. We classified states into four categories, based on the proportion of health facilities, which could attain the maximal possible score for that domain, as the following:
    - Aspirant: 0% –49%
    - Performer: 50%–64%
    - Front-Runner: 65%–99%
    - Achiever: 100%

The classification benchmark is similar to what National Institution for Transforming India(NITI Aayog), the policy think tank of Government of India uses to classify states as per the sustainable development goal (SDG) India Index. [27] [28]

Assessment of adequacy of provision of critical elements for continuum of snakebite care

Continuum of snakebite care within the public primary health care system in India implies a patient with snakebite would need to reach a PHC, receive care in a PHC, be referred to a CHC, receive care in a CHC, and might be subsequently referred from a CHC to a higher facility. We developed a conceptual model on continuum of snakebite care with five domains, which is reflective of the journey of a person bitten by snake in the public healthcare system. (Figure 2)

Figure 2: Conceptual framework for provision of critical elements for continuum of snakebite care



We report descriptive statistics for all analyses. All data analysis was conducted in SPSS.

Ethics

This study is a secondary analysis of facility level data from a de-identified publicly available national survey. The original DLHS-4 survey received ethics approval from

the ethics committee of the International Institute for Population Science (IIPS). Data was requested and obtained from the IIPS Data centre. The data is shared as per a registered access system in accordance with the National Data Sharing and Accessibility Policy of the Government of India. [29]

Results

The DLHS-4 facility survey was conducted nationwide, but we included only those states and union territories (UT) for which data was made publicly available. Data was not available for two states (Gujarat, Jammu and Kashmir – this also includes the current UT of Ladakh which was part of Jammu and Kashmir, when the survey was conducted) and four union territories (Dadra and Nagar Haveli, Daman and Diu, Delhi, and Lakshadweep). Overall, our study included data from involving 8540 PHC' s from 29 states and 4810 CHCs from 30 states. There was no data from PHC' s in one state (Chandigarh).

Structural capacity for acute management of snakebite at PHC level

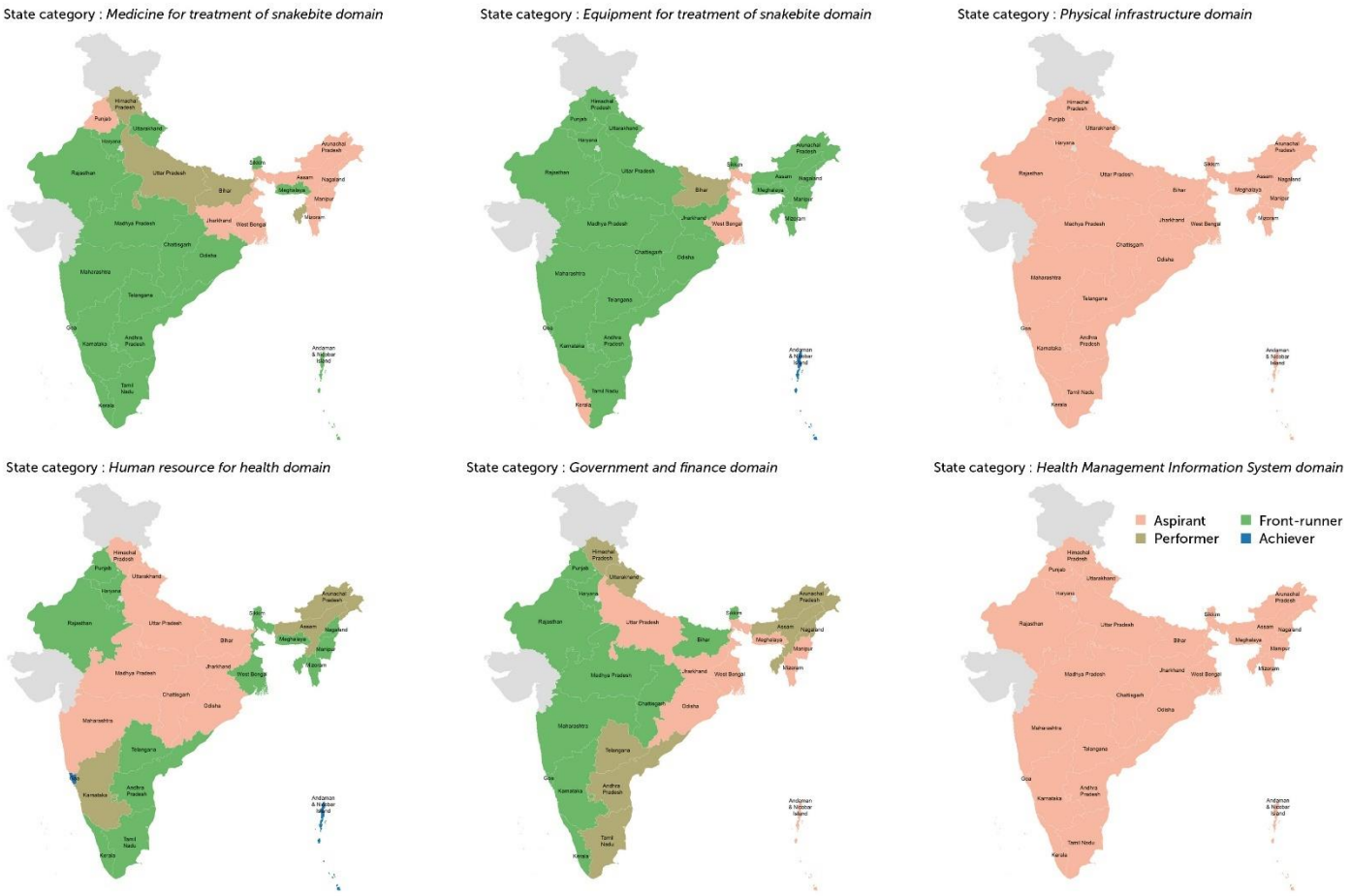
We found that none of the 29 states were front-runners or achievers in all six domains of structural capacity in PHC. The state-level structural capacity for different domains is presented graphically in Figure 3 and actual scores are presented in Supplementary Appendix 2.

Four of the 29 states (Rajasthan, Haryana, Sikkim, Andhra Pradesh, Goa) were at the front-runner level on four domains (Medicine for treatment of snakebite, Equipment for treatment of snakebite, Human Resources for Health, Governance and Finance), which

was the highest level attained. Summary statistics of the structural capacity of PHC in states/UT for snakebite care in different domains are:

1. Medicine for treatment of snakebite domain: 17 states /UT were front-runners, four were performers and eight aspirants.
2. Equipment for treatment of snakebite domain: One UT (Andaman and Nicobar Island) was an achiever, 25 states were front-runners, one was a performer and two aspirants.
3. Physical infrastructure domain: 29 states /UT were aspirants.
4. Human Resources Domain: 17 states/UT were front-runners, three were performers and nine were aspirants.
5. Governance and Finance domain: 12 states/UT were front-runners, eight were performers and nine were aspirants.
6. Health Management Information Systems domain: 29 states /UT were aspirants

Figure 3: State categorisation of different domains of structural capacity in Primary Health Centres



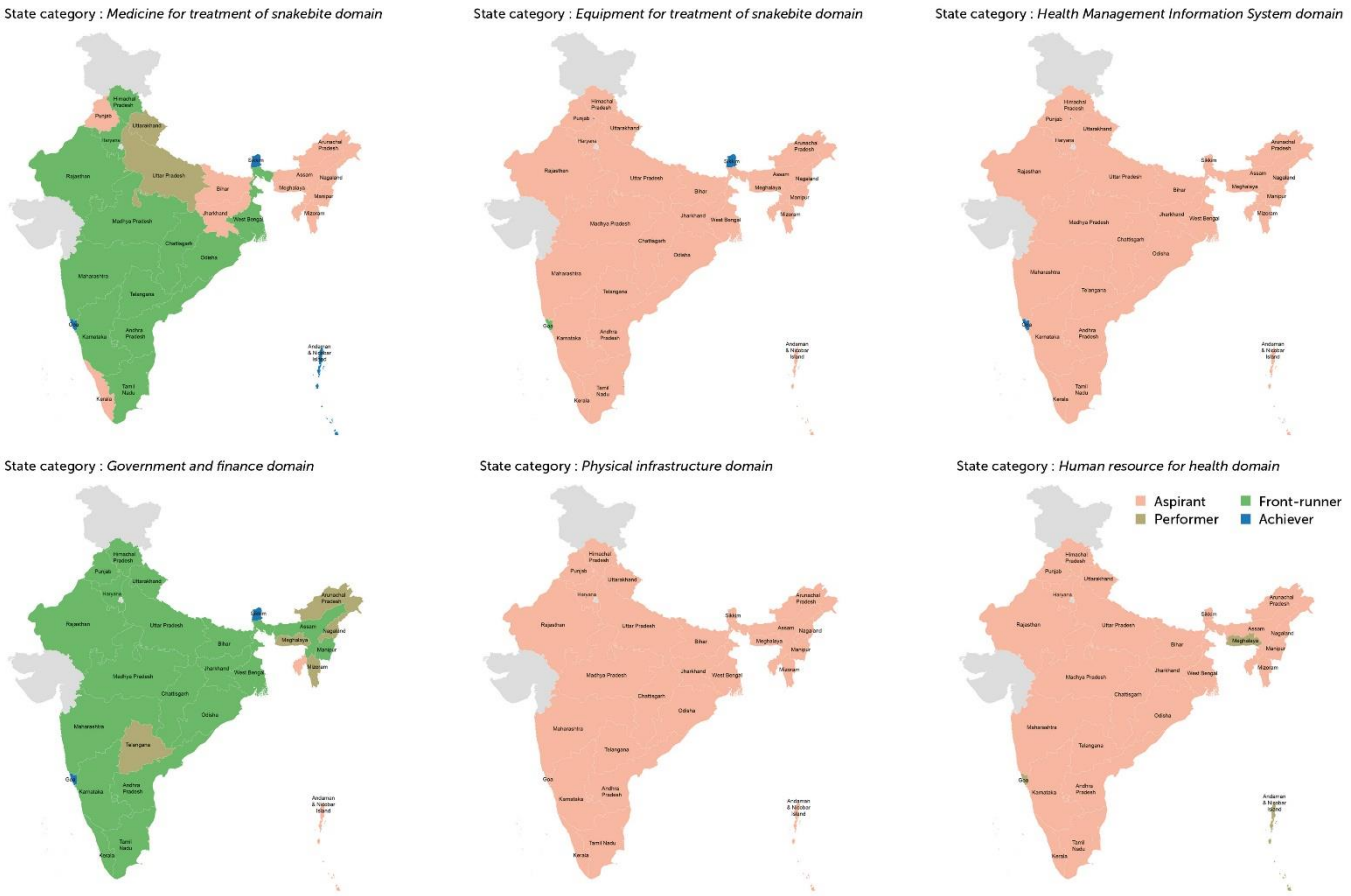
Structural capacity for acute management of snakebite at CHC level

Overall, we found that none of the 30 states were front-runners or achievers in all six domains of structural capacity in CHCs. The state-level structural capacity for different domains is presented graphically in Figure 4 and actual scores are presented in Supplementary Appendix 3.

Sikkim was an achiever in three domains (Medicine for treatment of snakebite, Equipment for treatment of snakebite, Governance and finance) and Goa was an achiever in two domains (Medicine for treatment of snakebite, Governance and finance) and front-runner in one domain (Equipment for treatment of snakebite). These two states attained the highest levels. The structural capacity of CHCs in states/UT for snakebite care in different domains are:

1. Medicine for treatment of snakebite domain: Three states /UT are achievers (Sikkim, Goa, Andaman and Nicobar Islands), 13 states /UT were front-runners, three were performers and 11 aspirants.
2. Equipment for treatment of snakebite domain: Two states /UT are achievers (Chandigarh and Sikkim), one is a front-runner, and 27 are aspirants.
3. Physical infrastructure domain: 30 states /UT were aspirants
4. Human Resources Domain: Four were performers and 26 were aspirants.
5. Governance and Finance domain: Two states were achievers (Sikkim and Goa), 19 states/UT were front-runners, six were performers and three were aspirants.
6. Health Management Information Systems domain: 30 states /UT were aspirants

Figure 4: State categorisation of different domains of structural capacity in Community Health Centres



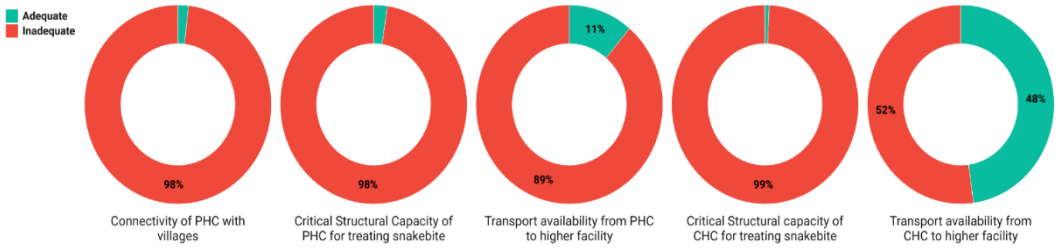
Adequacy of continuum of snakebite care

Overall, we found that none of the districts in any of the 30 states had adequate provision of continuum of snakebite care in the public primary health system. The overall nation-wide summary of district-level domains which constituted continuum of snakebite care is summarised below and in Figure 5 (details, including with names of districts in each state is included in the Supplementary Appendix 4):

1. accessibility of PHC throughout the year: was adequate in ten districts in three states,
2. structural capacity of PHC to manage acute snakebite care: was adequate in 13 districts in six states,
3. availability of functional transport system for referral from PHC to higher centre: was adequate in 61 districts in 15 states,
4. structural capacity of CHC to manage acute snakebite care CHC: was adequate in four districts in three states,
5. availability of functional transport system for referral from CHC to higher centre was adequate in 262 districts in 29 states.

West Bengal was the only state where all districts were found to be inadequate for all domains which constituted continuum of snakebite care. In 10 states (Telangana, Goa, Karnataka, Andhra Pradesh, Tripura, Manipur, Nagaland, Sikkim, Odisha, Uttar Pradesh), all districts were found to be inadequate for four of the five domains which constitute continuum of snakebite care.

Figure 5: Proportion of districts (nation-wide) deemed adequate for different domains for continuum of snakebite care



Discussion

Summary of key results

This study presents state-level data on structural capacity and district-level data on adequacy of continuum of snakebite care for multiple domains in India – the first such study globally. We found that broader health systems domains (physical infrastructure, human resources for health, health management for information systems) are structurally weaker than the domain of medicines required for treatment of snakebite (snake anti-venom, anaphylaxis management drugs and normal saline) for almost all states, both at PHC and CHC level, although they were also not optimal. Availability of human resources for health and equipment was of greater concern in CHC than at PHC in many states. The continuity of care analysis affirms the above finding. The lack of accessibility of PHC throughout the year and the lack of effective referral linkage from PHC to higher centre, are additional critical gaps identified through the continuum of care analysis. Critical structural capacity at PHC and CHC, which is the minimum

capacity required for delivery of snakebite care was inadequate in almost all districts of India. There was, however, inter-state and intra-state variation.

Study findings within the context of what is previously known

The results of the study are based on the most recent nation-wide data that is available publicly, which was collected in 2012-2013. As such, the study provides insight on priority areas of focus for comprehensive health systems strengthening and establishes a baseline for monitoring progress. The results of the study should also be seen considering other data, available over time, for some indicators. The Rural Health Statistics 2012, which correspond to the period when the DLHS-4 was conducted, reported a shortfall of 10.3% for medical doctors at PHC level and 79.6% for physicians at CHC level [30] The shortfall reported in Rural Health Statistics of 2021, is 4.3% for medical doctors in PHC and 82.2% for physicians in CHC. [31] This indicates discordance between administrative data (which reports data 'on paper' basis) with survey data. The administrative data shows improvement in medical doctor at PHC level and deterioration at CHC level in the past decade.

There has been broader economic development, much of which might impact the infrastructure domain of structural capacity. As for example, between 2012 and 2020, access to electrification (%age of population) has increased from 79.9% to 99.0% in India. [32] However, the Annual Health Statistics , as reported in 31st March 2021, show 4.8% of rural PHCs still have no electric supply at all. [31] It is known that poor availability of electricity in PHC is disproportionately associated with access and quality of maternal care in India. [33] A quasi-experimental evaluation of the *Pradhan Mantri Gram Sadak Yojana*(which is tasked with constructing all-weather roads in all eligible unconnected rural habitations) found that between 2010 and 2015 the program

led to a statistically significant increase in the probability of a woman being delivered in a health facility, but there was no evidence of decreased neonatal mortality rate or post-partum complications. [34] This indicates need for focussing on quality of care. The same principle would hold true for health systems strengthening for snakebite care. Previous analysis of capacity for health for intrapartum care and cervical cancer, in India, have also identified infrastructure and staffing as critical gaps in continuum of care. [35] [36]

Strengths and limitations

The DLHS-4 facility survey is primarily geared towards reproductive, maternal and child health. Our analysis is focussed on assessment of structural capacity on snakebite care. The elements analysed are only those that are incidentally captured in the survey. The study results should be seen in this light, implying a more comprehensive assessment of health facilities, might demonstrate an even worse result.

Overall, this study provides a baseline, for future assessments. It is also noteworthy, that the results of the study are indicative of only structural capacity and does not provide any information on functional capacity or quality of care. There is also a need to understand and address the "intangible software" of health systems, i.e., the "ideas, norms, values and issues of power or trust that affect the performance of health systems." [37]

We did not calculate any overall score for structural capacity or continuum of care, and instead provided domain wise information to enable better visualisation of systems gaps and key areas of improvement. An overall scoring obliterates identification of bottle necks especially in the scenario when individual domain scores vary tremendously, as in our case. Another limitation also pertains to the reliability and specificity of the few

questions related to infrastructure in DLHS-4 itself. Instead of subjectively asking respondents whether the power supply was regular, or sewerage facility was proper, or whether the toilet was proper and in-use, future iterations of DLHS should use more objective measures. For example, the number of hours of power supply in the last 24 hours and structure observation on sewerage and toilet would enhance data quality. Elements form the questionnaire of the National Annual Rural Sanitation Survey [38] might be comprehensive for assessment of sewerage and sanitation in health facilities assessments in the future.

Implications for policy and practice

The roadmap by the Indian Council of Medical Research - National Task Force for Research on Snakebite focussed on development of rapid diagnostics kits and snake antivenom, guideline dissemination, legislative changes, awareness, and media outreach).[39] The Mission Steering Group, the apex decision making body for strategy development as well as implementation of the National Health Mission, in its 7th meeting held in September 2022 prioritised community awareness and capacity building of health workers for addressing snakebite. [19] However, based on our findings we contend that the piece-meal approach will not lead to the adequate health system strengthening for addressing the snakebite burden. A comprehensive approach is required to deliver on the continuum of primary health care for desired reduction in the snakebite burden. In policy terms, the Union Government of India should also consider commissioning a nationwide health facility assessment in high snakebite burden states.

Our analysis and available information indicate that even a decade back, the weakest elements of structural capacity were infrastructure, equipment, availability of human resources for health and health management information systems

The dominant focus of global funders and researchers is to develop newer or region specific snake anti-venoms. [40] With up to 64,100 Indians dying from snakebite every year in India, [3] re-orienting investments for snakebite towards comprehensive strengthening of primary healthcare (along with prevention), has the potential to save many lives in the immediate and medium term, and guarantee delivery of newer and improved therapeutic products, as and when they become available in the distant future.

Our data is from India, however similar scenario might be expected in other high-burden nations in Asia, and Africa, which are known to have weak health systems. [41 42] In general, there is need for health facility assessments with focus on snakebite. Currently there is no facility checklist or standard for snakebite care in India or globally. Development of a comprehensive health facility checklist and facility level standards of snakebite care (best not as standalone but integrated within existing ones or multi-disease in nature), will enable strengthening of the public primary health care system, leading to decreasing the burden of snakebite. Development of contextually relevant facility standards and checklist will enable more comprehensive assessment of capacity of snakebite care in high-burden nations.

The NITI Aayog Health Index uses similar methodology to categorise states for health systems functioning. [28] The index however is derived from indicators pertaining mostly to reproductive, maternal, and child health, tuberculosis, and HIV (Human Immunodeficiency Virus). There are no indicators specific to snakebite, or acute medical emergencies, for other conditions. Our data shows, that even high-performing states (as per NITI Aayog) did not have good scores for structural capacity for snakebite care. Integration of indicators related to care for snakebite, a neglected tropical disease, within the NITI Aayog Health Index can make the index more equity sensitive. Such an

integration aligns with the Union Government commitment to “leave no one behind” by making the index more comprehensive and realistic, and act as a nudge for states to address snakebite.

Conclusion

Comprehensive health system strengthening, focussing on all health systems blocks, and throughout the continuum of snakebite care in the primary health care system, instead of a piece-meal approach towards health systems strengthening, is critical for reducing the burden of snakebite in India, and potentially in other high-burden nations with weak health systems. For this purpose, nationwide facility surveys are necessitated. In India, we also suggest the addition of indicators related to snakebite care in future iterations of the NITI Aayog Health Index. This would make the index more comprehensive, realistic and equity focussed.

Availability of data and materials

The data underlying the results presented in the study, available as supplementary appendices. All data underlying the results is from a freely available public data set of the District Level Household and Facility Survey (DLHS-4). The data is available for academic research on request to the Data Centre of the International Institute for Population Sciences (IIPS), an autonomous institute under the aegis of Ministry of Health and Family Welfare, Government of India. The datasets underlying this article is available from the following source: https://www.iipsindia.ac.in/content/data-request

Competing interests

The authors declare that they have no competing interests.

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Supplementary appendix 1: structural capacity of snakebite care

A. Variable definitions and mapping in facility DLHS-4 Questionnaire for structural capacity in PHC

Sl. no.	Question DLHS	Variable number in DLHS-4 questionnaire
PHYSICAL INFRASTRUCTURE		
1.	Designated government building available for PHC	4.2
2.	Running water supply for 24 X 7	4.9
3.	Regular power supply	4.10
4.	Proper sewerage facility available	4.12
5.	Toilet available and in use	4.14 a
6.	Biomedical waste segregated and treated before disposal	4.23
7.	Residential facility available for doctor (available AND staying)	4.26 a-C
8.	Residential facility available for nurse (available AND staying)	+4.26 d-C
9.	Operational laboratory	1.12
HUMAN RESOURCES FOR HEALTH		
1.	At least one medical doctor	21 a OR 21 b OR 22 a OR 22 b
2.	At least one staff nurse	2.5 a OR 2.5 b
GOVERNANCE AND FINANCE		
1.	PHC plan	8.29
2.	Supervisory officer visited last month	8.35
3.	Received untied fund in last FY	8.43
HEALTH MANAGEMENT INFORMATION SYSTEMS		
1.	Facility wise data uploaded on HMIS	9.10
2.	Training on HMIS BY MO (EVER)	3.12 b ever
3.	Training on HMIS BY paramedical (EVER)	3.18 ever
MEDICINE FOR ACUTE SNAKEBITE TREATMENT		
1.	Availability of snake anti-venom/anti-dotes AND	6.11 a
	NO Stock-out of snake anti-venom/anti-dotes	6.11 b
	Snake antivenom availability	6.11 a+6.11 b
2.	Availability of Normal saline AND	6.14 b1
	NO Stock-out of Normal saline	6.14 b2
	Normal saline availability	6.14 b1 + 6.14 b2
3.	Availability of anti-allergic and drugs used in anaphylaxis AND	6.1 a

	NO Stock-out of anti-allergic and drugs used in anaphylaxis	6.1 b
	Anaphylaxis drug availability	6.1 a + 6.1 b
EQUIPMENT FOR SNAKEBITE CARE		
1.	Available and functional Blood/Saline Stand	4.43
2.	Available and functional BP instrument	4.52
3.	Available and functional Stethoscope	4.53

B. Variable definitions and mapping in facility DLHS-4 Questionnaire for structural capacity in CHC

No.	**Questions in the DLHS survey**	**Variable number in DLHS-4 questionnaire**
PHYSICAL INFRASTRUCTURE		
1.	Designated government building available for CHC	5.2
2.	Running water supply 24*7	5.9
3.	Regular power supply	5.12
4.	Proper sewerage facility available	5.16
5.	Toilet available and in use	5.18 a
6.	Biomedical waste segregated and treated before disposal	5.25
7.	Residential facility available for Physician (available AND staying)	5.32
8.	Residential facility available for staff nurse (available AND staying)	5.36
9.	Operational laboratory	5.59
10.	Designated emergency room / casualty room available in CHC	5.70
11.	License for blood bank/ approval for blood storage	1.8
HUMAN RESOURCES FOR HEALTH		
1.	At least one Physician	2.2 a OR 2.2 b
2.	At least one Medical Officer (General Deputy)	2,9 a OR 2.9 b
3.	At least one staff nurse	2.13 a OR 2.13 b
GOVERNANCE AND FINANCE		
1.	CHC plan	11.1
2.	Supervisory officer visited last quarter	11.3
3.	Received untied fund in last FY	11.8
HEALTH MANAGEMENT INFORMATION SYSTEMS		
1.	Facility wise data uploaded on HMIS	12.11
2.	Training on HMIS BY MO (EVER)	3.20 b ever

3.	Training on HMIS BY paramedical (EVER)	3.29 bever
MEDICINE FOR ACUTE SNAKEBITE TREATMENT		
1.	Availability of anti-dotes / snake anti-venom AND	811 a
	NO Stock-out of anti-dotes / snake anti-venom	811 b
	Snake antivenom availability	811 a + 811 b
2.	Availability of Normal saline AND	8.14 b1
	NO Stock-out of Normal saline	8.14 b2
	Normal saline availability	8.14 b1 + 8.14 b2
3.	Availability of anti-allergic and drugs used in anaphylaxis AND	81 a
	NO Stock-out of anti-allergic and drugs used in anaphylaxis	81 b
	Anaphylaxis drug availability	81 a + 81 b
EQUIPMENT FOR SNAKEBITE CARE		
1.	Available and functional Blood/Saline Stand	5.86 c
2.	Available and functional BP instrument	5.86 j
3.	Available and functional Stethoscope	5.86 k
4.	Available and functional mobile ventilator	7.3

Supplementary appendix 2: Proportion of PHCs having highest score in different domains of structural capacity for snakebite care in India

Name of State	Medicine for treatment of snakebite	Equipment for treatment of snakebite	Physical Infrastructure	Human Resources for Health	Governance and Finance	Health Management Information System
Uttarakhand	72.6%	86.9%	7.1%	46.4%	55.4%	0.0%
Rajasthan	79.5%	81.4%	3.3%	71.1%	72.3%	1.3%
Uttar Pradesh	60.3%	70.5%	0.1%	4.8%	23.5%	2.0%
Bihar	52.7%	60.7%	2.1%	38.6%	72.7%	5.4%
Assam	47.7%	93.1%	9.6%	61.6%	53.6%	0.7%
Jharkhand	37.0%	69.1%	0.0%	14.5%	34.5%	0.0%
Odisha	77.6%	78.9%	0.0%	8.1%	31.8%	0.4%
Chhattisgarh	77.8%	91.7%	2.0%	22.2%	66.3%	0.0%
Madhya Pradesh	84.1%	83.0%	1.6%	12.5%	72.8%	0.0%
Himachal Pradesh	58.8%	73.9%	1.3%	28.1%	61.4%	18.2%
Punjab	26.5%	81.5%	0.6%	66.0%	72.8%	0.0%
Haryana	81.7%	91.5%	1.6%	78.9%	85.4%	8.3%
Sikkim	75.0%	91.7%	29.2%	66.7%	66.7%	0.0%
Arunachal Pradesh	17.1%	81.7%	2.4%	50.0%	50.0%	0.0%
Nagaland	28.4%	86.4%	3.4%	73.9%	51.1%	15.0%
Manipur	23.7%	81.4%	0.0%	81.4%	37.3%	0.0%
Mizoram	42.9%	97.6%	31.0%	92.9%	47.6%	16.7%
Tripura	63.6%	90.9%	11.4%	93.2%	62.8%	12.9%
Meghalaya	92.0%	97.3%	16.0%	73.3%	9.3%	0.0%
West Bengal	12.7%	39.9%	4.8%	75.9%	36.0%	0.0%

Maharashtra	96.5%	97.0%	25.4%	28.4%	91.4%	2.6%
Andhra Pradesh	92.5%	94.2%	0.3%	86.7%	64.5%	4.2%
Karnataka	83.7%	95.7%	1.3%	56.0%	86.1%	2.3%
Goa	76.5%	88.2%	0.0%	100.0%	76.5%	0.0%
Kerala	76.2%	44.2%	1.1%	77.9%	76.1%	5.3%
Tamil Nadu	86.8%	93.9%	2.8%	73.6%	62.9%	0.0%
Puducherry	77.3%	95.7%	13.0%	69.6%	36.4%	0.0%
Andaman and Nicobar	94.4%	100.0%	16.7%	100.0%	33.3%	0.0%
Telangana	94.9%	94.9%	2.0%	90.9%	64.0%	5.4%

Supplementary appendix 3: Proportion of CHCs having highest score in different domains of structural capacity for snakebite care in India

Name of State	Medicine for snakebite Treatment	Equipment for Acute Snakebite treatment	Physical Infrastructure	Human Resources for Health	Governance and Finance	Health Management Information System
Uttarakhand	55.0%	10.0%	0.0%	13.3%	68.3%	0.0%
Rajasthan	75.2%	12.7%	3.8%	24.1%	86.4%	0.7%
Uttar Pradesh-	62.2%	3.2%	0.1%	16.1%	77.7%	0.8%
Bihar –	48.5%	20.6%	1.5%	27.9%	75.0%	0.0%
Assam	19.7%	4.7%	0.9%	14.5%	80.4%	0.0%
Jharkhand	36.3%	7.2%	0.0%	3.9%	77.2%	0.0%
Odisha	78.2%	5.6%	0.3%	10.3%	73.1%	0.0%
Chhattisgarh	76.1%	4.3%	0.0%	10.5%	79.0%	0.0%
Madhya Pradesh-	88.4%	6.8%	2.2%	10.6%	88.3%	0.0%
Himachal Pradesh	71.4%	11.7%	1.3%	7.8%	72.4%	14.9%
Punjab	41.2%	28.3%	0.8%	33.3%	79.2%	7.1%
Chandigarh	50.0%	100.0%	0.0%	50.0%	50.0%	0.0%**
Haryana	85.7%	7.5%	0.9%	2.8%	89.5%	0.0%
Sikkim	100.0%	100.0%	0.0%	0.0%	100.0%	0.0%
Arunachal Pradesh	22.6%	5.7%	0.0%	5.7%	56.6%	0.0%
Nagaland	5.0%	19.0%	0.0%	23.8%	61.9%	40.0%
Manipur	0.0%	6.3%	0.0%	6.3%	68.8%	8.3%
Mizoram	36.4%	27.3%	0.0%	18.2%	63.6%	12.5%
Tripura	28.6%	0.0%	0.0%	0.0%	45.5%	0.0%
Meghalaya	0.0%	21.4%	0.0%	57.1%	64.3%	0.0%
West Bengal	82.8%	4.6%	0.3%	7.4%	67.4%	0.0%

Maharashtra	93.2%	32.9%	3.2%	12.9%	89.9%	4.5%
Andhra Pradesh-	85.0%	3.8%	1.9%	6.4%	81.3%	0.0%
Karnataka	85.2%	15.1%	0.5%	8.6%	88.2%	4.0%
Goa	100.0%	75.0%	0.0%	50.0%	100.0%	0.0%**
Kerala	42.7%	29.9%	14.6%	37.2%	88.2%	35.7%
Tamil Nadu	89.7%	19.9%	1.2%	31.7%	87.2%	0.9%
Puducherry	85.7%	71.4%	0.0%	28.6%	42.9%	0.0%
Andaman and Nicobar	100.0%	0.0%	0.0%	50.0%	25.0%	0.0%
Telangana	81.6%	13.6%	2.3%	9.1%	64.3%	16.4%

Supplementary Appendix 4: State-wise listing of Indian districts with adequate continuum of snakebite care under different domains

Name of State	Connectivity of PHC with villages	Critical Structural Capacity of PHC	Transport availability from PHC to higher facility	Critical Structural capacity of CHC	Transport availability from CHC to higher facility
Uttarakhand	1. Rudraprayag	1. Uttarkashi 2. Rudraprayag 3. Champawat	1. Uttarkashi 2. Rudraprayag 3. Garhwal 4. Nainital	1. Champawat	1. Uttarkashi 2. Chamoli 3. Rudraprayag 4. Tehri Garhwal 5. Dehradun 6. Garhwal 7. Pithoragarh 8. Bageshwar 9. Champawat 10. Udham Singh Nagar
Rajasthan-	0	0	1. Sirohi	0	1. Ganganagar 2. Hamumagarh 3. Bikaner 4. Churu 5. Karauli 6. Sawai Madhopur 7. Dausa 8. Jaipur 9. Nagaur 10. Sirohi 11. Pali 12. Ajmer 13. Tonk 14. Bundi 15. Bhilwara
Uttar Pradesh	0	0	0	0	1. Saharanpur 2. Jyotiba Phule Nagar 3. Aligarh 4. Hathras 5. Firozabad 6. Etah 7. Mainpuri 8. Budaun 9. Pilibhit 10. Shahjahanpur 11. Kheri

					12. Lucknow 13. Rae Bareli 14. Etawah 15. Auraiya 16. Jhansi 17. Lalitpur 18. Chitrakoot 19. Barabanki 20. Basti 21. Azamgarh 22. Sant Ravidas Nadar Bhadohi 23. Sonbhadra
Bihar	0	0	0	1. Muzzafarpur 2. Lakhisarai	1. Pashchim Champaran 2. Purba Champaran 3. Sheohar 4. Supaul 5. Araria 6. Kishanganj 7. Purnia 8. Katihar 9. Madhepura 10. Saharsa 11. Muzaffarpur 12. Vaishali 13. Samastipur 14. Khagaria 15. Munger 16. Lakhisarai 17. Sheikhpura 18. Patna 19. Bhojpur 20. Rohtas 21. Jehanabad 22. Aurangabad
Assam	1. Hailakandi	0	1. Hailakandi	0	1. Kokrajhar 2. Goalpara 3. Nagaon 4. Golaghat 5. Karbi Anglong 6. North Cachar Hills 7. Hailakandi
Jharkhand	1. Kodarma	0	1. Kodarma 2. Giridh 3. Godda	0	1. Godda 2. Bokaro

	2. Purbi Singhbhum				3. Purbi Singhbhum
Odisha	0	0	0	0	1. Kendrapara 2. Nuapada 3. Rayagada 4. Koraput 5. Malkangiri
Chhattisgarh	0	0	1. Kawardha 2. Rajnandgaon	0	1. Koriya 2. Jashpur 3. Bilaspur 4. Kawardha 5. Rajnandgaon 6. Raipur 7. Mahasamund 8. Dhamtari 9. Bastar 10. Dantewada
Madhya Pradesh-high burden	0	0	1. Panna 2. Umaria 3. Shahdol 4. Ujjain 5. Jhabua 6. Seoni	0	1. Sheopur 2. Guna 3. Tikamgarh 4. Chhatarpur 5. Panna 6. Damoh 7. Umaria 8. Mandsaur 9. Ratlam 10. Ujjain 11. Dewas 12. Jhabua 13. Dhar 14. Indore 15. Barwani 16. East Nimar 17. Rajgarh 18. Bhopal 19. Raisen 20. Betul 21. Katni 22. Dindori 23. Seoni 24. Balaghat
Himachal Pradesh	0	0	1. Kullu	0	1. Chambra 2. Kullu 3. Hamirpur 4. Bilaspur 5. Sirmaur
Punjab	0	0	1. Rupnagar 2. Fatehgarh Sahib	0	1. Gurdaspur 2. Amritsar 3. Kapurthala

					4. Shahid Bhagat Singh Nagar 5. Rupnagar 6. Fatehgarh Sahib 7. Ludhiana 8. Moga 9. Faridkot 10. Mansa 11. SAS Nagar 12. Barnala 13. Taran Taran
Chandigarh	NA	NA	NA	0	1. Chandigarh
Haryana	0	1. Panchkula	1. Kurukshetra 2. Karnal 3. Jind 4. Bhiwani 5. Rohtak	0	2. Panchkula 3. Ambala 4. Yamunanagar 5. Kurukshetra 6. Kaithal 7. Karnal 8. Panipath 9. Jind 10. Fatehabad 11. Hisar 12. Rohtak 13. Faridabad 14. Mewat 15. Palwal
Sikkim	0	0	0	0	1. South Sikkim
Arunachal Pradesh	1. Lower Subansiri 2. Upper Siang 3. Dibang Valley	0	1. Lohit	0	1. Tawang 2. West Kameng 3. East Kameng 4. Papumpare 5. Changlang 6. Anjaw
Nagaland	0	0	0	0	1. Mon 2. Tuensang 3. Mokokchung 4. Zunheboto 5. Dimapur 6. Kohima 7. Phek 8. Paren
Manipur	0	0	0	0	1. Tamenglong 2. Imphal West
Mizoram	0	0	0	1. Kolasib	1. Kolasib 2. Aizawl 3. Champhai

					4. Serchhip 5. Lunglei 6. Lawngtlai
Tripura	0	0	0	0	1. Dhalai
Meghalaya	0	0	1. West Garo Hills 2. East Garo Hills 3. South Garo Hills 4. West Khasi Hills 5. Ri Bhoi	0	1. West Garo Hills 2. South Garo Hills 3. West Khasi Hills 4. East Khasi Hills 5. Jaintia Hills
West Bengal	0	0	0	0	0
Maharashtra	**0**	1. Nandurbar 2. Dhule 3. Amrawati 4. Jalna 5. Satara	1. Nandurbar 2. Dhule 3. Jalgaon 4. Buldana 5. Washim 6. Amrawati 7. Nagpur 8. Bhandara 9. Gondiya 10. Gadchiroli 11. Chandrapur 12. Yavatmal 13. Jalna 14. Aurangabad 15. Nashik 16. Thane 17. Pune 18. Ahmadnagar 19. Latur 20. Osmanabad 21. Solapur 22. Satara 23. Ratnagiri 24. Sindhudurg 25. Kolhapur	0	1. Nandurbar 2. Dhule 3. Jalgaon 4. Buldana 5. Akola 6. Washim 7. Amrawati 8. Wardha 9. Nagpur 10. Bhandara 11. Gondiya 12. Gadchiroli 13. Chandrapur 14. Hingoli 15. Parbhani 16. Jalna 17. Aurangabad 18. Nashik 19. Raigarh 20. Pune 21. Ahmadnagar 22. Bid 23. Latur 24. Osmanabad 25. Solapur 26. Satara 27. Ratnagiri 28. Sindhudurg 29. Kolhapur 30. Sangli
Andhra Pradesh-high burden	0	0	0	0	1. Prakasam 2. Anantpur 3. Chitoor

Karnataka	0	0	0	0	1. Bagalkot 2. Gulbarga 3. Bidar 4. Raichur 5. Koppal 6. Gadag 7. Dharwad 8. Uttara Kannada 9. Haveri 10. Bellary 11. Shimoga 12. Kolar 13. Mysuru (Mysore) 14. Chamarajanagar 15. Yadgir
Goa	0	0	0	0	1. North Goa 2. South Goa
Kerala	1. Idukki 2. Pathanamathitta 3. Thiruvanthapuram	1. Pathanamthittta	1. Pathanamthittta	0	1. Mallappuram 2. Palakkad 3. Idukki 4. Pathanamthitta
Tamil Nadu	0	1. Namakkal 2. Puduukkottai	1. Thiruvarur 2. Thanjavur 3. Theni	0	1. Thirruvallur 2. Dharmapuri 3. Tiruvannamalai 4. Erode 5. Nilgiris 6. Coimbatore 7. Karur 8. Peramnalur 9. Ariyalur 10. Nagapattinam 11. Sivaganga 12. Madurai 13. Theni 14. Ramanathapuram 15. Thoothukkudi 16. Tirunelveli 17. Krishnagiri 18. Tiruppur
Puducherry	0	0	1. Puducherry	0	1. Puducherry (Pondicherry) 2. Mahe

			(Pondicherry)		3. Karaikal
Andaman and Nicobar	0	1. South Andaman	0	0	1. North and Middle Andaman 2. South Andaman 3. Nicobar
Telangana	0	0	0	0	1. Karimnagar 2. Mahbubnagar 3. Warangal

5. Effect of COVID-19 on snakebite care in India

5.1. Chapter overview

In this chapter, I aim to understand the effect of COVID-19, and consequent containment measures, on prevention and control on snakebite care. The idea was to explore how the health system shock due to COVID-19 affected snakebite care. I conducted two studies. I first, conducted a quantitative study, to understand the facility-level impact of COVID-19 containment measures. The study was conducted during the national lockdown and had the modest objective of getting a quantitative sense of the problem. To the best of my knowledge, it is the only quantitative study globally on the effect of COVID-19 on snakebite. The second study presented in the study is a qualitative study. It was conducted to better understand how access to snakebite care was affected during the first two waves of COVID-19. The study was conducted in the high burden state of West Bengal, but in two contrasting areas (rural- deltaic and semiurban, connected to highway) to enable comparison, and enhance better understanding of factors. In the study, we were able to map factors specific to COVID-19, as well as factors which are long standing and systemic in nature. Both the studies contribute to understanding pandemic resilience of health systems, with a focus on snakebite care.

This chapter contains two manuscripts:

1. The first manuscript (Section 5.3), a quantitative study to get clues on the facility-level impact of COVID-19 on snakebite care in India, is the accepted, (subject to minor revisions) version of the article in Rural and Remote Health:

- **Bhaumik S**, Tanna GLD, Beri D, Bhattacharya A, Kumar P, Giri S, et al. Effect of COVID-19 containment measures on access to snakebite care in India. Rural and Remote Health. 2023

The publication is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in the thesis.

2. The second manuscript (Section 5.4), a qualitative study to understand access to snakebite care through first two waves of COVID-19 in West Bengal, India, has been submitted in a journal:
    - **Bhaumik S**, Beri D, Zwi A, Jagnoor J. Snakebite care during the first two waves of COVID-19 in West Bengal, India: a qualitative study. This is the submitted version of the paper in Toxicon X. During the course of the examination of the thesis, the paper was accepted and published in Toxicon X. It is available here.

5.2. Candidate's contribution to the work

For manuscript presented in Section 5.3

I conceptualised this study with my primary supervisor and candidate set up the data collection platform and oversaw the data collection process. I conducted the analysis, validated the results, and wrote the first draft of the manuscript. I coordinated and incorporated feedback from the co-authors to prepare and submit the manuscript to the journal.

For manuscript presented in Section 5.4

I conceptualised and designed the study which this Chapter contains. I obtained the data, developed the protocol and statistical analysis plan. I conducted the analysis, validated the results, and wrote the first draft of the manuscript. I coordinated and incorporated feedback from the co-authors to prepare and submit the manuscript to the journal.

5.3. Manuscript: quantitative exploration of the effect of COVID-19 on access to snakebite care in India

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Effect of COVID-19 containment measures on access to snakebite care in India

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Abstract

Introduction

Extensive spread of COVID-19 meant action to address the pandemic took precedence, over routine service delivery, thus affecting access to care for many health conditions, including snakebite.

Method

We prospectively collected facility-level data from multiple health facilities (HFs) in India, including number of snakebite admissions and snakebite envenoming admissions on modality of transport to reach the HF. To analyse the effect of a HF being in cluster-containment zone, we used negative binomial regression analysis.

Result

Our findings suggest that that HFs located within a COVID containment zone saw significant decrease in total snakebite admissions [IRR = 0.64(0.43 to 0.94), SE=0.13, P>|z|=0.02)] and envenoming snakebite admissions [IRR = 0.43(0.23 to 0.81), SE=0.14, P>|z|=0.01], compared to when HFs were not within a COVID containment zone. There was no statistically significant difference in non-envenoming admissions, and modalities of transport used to reach HF.

Conclusion

The article provides the first quantitative estimation of the impact of COVID-19 containment measures on access to snakebite care. More research is needed to understand how containment measures altered care-seeking pathway and the nature of

snake-human-environment conflict. Primary healthcare systems need to be safeguarded for snakebite care to mitigate effects of cluster-containment measures.

Introduction

Snakebite was recognised as a neglected tropical disease by the World Health Organization (WHO) in 2017. Subsequently, in 2019, the WHO released a global strategy to decrease its burden to 50% by 2030[1]. Extensive spread of COVID-19 meant action to address the pandemic (diversion of health system resources, mobility restrictions and economic impacts) took precedence over action on other health conditions, including snakebite. [2] To the best of our knowledge, currently there is no quantitative estimation on the effect of containment measures for COVID-19 on snakebite care. Understanding the effect is important for public health agencies, health service providers, as well as policymakers to plan for future health systems resilience. We, thus, aimed to fill this gap by trying to understand the association between access to snakebite care in India with a health facility being within a COVID-19 cluster-containment zone.

The cluster-containment strategy to prevent spread of COVID-19 was operationalised in India from May 2020. Broadly the strategy consisted of setting up a perimeter with restricted movement (together with enhanced surveillance and contact tracing) called "containment area," in a defined geographic area with a cluster of COVID-19 cases, based on risk assessment. [3] The strategy was largely successful in containing COVID-19 in the first wave of COVID-19 in India but has been concerns on the strategy not being able to safeguard other acute medical emergencies has been previously raised.

Methods

We collected data prospectively from seven health facilities (HF): from Assam (one community health centre), Bihar (one rural general practice), Maharashtra (one nursing home and one rural general practice), Rajasthan (one tertiary care centre), and Karnataka (one tertiary care hospital and one non-profit primary health centre) on hospital admission due to snakebite, referral and modality of transport used to reach the HF. We used facility-level data and treating physicians made decisions on whether it was envenoming or non-envenoming, as per facility protocols. Data was entered every two weeks using a secure online platform (Redcap) from May 2020 to October 2020. We also collected information on whether a HF was located within a government declared COVID-19 containment zone or not in parallel.

To analyse the effect of a HF being in cluster-containment zone, we used negative binomial regression analysis. Negative binomial regression analysis is based on Poisson-gamma mixture distribution and can be used to predict count-based data. We choose this analysis method, because our dependent variables (number of admissions, referrals and types of transport used) consist of only non-negative integer values and the variance of the dependent variables were greater than the mean. A Poisson mixed model also allows for incorporation of both fixed and random effects for count data. [4] In our study, this allowed us to incorporate differences in the dependent variable between hospitals (random effect) and within hospital (fixed effect) wherein, the data has been collected at equal repeated time intervals. The study has been approved by the institutional ethics committee of The George Institute for Global Health (09/2020), All India Institute of Medical Sciences, Jodhpur (2020-21 /2032), and Mysore Medical College and Research Institute and Associated Hospitals (dated 12th May 2020). The

study is conducted in accordance with National Guidelines for Ethics Committees Reviewing Biomedical and Health Research During Covid-19 Pandemic (April 2020).

Results

There were 451 admissions due to snakebite (179 envenoming, 39.69%; 272 non-envenoming, 60.31%) in seven HFs.

For regression, we used data of 352 admissions due to snakebites (127 venomous, 36.08%; 225 non-envenoming, 63.92%) from 5 participating HFs. We excluded one HF which was declared as a COVID-19 facility, leading to surge of cases, rendering data collection impossible, and another HF which recorded only 1 snakebite admission during the entire study period.

We found that HFs located within a COVID containment zone saw a 36% significant decrease in total snakebite admissions [Incidence rate ratios (IRR)= 0.64; 95% CI=0.43 to 0.94; SE=0.13; P>|z|=0.02)] and 57% of envenoming snakebite admissions[IRR = 0.43; 95% CI= 0.23 to 0.81; SE=0.14; P>|z|=0.01], in comparison to when they were not within a COVID containment zone. There was no statistically significant difference between a HF being located within a COVID-cluster zone or not for number of non-envenoming snakebite admissions, or due to different modalities of transport used to reach health facilities (Table 1).

Table 1: Association of incidence rate ratios between facility location within a COVID containment zone or not with facility-level snakebite parameters

	Incidence rate ratios (IRR)	95% Confidence Interval	Standard Error	P>|z|
Hospital admissions due to snakebite				
Total snakebite admissions	0.64	0.43 to 0.94	0.13	0.02*
Snakebite envenoming admissions	0.43	0.23 to 0.81	0.14	0.01*
Non-envenoming snakebite admissions	0.84	0.49 to 1.44	0.23	0.53
Referral from other health facilities for snakebite				
Referral from other health facilities	0.50	0.21 to 1.23	0.23	0.13
Modality of transport to reach health facility for snakebite				
Used ambulance (any type)	0.61	0.22 to 1.66	0.31	0.33
Used a non-ambulance private/hired four-wheeler(car)	0.79	0.42 to 1.49	0.26	0.48
*Indicates statistically significant				

Discussion

The findings of this study suggest a significant decrease in total and envenoming admissions with no difference in non-envenoming admissions, or transport modalities due to institution of COVID-19 containment measures in India.

The decrease in total admissions and snakebite envenoming admissions might be due to decrease in community incidence, or alternation in care seeking pathway. The decrease in incidence of snakebite in community is plausible because the change in human activity (less mobility and increased time spend in and around dwelling) due to containment measures might have altered the human-snake-environment interface. It is known that this interface is altered by anthropogenic activity. [5] It is also possible that the decreased admissions is a result of care seeking pathway. A qualitative study [6] involving key informants reported perceptions on decreased number of snakebite admissions due to avoidance of HF for fear of COVID-19, barriers in testing and several other access issues. Considering the non-significance for non-envenoming admissions, and the transport modalities to reach HF, it is possible that a more complex interaction consisting of differential alteration of both human-snake-environment interface and care-seeking pathway between envenoming and non-envenoming cases occurred.

The findings of the current study are context-specific but based on data from diverse but limited number of health facilities in India. Longitudinal mapping and data collected by transdisciplinary teams, on the changing nature of human-snake interactions are needed to understand the issue better. Modelling using data from a wider set of HFs for multiple years can provide better understanding of the effect of COVID-19 on snakebite including quantitative estimation of the impact and across diverse types of HFs. Data from national health profile and Integrated Disease Surveillance Programme might be used for this purpose but it does not report on modalities of transport, [7]and is mostly limited to public health facilities. It is also known that the official statistics for snakebite cases as captured through these portals is massively undercounted. Research to better

understand how care-seeking pathway altered due to COVID containment measures is also necessitated.

Conclusion

To the best of our knowledge, this is the only study providing quantitative evidence on the effect of COVID-19 containment measures on access to snakebite care. Understanding the effect of pandemic on snakebite can help develop better multicomponent health systems interventions [8] which are resilient to crisis such as pandemics and climate change. Augmentation and safeguarding of snakebite care at the primary healthcare system is necessary when containment measures for pandemic control are being instituted.

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None.

Competing interests

None declared.

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5.4. Manuscript: qualitative study on the effect of COVID-19 containment measures in West Bengal, India

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Snakebite care through the first two waves of COVID-19 in West Bengal, India: a qualitative study

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Abstract

Background

Snakebite is a public health problem in many countries, with India having the highest number of deaths. Not much is known about the effect of COVID-19 on snakebite care.

Methods

We conducted 20 in-depth interviews with those bitten by venomous snakes through the two waves of COVID-19 (March-May 2020; May-November 2021), their caregivers,

health care workers and social workers. We used a constructivist approach and conducted a thematic analysis.

Results

We identified the following themes: 1. Snakebite continued to be recognised as an acute emergency during successive waves of COVID-19; 2. COVID-19 magnified the financial woes of communities with high snakebite burden; 3. The choice of health care provider was driven by multiple factors and consideration of trade-offs, many of which leaned toward use of traditional providers during COVID-19; 4. Rurality, financial and social disadvantage and cultural safety, in and beyond the health system, affected snakebite care; 5. There is strong and shared felt need for multi-faceted community programs on snakebite.

We mapped factors affecting snakebite care using the three-delay model, originally developed for maternal mortality.

Conclusion

Multi-faceted community programs, are needed for addressing factors affecting snakebite care, including during disease outbreaks- thus improving health systems resilience. Community programs for increasing formal health service usage, should be accompanied by health systems strengthening, instead of an exclusive focus on awareness against traditional providers.

1. Background

Snakebite is a significant public health problem in several countries, with India having the highest number of deaths. [1-4] In 2019, India had the second highest age-standardised mortality rate(4.0 per 100,000) , indicative of inadequate snakebite care. [4]

In September 2019, the World Health Organization (WHO) released a strategy with the explicit target of halving the global burden of snakebite by 2030. [5] Few months after the release of the WHO strategy, in 30 January 2020, COVID-19 was declared as a Public Health Emergency of International Concern by WHO. [6] Subsequently, as COVID-19 spread globally, its control through containment measures (social, economic, and mobility-related), together with diversion of scarce health systems resources to scale up the COVID-19 response affected healthcare delivery. The impact of COVID-19 on care for several conditions has been studied, [7-13] but little is known with respect to snakebite. To the best of our knowledge, only one qualitative study, [14] has been undertaken in the early phase of the pandemic to understand perceptions of key informants.

We aimed to fill this gap by conducting a qualitative study to explore the effect of COVID-19 on access to appropriate and timely care for snakebite envenomation through the two waves of COVID-19 in West Bengal, a state in eastern India.

2. Methods

2.1. Study context

The Union Government of India, during the first phase of the COVID-19 pandemic, implemented a complete nationwide lockdown from 25th March 2020 to 31st May 2020.

Restrictive measures were gradually eased up until November 2020. These first wave lockdowns have been largely successful in containing COVID-19 deaths. However, from March 2021, a surge of COVID-19 cases led to overburdened health systems with unprecedented deaths and suffering due to COVID-19. [15] During the second wave, state governments once again instituted containment measures; in West Bengal these were imposed from May to November 2021.

2.2. Study setting and design

The study was carried out in two geographic areas: semi-rural communities in Hooghly, and rural communities in the Sundarbans of West Bengal, India. Hooghly is known for its high agricultural productivity and proximity to the National Highway which enables connectivity to tertiary health facilities in Kolkata, the state capital. The Sundarbans is a deltaic region and is one of the poorer districts in the state. Transport connectivity is not well developed, and the area is largely rural. The two study areas were chosen purposively noting the difference in terms of degree of rurality and accessibility.

2.3. Methodological orientation and theory

We use a constructivist approach. Constructivism [16] allowed us to emphasise how participants constructed their reality and simultaneously acknowledge the subjective nature of its interpretation during analysis.

2.4. Participant selection

We conducted maximum variation purposive sampling based on study areas and the timing in which a person was bitten (first lockdown in 2020, second lockdown in 2021, and when no lockdown measures were in place). We conducted in-depth interviews

with adult participants in Sundarbans and Hooghly, who were survivors or caregivers of venomous snakebite, and were either bitten when COVID-19 containment (lockdown) measures were in place (first and second waves) or when they were lifted (period between two waves or after second wave) irrespective of hospitalisation, and with healthcare and social workers involved in snakebite care. We excluded those with diagnosed cognitive/mental impairment and those not able to provide informed consent. We also excluded participants who were bitten by snakes after February 2022. We disseminated information about the study to potential participants with the help of local organisations. The interviews were all conducted at the homes of survivors, caregivers, and social workers. Healthcare workers were interviewed at their home or at health facility, based on their preference. Interviews were conducted in the absence of non-participants.

2.5. Data collection

A semi-structured topic guide, iteratively revised as the study progressed, was used for in-depth interviews (IDIs) in Bangla and English (only one). No order of questioning was followed, allowing emphasis on the flow of conversation. The IDIs lasted for 14-65 minutes. The IDIs were audio recorded, with supplementary field notes taken. We interviewed participants on a single occasion.

2.6. Analysis

We transcribed IDIs verbatim. Transcripts were not returned to the participants. We conducted data collection simultaneously with the process of coding, organising the data and facilitating constant comparison in an iterative and reflective manner. We used thematic analysis. Open coding was done on five transcripts by two authors

independently (SB- without any translation and DB on translated transcripts in English). After that, the research team jointly looked for utility and conceptual relations between codes to develop concept maps, which served as the initial coding tree. At this instance codes applied were data-driven, with more interpretive analysis occurring later. This initial coding tree was applied to other transcripts (with no translation by SB). As interviews progressed, the existing coding tree was changed iteratively (in consultation with others). The process continued until data saturation was reached for both the study areas separately. The final coding tree was applied to all transcripts. We used NVIVO 11 (Version NVivo Pro). No participant checking was done.

We mapped all factors affecting snakebite care diagrammatically using the three-delay model (originally developed [17] for maternal mortality): decision to seek care from formal health systems; reaching appropriate health facilities, and; receiving appropriate care after reaching health facility.

2.7. Research team and reflexivity

The research team included professionals with backgrounds in medicine, public health, injury research, snakebite, and social work and was gender balanced. All authors had prior experience of qualitative research. The lead researcher (SB) is from West Bengal, an insider. At the same time, considering socio-economic privileges, he is an outsider to the lived realities of the study participants (except for clinicians in the category of health care workers). Others are outsiders. Consistent with a constructivist approach, we worked reflexively, pausing to reflect on any assumptions about the data, discussing with team members to maintain emphasis on the reality as seen by participants.

3. Results

We conducted 20 interviews (Table 1: Summary Characteristics of participants).

Table 1: Summary characteristics of participants

Study areas	- Hooghly: 9 - Sundarbans: 11
Gender	- Male: 10 - Female: 10 - Other: 0
Age Group	- 18-30 years: 7 - 30 to 50 years: 11 - > 50 years: 2
Type of study participant	- Snakebite survivors / caregivers: 10 - Healthcare worker: 6 - Social worker (associated with community-based organisations or community clubs):4

Many snakebite survivors and caregivers acknowledged their lack of a reference point about how snakebite care may have been affected by COVID-19 and described how they navigated a complex set of factors to access snakebite care, including some related to COVID-19. Healthcare workers and social workers on the other hand described many challenges due to COVID-19 containment, over and above the already existing challenges in delivering care for snakebite.

3.1. Themes

Our analysis of the social understanding of the effect of COVID-19 on snakebite care is presented in the form of five themes, summarised in Figure 1.

Figure 1: Access to snakebite care during COVID-19 waves: summary of themes

3.1.1. Theme 1: Snakebite continued to be recognised as an acute emergency during successive waves of COVID-19

Participants recognised that snakebite is an acute medical emergency for which care needs to be sought. This understanding was sustained through the waves of COVID-19. Some participants described fear of contracting COVID-19 as leading to some delay, as they waited for envenoming symptoms to evolve before making the decision to seek care.

> *"People were afraid of COVID... Perhaps they thought a bit before going to the hospital, but the effect of COVID is not much (on decision to seek care)."*
>
> *-IDI 009 Snakebite Survivor, Hooghly*

Some participants considered the odds, deciding that the probability of fatality from snakebite was higher than the likely consequences of COVID-19, particularly when taking adequate precautions. The rational frame was more dominant during the second wave of COVID-19 (2021), due to increased confidence and awareness of COVID-19 control measures.

"There was serious lockdown, but by then we had a mental map … We had a much clearer understanding of what we are facing or what we will be experiencing, what could be the consequences."

– IDI 006 Social worker, Hooghly

3.1.2. Theme 2: COVID-19 magnified the financial woes of communities with high snakebite burden

Most participants highlighted the poor socio-economic status of snakebite-affected communities and associated an incident of snakebite with inevitable out- of-pocket health care expenditure (costs for transportation and medicines, plus costs and expenses of caregivers while the patient was admitted to a health facility). The financial consequences added to the financial woes of communities with high snakebite burdens due to inflationary pressures.

"Ambulance, car rental costs a lot to go to the hospital from here."

- IDI 021, Survivor, Sundarban

"Those who are at the lowest strata of society have a problem. They earn daily and eat daily. They had problems when there were lockdowns. It was long." – IDI 014, CHW, Sundarban

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Several social workers and community health workers (CHW) mentioned that COVID-19 had made their financial condition more precarious:

"We do not get a lot of money. Those days we had to bear a lot of pain. … I sell vegetables to make ends meet, but at that time no one had money to buy… The cost of education of children has also increased. It needs a lot of money…. We were dependent on government relief[iv]. We did not have even money to buy rice and pulses." - IDI 016, CHW, Sundarban

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We found one community fund in Hooghly which provided financial risk protection for those with snakebite (and all other acute medical conditions), although its sustainability was described as challenging. The fund was accessible at any time, did not need any financial guarantees, and was available for all to meet out-of-pocket expenditure when seeking admission in formal health facilities. The seed for the fund was acquired from the West Bengal Chief Ministers grant-in-aid to community clubs and was replenished from time to time by well-off community members or by snakebite survivors.

[iv] In Sundarban, the Government of West Bengal provided relief for COVID-19 and co-incident Cyclone Amphan in May 2020 and Cyclone Yaas in May 2021

3.1.3. Theme 3: The choice of health care provider was driven by multiple factors and consideration of trade-offs, many of which leaned toward use of traditional providers during COVID-19

The choice of healthcare provider involved consideration of multiple factors and trade-offs, this included distance, availability, trust, affordability, and perceptions, of outcome.

"...Rs 100, Rs 50, or Rs 51, whatever we give, Ojha (traditional provider) heals us and is happy with that. That is why we all go to him. When we went there (hospital), the doctor says it would cost Rs 5000, or Rs 3000, he would write it in the prescription, we would have to bring the medicine, we would have to run around. The ferry does not run at night. How will we return? For traditional providers we pay Rs 10 to the van and we reach home"

- IDI 020, Snakebite Survivor, Sundarban

"From those who go to hospital, some recover, some are sick, some even die. Everyone who takes the medicine from the Ojha recovers. How will we know (predict) what happens in a hospital?"

IDI -013, Snakebite survivor, Sundarban

Factors promoting a preference for traditional providers were accentuated during COVID-19.

"I do not think they had any clue because everyone was so overwhelmed with COVID. If somebody required ventilators, they usually referred to higher facility, and the ventilators were already occupied by COVID patients there. Hospitals in our area, they did not get those extra ventilators …and I do not think they have those extra ventilators now also. So well in rural hospitals, they never have ventilators." '– IDI 006, Social Worker, Hooghly

A small number of participants mentioned that engagement with members of community-based organisations (CBOs) during the decision-making process moderated the trade-off positively towards accessing formal health systems.

3.1.4. Theme 4: Rurality, financial, social disadvantage, and cultural safety, in and beyond the health system, affected snakebite care

The navigation of snakebite care related to the intersection of rurality, financial and social disadvantage, and perceptions of cultural safety.

In Hooghly, which is semi-urban and connected to the National Highway, geographic access was of relative less concern. Barriers which were financial in nature, related to reaching an appropriate health facility, and receiving appropriate care on reaching the health facility were discussed more. Participants from Sundarbans additionally mentioned distance and availability of transport. Few participants from Sundarbans used an 'outside land' framing when discussing referral to tertiary care facilities (usually in urban areas), implying on their lack of familiarity and cultural safety. The lack of

cultural safety in accessing care for people in Sundarbans was a challenge to access care for acute medical emergencies, like snakebite.

> *"Humans are bitten by snakes everywhere, but we have no hospital here for snakebites. We have to go outside. - IDI 016, Healthcare Worker, Sundarbans*

Some participants expressed that attitudes, behaviours, and communication of medical staff influenced care delivery in health facilities (in both Hooghly and Sundarban). Participants mentioned that a condescending and unconcerned attitude in emergency departments made health systems navigation difficult.

> *"… We entered the emergency office… She (medical doctor) said, you first get the ticket and then do what they say from there. I said, are you crazy? A baby boy is bitten by a snake, and I go outside and get a ticket and then come to you! By then, something serious could happen to the boy. You seem to know a lot, she told me.…Doctors do not behave well in the hospitals. Doctors must be called from their quarters … even if the treatment is started 5 minutes ago, then it increases the probability of their survival. There is a lot of negligence seen." - IDI 001, Social Worker, Hooghly*

Few participants identified that in first wave, the concerns about COVID-19 in medical staff, might have added to disrespectful behaviour: caregivers were often not communicated about prognosis, or even allowed to enter health facility premises. Health facilities, in which medical staff actively communicated to allay panic and respond to patients and caregiver concerns, were seen to be exceptions. This added to institutional legacy on community preference for specific health facilities for accessing around snakebite care, and many without consideration of distance or time.

"We counsel them that this is required, and this is not. We allay their panic. In case of any problem, we ask them to call us, and we tell them to come to our hospital."

IDI 007, Healthcare Worker, Hooghly

The need for health systems strengthening across all health facilities and learning from best practices of institutions with legacy of superior quality of care, was recognised as a as an enabler process for strengthening primary health care by few participants.

One participant mentioned about the discriminatory nature of police behaviour during the first lockdown was a barrier.

"a lot of general caste people, they look at suspicion, they do not want to help backward people. So, in a couple of cases where there were snakebites, when we were going to respond to the snakebite to evacuate them, take them to the hospital, we were stopped by the police," – IDI 006, Social Worker, Hooghly

3.1.5. Theme 5: There is a strong and shared felt need for multi-faceted community-based programs on snakebite

There is a strong and shared felt need for multi-faceted community-based programs on snakebite in high-burden communities. This need was expressed in both study areas and expressed by almost all participants either by giving suggestions for improving and scaling up existing activities or by identifying of absence of community-based programs

as a gap. Many social workers and patients / caregivers identified with the values of snake conservation, and the need to be non-violent towards “helpless” animals.

Participants identified the following facets of a community-based program:

- awareness on snakes, snakebite prevention and post-bite do’s and do-nots,
- mitigation of snake-human-environment conflict, including but not limited to ‘snake-rescue’ (translocation of snakes) and promotion of snake conservation,
- first-aid and bystander training,
- promotion of the use of the formal health system through snake identification, support for decision making on care-seeking, establishing contact, and arranging transport; support during referral to higher centres, and providing advance information to providers in health facilities to ensure preparedness on arrival, and
- advocacy for strengthening health systems capacity for snakebite care.

3.1.5.1. Sub-theme: Community health workers saw limited role for themselves and had little capacity for engaging in community-based programs on snakebite

For many participants, the role of CHWs (Accredited Social Health Activists or ASHAs) in community-based program on snakebite was seen to be limited. CHWs aligned their identity to working for reproductive, maternal, neonatal and child health services. CHWs were overburdened and COVID-19 related services (and extreme weather events, like cyclones, in Sundarbans) added to the challenge.

"As an ASHA, our work is mainly on maternal and child health – that was how we started initially. Not only do we take care of mothers and children but over and above, additional jobs are thrust on us. Our workload continues to increase every passing day." -IDI 008, Healthcare worker, Hooghly

3.1.5.2. Sub-theme: Community-based organisations (CBO), where they existed, were recognised, and appreciated by communities

The CBOs, where they exist, and although challenged during COVID-19, were recognised, and appreciated by communities. Healthcare workers acknowledged support from CBOs and appreciated their capacity, while some survivors acknowledged their role in advocacy for health systems strengthening.

"CBOs explain it is not God, but a human who earns profits in the name of cure. The Canning Juktibadi (Science Rationalist) Organisation have capacity to convince people"- IDI 014, Healthcare worker, Sundarbans

"...if there is awareness, by CBOs it will be good. I do not think a government can do this, both need to work collaboratively to raise awareness – village by village, intensively through Jatras (folk theatre) then people will benefit" -IDI 019, Snakebite Survivor, Sundarbans

Through multiple interviews, some inherent advantages, of CBOs in delivering community-based programs was evident: being embedded and always accessible to

community, appreciation of cultural and social processes, capacity for snake identification, translocation of snakes (snake-rescue), perceived selflessness, and trust. Lack of recognition and resource constraints were identified as challenges by CBOs.

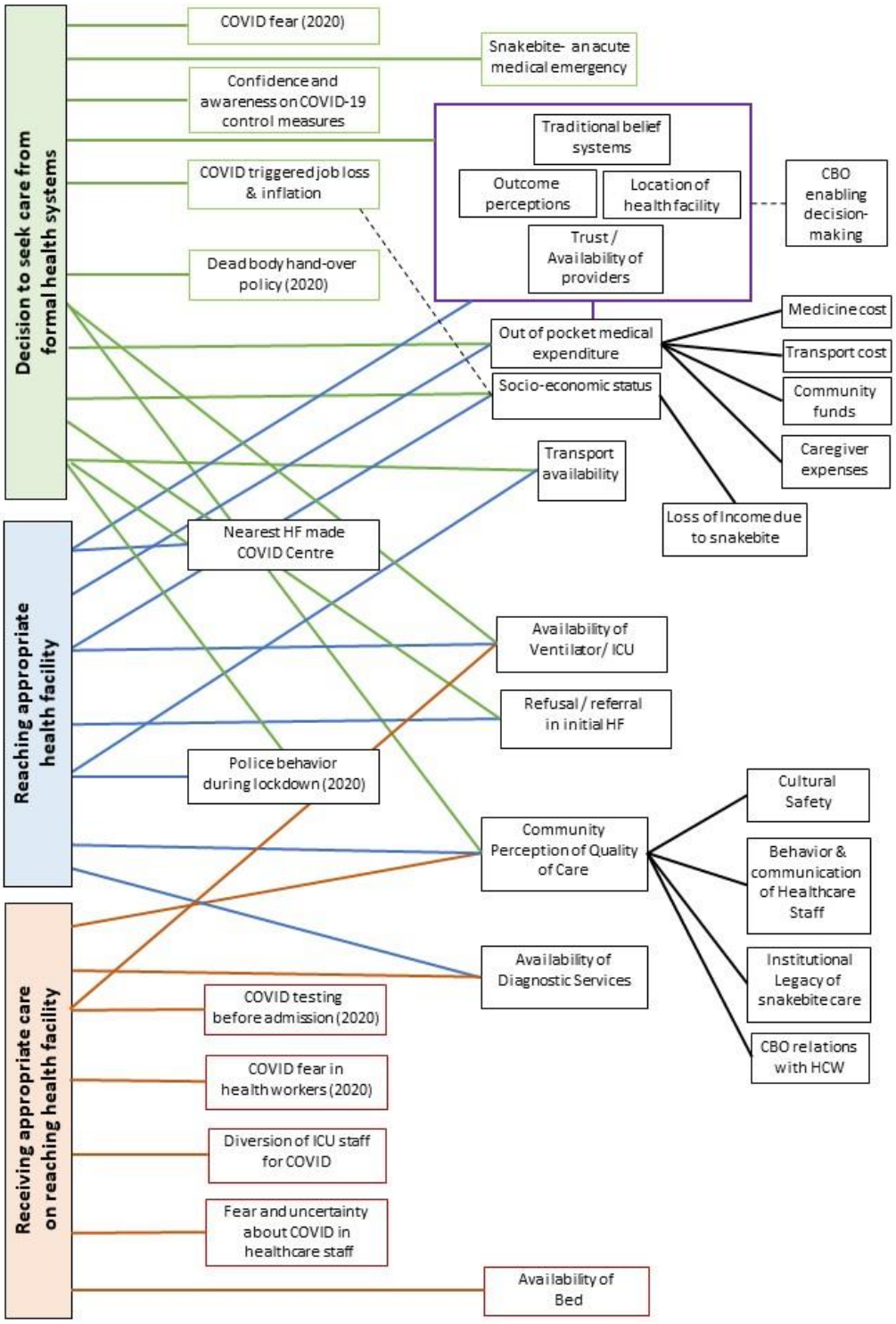
3.2. Summary of factors affecting snakebite care

The factors which affect snakebite care are mapped diagrammatically in the three delay model (originally developed [17] for maternal mortality) and shown in Figure 2. The factors map to three levels (often multiple) and are related to:

- decision to seek care from formal health system,
- reaching an appropriate health facility, and
- receiving appropriate care after reaching a health facility.

While some factors are pre-existing, some are specific to COVID-19.

Figure 2: Factors affecting snakebite care: mapped in three delay model



4. Discussion

Our study found that communities affected by snakebite are immensely challenged by weak health systems which was accentuated during the pandemic. Snakebite was recognised as an acute medical emergency and people navigated a multitude of factors which affected access to snakebite care, including distance, availability, trust, outcome perceptions, and affordability of formal health systems. We found that these factors (which accentuated during COVID-19), and not traditional belief systems alone, influenced the choice of healthcare provider. COVID-19 added to the financial risk of communities affected by snakebite. The lack of cultural safety and respectful care contributed to perceptions of inadequate quality of care. There is a strong and shared felt need for multi-faceted community-based programs on snakebite. However, we found that CHWs, saw a limited role in such a program. This contrasted with CBOs, where they existed, which were recognised and appreciated by communities. CBOs however were challenged due to lack of recognition and resource constraints.

The result of our study contextualises and brings forth evidence with respect to impact of COVID-19 on snakebite care in West Bengal, India. The previous global qualitative study [14] relied on key-informants alone and focussed on the initial phase of COVID-19. Our study was localised within a sub-national context and had community level participants, enabling us to look at the issue in more depth. Having two contrasting study areas within a state, also enabled comparison. The optimism of greater availability of ventilators for snakebite patients in the previous study, [14] is not reflected in our study. Our study on the other hand highlights the need for a simultaneous strengthening of primary health care systems and multi-faceted community-based programs to address snakebite and snake-human conflicts. The finding that CHWs did not see any significant

role in relation to snakebite, in the background of overwork, stress, and their identity, alignment with what has been seen in other studies on CHWs in India. [18-21] COVID-19 has exacerbated the issue, adding to concerns about financial security, occupational health and safety and psychosocial stress, leading to increasing collective action with some state governments around labour rights. [18-21]

Difficulties in accessing care for multiple conditions due to COVID-19, has been noted in other studies from India, as well as globally. [7-11 22-24] With most global deaths due to snakebite occurring in India [3 5] action to reduce the burden in India is a priority to meeting the global reduction target. Our study provides a nuanced understanding, away from the dominant dichotomous framing (traditional belief systems versus modern medicine) [1 2 25 26] around choice of healthcare providers for snakebite. The multi-factorial nature of decision- making to choose healthcare provider for snakebite has also been previously reported in Cameroon and Kenya. [27 28] Our study has relevance beyond West Bengal - in similar contexts of high snakebite burden and under-resourced health systems. Potential implications for policy, practice and research are presented in Table 2.

Table 2: Implications of study findings for practice, policy, and research

1. Well-resourced multi-faceted community programs, involving local CBOs, have the potential to address factors which affect snakebite care, including during disease outbreaks, this improving health systems resilience. Well-resourced community-based programs which aim for awareness, prevention (using contextually relevant modes and medium, as for example *Jatras* in West Bengal), increasing use of formal health services, and mitigation (snake-rescue) of snake-human conflict.

2. Community-based programs aiming to increase use of formal health services should be accompanied by health systems strengthening instead of an exclusive focus on awareness against traditional providers, with the underlying assumption that their acceptability is solely due to traditional belief systems.
3. Training for doctors and nurses for in-facility management of snakebite should include training on culturally appropriate and empathetic patient communication. Such training will reap benefits across all health conditions.
4. There is a need for studies for understanding out-of-pocket expenditure due to snakebite. This can inform development of unconditional direct benefit transfer (DBT) schemes to enable protection of those affected by snakebite. The DBT scheme for tuberculosis has been found to be beneficial. [29]
5. High burden states should commission district level evaluation of emergency response services to inform district level plans for ensuring adequate density and dispersion of ambulances, which are free and available 24X 7.
6. Good practices from primary care facilities, should be formally documented by the government and scaled up.
7. In Sundarbans, and other hard to reach areas, surrounded by waterways, studies are needed for appropriate localisation of primary health centres and development of ferry-based emergency response. Geographic Information System based studies on snakebite epidemiology for the purpose have been conducted in other countries [30 31] and are underway in Hooghly, West Bengal. [32]

We used standard qualitative research methods and reached saturation of themes. The decision of diagrammatic presentation using three delay model [17] was *post hoc*, and from a pragmatic standpoint of visualisation (rather than a descriptive list of factors). The three-delay model as it is widely known and understood in communities of public health practice and policies, and the data effortlessly fitted within the model. It is

envisaged that the figure will enable systems managers and policy actors to visualise factors related to snakebite care.

5. Conclusion

Well-resourced multi-faceted community programs, involving local CBOs, have the potential to address factors which affect snakebite care, including during disease outbreaks. Community-based programs aiming to increase use of formal health services should be accompanied by health systems strengthening (focussing on access, quality, cultural safety in practice and resilience) instead of an exclusive focus on awareness against traditional providers.

Ethical considerations

Ethics approval was obtained from The George Institute of Global Health, India (09/2020), and University of New South Wales (UNSW) Research Ethics Committee (HC220177). We provided a participant information sheet (in Bangla) and supplemented this with verbal explanations. Written informed consent was obtained from all participants.

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Conflict of interests

Financial support was provided by Royal Society of Tropical Medicine and Hygiene for conducting this study. No other competing financial interests or personal relationships that could have appeared to influence the work reported in this paper is reported.

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Data Availability Statement

The study is a qualitative study, and the underlying data of the study is not available to protect confidentiality of research participants.

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6. Impact of climate change on the burden of snakebite, and implications for primary healthcare

6.1. Chapter overview

In this chapter, I synthesised existing research evidence, on how the burden of snakebite, will be altered due to climate change. The study holds significance in the current context, wherein the Intergovernmental Panel on Climate Change (IPCC) projections estimated an increase of temperature beyond 1.5° C (from preindustrial levels) by 2030, with impacts across sectors. In health, the effect of climate change has been synthesised for multiple health conditions, but not for snakebite. Understanding the changing nature of burden due to climate change, the defining issue of our time, is essential to make our health systems future-ready.

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The publication is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in the thesis.

6.2. Candidate's contribution to the work

I conceptualised and designed the study which this Chapter contains. I developed and ran the search strategies, screened the studies, extracted the data, conducted formal analysis, validated the data, and wrote the first draft of the manuscript. A co-author did independent screening and data extraction, and disagreements were resolved by consensus. I coordinated and incorporated feedback from co-authors to prepare and submit the manuscript to the journal. I drafted response and amended the manuscript based on the peer-review comments and prepared the final draft which was published.

6.3. Published manuscript

Original Article

The impact of climate change on the burden of snakebite: Evidence synthesis and implications for primary healthcare

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Abstract

Introduction: Snakebite is a public health problem in rural areas of South Asia, Africa and South America presenting mostly in primary care. Climate change and associated extreme weather events are expected to modify the snake-human-environment interface leading to a change in the burden of snakebite. Understanding this change is essential to ensure the preparedness of primary care and public health systems. **Methods:** We searched five electronic databases and supplemented them with other methods to identify eight studies on the effect of climate change on the burden of snakebite. We summarised the results thematically. **Results:** Available evidence is limited but estimates a geographic shift in risk of snakebite: northwards in North America and southwards in South America and in Mozambique. One study from Sri Lanka estimated a 31.3% increase in the incidence of snakebite. Based on limited evidence, the incidence of snakebite was not associated with tropical storms/hurricanes and droughts in the United States but associated with heatwaves in Israel. **Conclusion:** The impact of climate change and associated extreme weather events and anthropogenic changes on mortality, morbidity and socioeconomic burden of snakebite. Transdisciplinary approaches can help understand these complex phenomena better. There is almost no evidence available in high-burden nations of South Asia and sub-Saharan Africa. Community-based approaches for biodiversity and prevention, the institution of longitudinal studies, together with improving the resilience of primary care and public health systems are required to mitigate the impact of climate change on snakebite.

Keywords: Climate change, epidemiology, extreme weather events, forecasting, planetary health, snakebite

Introduction

Snakebite is a public health problem in many countries, particularly in South Asia, sub-Saharan Africa and Latin America.[1-3] World Health Organization (WHO) estimates nearly 138,000 snakebite deaths, with 400,000 people facing permanent disabilities annually; majority of them presenting in primary care.[4] In 2019, the WHO released a global strategy, which aims to decrease death and disability due to snakebite to 50% by 2030.[4] The strategy recognises the need for empowering and engaging communities for prevention and improved access as well as strengthening health systems, that guarantee time-critical snakebite care.

Snakebite, at its core, reflects a human-snake conflict with the environment, climate and anthropogenic activity acting as mediators. Snakes being ectothermic animals, are susceptible to climate change—and the impact of climate change on snake population, their geographic range and behaviour continues to be

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researched by ecologists and conservation scientists.[5-7] As such, climate change that alters the human-snake-environment interface would impact the burden of snakebite. The Intergovernmental Panel on Climate Change (IPCC), an intergovernmental body of the United Nations, estimated that global warming will lead to an increase beyond 1.5°C (from preindustrial levels) by 2030, much earlier than previously predicted.[8,9] Climate change will also increase the intensity and frequency of extreme weather events (heatwaves, floods, droughts and tropical cyclones).[10,11] The impact of climate change on health has been investigated for many conditions of significance to primary care such as mental health, water-borne and vector-borne diseases.[12-17] To the best of our knowledge, there is no evidence synthesis on the effect of climate change on the burden, spatiotemporal distribution and at-risk population of snakebite.

A comprehensive understating of the effect of climate change on snakebite will enable resourcing for primary care and public health planning on climate change resilience at regional, national and sub-national levels. We thus aimed to evaluate the scientific evidence on the impact of climate change, and consequent extreme weather events, on the burden of snakebite. The result of the review maps primarily to the strengthening health systems pillar of the WHO strategy, and also provides information relevant to the community engagement pillar.[4]

Methods

We did not register the evidence synthesis publicly but a priori protocol was developed with the lead author SB acting as guarantor. Protocol deviations are noted subsequently.

Eligibility criteria

We included studies that met any of the following two criteria:

1. The study is on or modelled, the impact of climate change on incidence/prevalence, risk, mortality, morbidity and socio-economic burden of snakebite.
2. The study is on, or modelled, the impact of extreme weather events (heatwaves, floods, droughts and tropical cyclones), specifically related to climate change or climate variation on incidence/prevalence, risk, mortality, morbidity and socio-economic burden of snakebite.

Studies were included irrespective of the setting, country of conduct, date of publication and publication language. We used snakebite risk as a broad term, as defined by the study authors, to be inclusive and in recognition of the complexities of defining it in relation to the human-snake-ecosystem interface. We did not include studies that reported the impact of climate change on snake population, their abundance or diversity, without reporting snakebite burden or risk. We did not include studies that focussed on the relationship between climatic, meteorological or seasonal variables with snakebite burden or risk if they did not explore the role of climate change.

Information sources

Electronic database search

We searched the following electronic databases: Ovid MEDLINE (R), Global Health (EBSCO), Embase Classic + Embase, Zoological Record Global Health and Environment file (through EBSCO). The full search strategies for all databases are presented in Appendix 1.

Other methods for searching

We hand searched the website of the WHO (Snakebite as topic section only), Kenya Snakebite Research and Intervention Centre (KSRIC), the Nigeria Snakebite Research & Intervention Centre (NSRIC) and the Global Biodiversity Information Facility (GBIF) to identify additional studies. We screened reference lists of included studies to identify additional studies for inclusion.

Screening process

In the first phase, two authors (S.B. and D.B.) independently screened each study retrieved based on titles and/or abstracts and marked each record as 'exclude' or 'include'. We conducted the simultaneous first phase of screening in a cloud-based artificial intelligence guided platform (Rayyan[18]) for evidence synthesis. Disagreements at this phase were resolved by discussion, between the two authors. In the second phase of screening, we obtained full texts of all studies marked as 'include' by consensus in the previous phase. All records were obtained and reviewed independently by two authors for consideration of inclusion based on the eligibility criteria.

Data management and analysis

We extracted data in a predesigned data extraction form using Microsoft Excel and disagreements were resolved by consensus between two authors (D.B. and S.B.). Authors of studies were not contacted for additional data and only data as reported in the published version were included. We synthesised the data narratively without conducting any additional statistical analysis.

Differences between protocol and full review

We did not initially plan to search Global Health (EBSCO) database, this was added and searched concurrently while other searches were run. We included the study on the relationship between climate variation patterns and snakebite to be inclusive and considering relatedness of the topic.

Ethics

The study is a review of existing published literature available in public domain with no human or animal participants. It does not require ethics approval.

Results

Selection of studies

We retrieved 474 records from five electronic databases and removed 118 duplicates to screen 356 titles and/or abstracts.

We identified one study from a website and six studies through manual checking (hand search) of references of included studies for full-text consideration. We finally, included eight studies that met the inclusion criteria. Reasons for exclusion at full-text level are presented in Appendix 2 and PRISMA flow chart for included studies is presented in Figure 1.

Characteristics of included studies

Of the eight included studies, four studies predicted the future impact of climate change on snakebite or snakebite risk.[19-22] Of these eight studies, three studies reported on the association/correlation between snakebite or snakebite risk and extreme weather events related to climate change (heatwave in Israel,[23] tropical storms/hurricanes,[24] and droughts[25] in the United States) and one study with climate variation (El Niño–Southern Oscillation/ENSO in Costa Rica[26]). Studies used a variety of data sources and analytical approaches. Characteristics of included studies have been detailed in Table 1.

Projected impact of climate change on incidence and risk of snakebite

We included four studies in this domain.

The study from Argentina[19] modelled future projections (2030, 2080) of suitable climate spaces (the change in multi-dimensional climatic conditions in an area over time) for five widely distributed venomous snakes using ecological niche modelling (ENM). The study found that by 2080, climate change would result in a moderate to a greater increase in potentially suitable spaces for snakes within Argentina for four species (*B. alternatus, B. diporns, C. durissus terrificus* and *M. pyrrhocryptus)* with only minor change predicted for *B. ammodytoides.* A north-to-south geographic shift is predicted with some urban centres in south and central Argentina becoming suitable climactic space for *B. diportus* and *C. durissus terrificus.*

The ENM study from Mozambique looked at 13 venomous snakes[20] and estimated a similar north-to-south shift in snakebite risk in Mozambique for the recent climate scenario (1950–2000), which would further expand in the future scenario (2070–99). The study predicted that by 2070–99 there would be an expected increase in snakebite risk in an additional 11.04% of areas. The study also predicted that 4.65% of areas, which are currently classified to have high snakebite risk might have a decreased risk by 2070–99.

The study from Sri Lanka[21] projected an increase in the annual snakebite incidence by 31.3% (95% CI: 10.7–55.7) and the annual increase in snakebite incidence to 144,000 (95% CI: 122,000–166,000) due to climate change in 25–50 years into future (as reported in the study), for a climate scenario of 2.5% reduction in maximum relative humidity, (equivalent to a 0.5°C increase in maximum temperature levels). In an alternate climate scenario of an increase of temperature by 1°C for 6 dry months (with no change in the remaining 6 months), the overall monthly incidence of snakebite will increase to 62.2/100,000 (95% CI: 49.1–74.1) and the total number of snakebites as projected to increase to 147,000 (95% CI: 120,000–1,740,000) by 2038–63. The

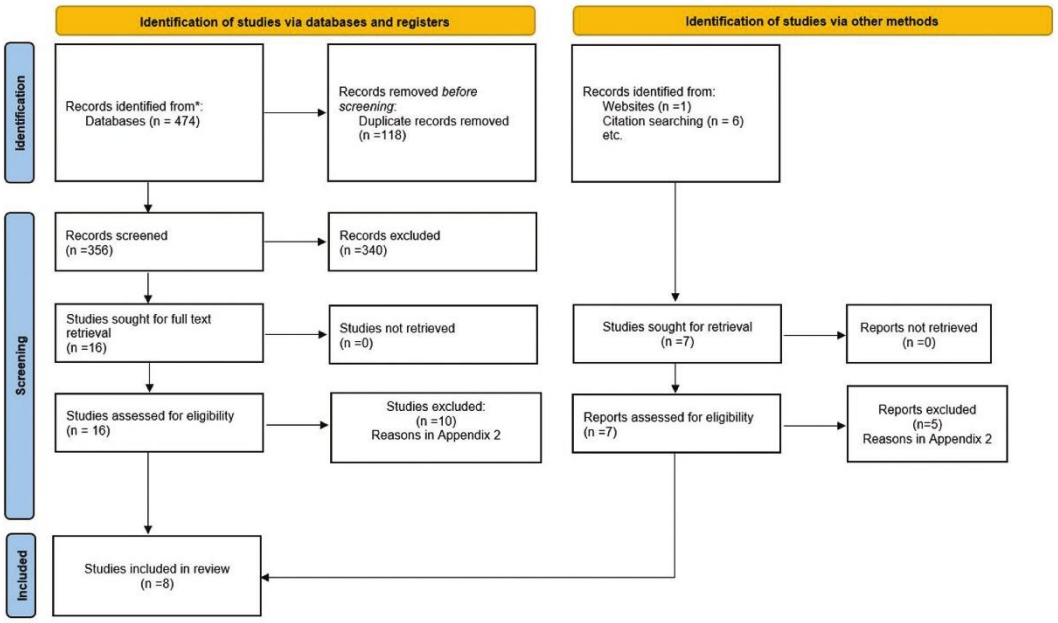

Figure 1: PRISMA Flow diagram showing a selection of studies

Table 1: Characteristics of included studies

Study ID	Country (ies) of study (& Study period)	Data source (s)	Methodology	Funding
Ediriweera 2018	Sri Lanka (2012-2013; projection 25-50 years in future)	Snakebite - from Community-based National Snakebite Survey (multistage cluster design) Meteorological measurements - Department of Meteorology, Sri Lanka	Log-linear models were developed and fitted to estimate expected monthly number of snakebites adjusting for seasonal trends and weather conditions, and taking onto account factors related to survey methodology	National Health Medical Research Council, Australia and Medical Research Council, UK Type of Funder: Public
Nori 2014	Argentina (Present - 2014; 2030; 2080)	Snake species/data records - herpetological collections of Colección Boliviana de Fauna, La Paz, Bolivia (CBF), Museo de Historia Natural Noel Kempff Mercado, Santa Cruz, Bolivia (MNKR), Museu de Zoologia, Universidade de São Paulo, São Paulo, Brazil (MZUSP), Fundación Miguel Lillo, Tucumán, Argentina (FML), Museo de Ciencias Naturales de La Plata, Argentina (MLP), Museo Argentino de Ciencias Naturales, Buenos Aires, Argentina (MACN), Centro de Zoología Aplicada, Córdoba, Argentina (CZA) and from relevant literature. Climatic data - WorldClim climate data archive.CCAFS-Climate data portal Snakebite data - Ministerio de Salúd de la República Argentin Population count - Raster dataset	Species distribution modelling was done to estimate the relationship between species records and environmental and/or spatial characteristics of the sites. Four different algorithms for seven projections of five studied species (one for present, one for each of the three selected Global Circulation Models (GCMs) for 2030 and 2080) were developed. A final map was developed from consensus maps of different GCMs estimating trends for each species. Vector maps were then developed for predicted future trends	Ministerio de Ciencia y Tecnología, Argentina and Secretaría de Ciencia y Tecnología–UNC Argentina Type of Funder: Public
Yañez-Arenas 2016	North and South America (Present - 2015; 2050)	Species unit selection - The Reptile Database, Integrated Taxonomic Information System, Campbell and Lamar 2004) & recent systematic studies. Occurrences of species - Global Biodiversity Information Facility, VertNet data portals. Data layers for characterising climates - WorldClim climate data archive. Snakebite - states or provinces of Argentina, Bolivia, Brazil, Colombia, Mexico, USA, Venezuela (different time periods) and also country level snakebite information for Central Africa	Current and future snakebite risk was modelled using ecological niche models (ENMs) for 90 venomous snake taxa. Four snakebite risk indices (representing probability of being bitten by a venomous snake at a particular location) were developed. The predictive ability of each was tested with snakebite data from published papers and reports and one which best explained snakebite incidence was chosen. Snakebite risk categorisation was done using rescaled snakebite risk maps	Consejo Nacional de Ciencia y Tecnología, Ecuador Type of Funder: Public
Zacarias 2019	Mozambique (Current estimates - 1950-2000 ; Future estimates - 2070-2099)	Species occurrence records - Global Biodiversity Information Facility, Vertnet. Environmental variables - Worldclim database	Ecological niche modelling was done for current and future distribution of all 13 dangerous snakes in Mozambique to assess the likely impacts of climate change estimated as the difference between lost and gained climatic suitable area per species. A normalised index of snakebite risk was developed based on species diversity and species-specific traits for each time slice. This index was superimposed on to data on human population density to identify burden prone areas	Conselho Nacional de Desenvolvimento Científico e Tecnológico & Financiadora de Estudos e Projetos, Ministério da Ciência, Tecnologia, Inovações e Comunicações and Fundação de Amparo à Pesquisa do Estado de Goiás, Brazil Type of Funder: Public
Schulte 2020	Texas, USA (2000 - 2017)	Weather data - National Weather Service (NWS), County classification – as per Federal Emergency Management Agency (FEMA) Snakebite data - the Texas Poison Control Network	Comparison between following two groups of counties of Texas in USA was done (sing pooled analysis of the 9 storms using descriptive methods and χ^2 testing for proportions) 1. Counties designated for individual	Not reported

Contd...

Table 1: Contd...

Study ID	Country (ies) of study (& Study period)	Data source (s)	Methodology	Funding
			assistance (impact counties) by the Federal Emergency Management Agency (those in which damage due to tropical storms and hurricanes is worst) 2. All other counties (non-impact counties).	
Phillips 2019	California, USA (1997-2017)	Snakebite cases (excluding non-venomous bites) - California Poison Control System County-level drought data - US Drought Monitor for 2000–2017. Air temperature & precipitation - National Aeronautics and Space Administration's North America Land Data Assimilation Systems (NLDAS) dataset from 1979 to 2017. Demographic time series data - US Census Bureau (UCB) annual summaries including population data from the UCB summarised by National Institutes of Health's National Cancer Institute from 1960 to 2016; county-level demographic data from the UCB including age and sex characteristics for 2016, Geological and ecological classifications from US Environmental Protection Agency, Land cover - National Land Classification Database Multi-resolution Land Characteristics Consortium	Aggregation of venomous snakebite reports was done by location and correlated per county with weather data, air temperature, precipitation, population data, eco-regions and land characteristics. A time series decomposition by seasonality and trend, regression and autocorrelation was conducted to understand association.	Not reported
Shashar 2018	Israel (2008–2015)	Medical evacuations - Magen David Adom (MDA), (the sole emergency medical service provider for the country). Environmental Data - Monitor stations (National Air Monitoring Network website) operated by the Ministry of Environmental Protection.	Conditional logistic regression was applied to estimate the association. Analysis was stratified by regions and seasons.	Not reported
Chaves 2015	Costa Rica (2005 – 2013)	Snakebite data from Costa Rican Ministry of Health collected under the administration of the Costa Rican Social Security Trust. Average elevation estimates from Global Land Survey Digital Elevation Model. Satellite images were acquired from the Goodard Earth Science Data and Information Services Center of NASA. For ENSO, data was obtained from US National Oceanic and Atmospheric Climate Prediction Centre.	**1. Spatial analysis** - considering each canton for "(i) average elevation;(ii) annual average precipitation; (iii) poverty gap index, which quantifies the percentage of houses with income below the poverty line; (iv) percentage of destitute housing (i.e., lacking services and made of inadequate materials)." **2. Time series analysis** - temperature and rainfall time series was used to quantify impact of ENSO (El Niño Southern Oscillation) on snakebites.	University of Costa Rica, Nagasaki University, and Taiwan Ministry of Science and Technology Type of Funder: Public

study noted a baseline overall monthly incidence of snakebite of 45.7/100,000 (95% CI: 35.4–59.0) leading to 119,000 snakebite deaths (95% CI: 103,000–134,000) in the year 2012.

One ENM study[22] modelled the effect of climate change on snakebite risk multi-nationally for 90 venomous taxa in the entire North and South America. The study projected that by 2050, almost all countries in North and South America would have an increased risk of snakebite with areas in Mexico, Guatemala, Honduras, Nicaragua, Costa Rica, Panama, Colombia, Ecuador and some parts of southern United States of America (USA) being classified as high-risk. The study forecasted that there will be a shift in snakebite risk areas northward in Canada and Southward in Argentina and Chile by 2050. An increase in 2.74-18.38% of rural population being exposed to the risk of snakebite by 2050 is estimated.

Extreme weather events related to climate change and snakebite

We found three studies[23-25] under this domain. One study from the United States found no statistically significant difference in snakebites between counties in Texas affected by tropical storms/cyclones (nine incidences between 2000 and 2017) and counties not affected by it, either overall or 30 days after landfall[24]: this did not change by patient demography, type of snake and care patterns pre- and post-storms. The other study from the United States also found no statistically significant decrease in incidence of snakebite per million (mean during drought = 15.10; mean outside drought = 18.57; 95% CI = 0.12–6.83; $P = 0.04$) due to droughts between 1997 and 2017 in California.[25] However, it found a statistically significant correlation in snakebite incidence after a period of no drought, which declined during periods of drought ($r = -0.41$, $P < 0.01$). The study from Israel[23] found that the incidence of snakebite was significantly associated with heatwave, both during the cold (OR 1.62; 95% CI = 1.01–2.60) and hot (OR 1.50; 95% CI = 1.18–1.92) seasons. None of the studies had provided futuristic estimates of how extreme weather-related events would impact snakebite. All the studies used retrospective facility data on snakebite.

Climate variation and snakebite

Only one study was found in this domain which investigated the effect of El Niño/La Niña–Southern Oscillation (ENSO) on snakebite in Costa Rica between 2005 and 2013.[26] The ENSO is a climatic cycle, resulting from periodic variation in sea surface temperature and the air pressure of the atmosphere overlying it. The ENSO affects both temperature and precipitation in large parts of the world and the impact of global warming on ENSO remains uncertain. The study[26] found that the peak monthly incidence of snakebite coincided with both the hot and cold phases of the ENSO in Costa Rica. The study also found that increase in temperature (above the average), high poverty index gap and percentage of destitute housing (especially in rural areas) were predictive of increase in the incidence of snakebite while the increase in rainfall (above average) was predictive of a decrease in snakebite incidence.

Discussion

Summary of main results

Our evidence synthesis summarises the impact of climate change on the burden of snakebite. Overall, the evidence is scarce, with limited studies available in the domain. The scarcity of studies on the impact of climate change from high-burden nations like India, Pakistan, Bangladesh and countries in sub-Saharan Africa highlights a crucial evidence gap.

Review findings in the context of previous research

To our knowledge, there is no other evidence synthesis on the topic. The predicted increased incidence of snakebite in the next few decades, seen in the existing studies in our review is quite in contrast with what might be expected due to likely overall decline in snake population due to anthropogenic causes, including climate change, changing land-use patterns and deforestation over a long time.[27-29] The increase in snakebite might be due to several factors: medically important snakes might be more resilient to climate change (e.g. rattle snakes[30]), rapid adaption to changes in climate and environment (e.g. Burmese pythons acting like an invasive species[31]) or benefitting from climate change (example improved food supplementation for urban-adapted snakes[32]). Climate change might also alter the hibernation of snakes, thus changing the duration and nature of human-snake conflict.[33,34] In addition, climate change is also expected to trigger human migration in many parts of the world due to associated problems of sea-level rise and food insecurity. Overall, the complex interface of environment-human-snake would change due to climate change and this needs to be understood better. Available evidence from our evidence synthesis shows that global climate change will lead to a shift in snakebite risk more northwards in North America and southwards in South America, including in Argentina.[19,22] The results are in alignment with findings from ecological studies, which have found a similar shift in snake species distribution in the American hemisphere.[35] A northward change in spatial distribution of snakes due to climate has also been noted in a study in China.[7]

Implications for policy, practice and research

The increase in snakebite and geographic shift of burden seen in studies included in our review, implies that newer areas and communities, which do not have snakebite as a public health problem currently, might potentially see an increasing incidence of snakebite because of climate change, in the future. Primary care systems in newer areas need to be adequately prepared for this change. Based on the IPCC's 2021 sixth assessment report,[8] it is reasonable to believe that the estimated change in burden of snakebite in included studies would be much earlier than expected. Plans to increase resilience of primary care and public health systems to climate change (which focuses prominently on response to extreme weather events, infectious diseases, food and water security[36-40]) must also consider snakebite. While adjusting supply chain and logistics for anti-venom supplies to a particular geolocation might be more manageable, securing enough and appropriate anti-venom supply (in the background of shifting snake populations) and training health workers on snakebite management might be more difficult requiring longer-term initiatives. Changes in species distribution might also lead to demand for newer varieties of specific snake anti-venom, which might not have been produced historically. There is a need for health system resilience plans to factor in the need for managing the dynamic nature of the burden of snakebites due to climate change. Integrating snakebite surveillance within infectious disease surveillance programs[40] might be considered.

There were only two studies[20,21] from South Asia and Africa. Together these regions represent majority of the current burden of snakebite.[1,3] Both studies predicted higher incidence of snakebites due to climate change. The evidence on extreme weather events related to climate change is scarce. Even in

countries, where the impact of climate change has been studied, for all except the study from Sri Lanka,[21] the analysis was based on existing facility-level data. Robust community-based cohort studies, linked with climate parameters and repeated over time are much needed in countries with high burden of snakebite.

The current evidence based on the impact of climate change on snakebite is limited to the understanding of the incidence of snakebite or snakebite risk using a spatial lens. The effect of climate change on mortality, morbidity and socio-economic burden of snakebite remains unexplored. It is important to note that none of the current studies have considered how snakebites would be impacted due to human migration expected due to climate change. Climate refugees often live in scarcely inhabited regions, a common strategy used during many refugee crises. This might also exaggerate human-snake conflict. Communities with lesser snake-human interaction may not be familiar with strategies to avoid snakes and snakebites.[41] Awareness, education and other community-based strategies to mitigate snakebite are essential.[4] Community-based initiatives is important not only from a prevention perspective but also from a snake conservation and biodiversity perspective, including in areas where snake populations (and consequently snakebites) are declining.[41] Snakes play a crucial role, not only in the ecosystem but also prevents agricultural loss and have a role in controlling the transmission of diseases spread by rodents and biomedical research.[42]

Understanding the issue in greater granularity using transdisciplinary approaches is required. Multi-disciplinary research teams consisting of primary care professionals, public health specialists, climate scientists and mathematical modellers together with herpetologists, ecologists, anthropologists, economists and agricultural scientists are essential. A cohesive response by multi-national and government agencies working on health and climate science to fund modelling studies and long-term cohort studies in countries with high snakebite burden and vulnerable to climate change is urgently required.

Strengths and weaknesses of the review

In our study, we used a specific eligibility criterion for the inclusion of studies, and searched multiple electronic databases (including environmental) using a robust search strategy, supplementary searches and independent screening and data extraction. We acknowledge that not searching Latin American electronic databases is a limitation (our team does not have linguistic capacity in Spanish and Portuguese) but contend, that this does not change the overall implications of the study.

Conclusion

Current evidence indicated that climate change will lead to a change in snakebite burden and there is a need for primary healthcare systems to be prepared for this. However, more transdisciplinary research is required to comprehensively understand the issue going beyond incidence, especially in countries with a high burden of snakebite. Community-based approaches for biodiversity and prevention, together with improving resilience of primary care and public health systems are required to mitigate the impact of climate change on snakebite.

Author contributions

Conceptualisation, methodology, formal analysis, project administration, writing of first draft -SB; Data curation - DB, SB; Supervision- JJ; Validation, Writing – review & editing- SB, DB, JJ, Guarantors- SB, DB, JJ

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Conflicts of interest

There are no conflicts of interest.

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Appendix

Appendix 1: Search Strategies

This appendix consists of search strategies used for Bhaumik S *et al.* The impact of climate change on the burden of snakebite: Evidence synthesis and implications for primary healthcare

Contents

Ovid MEDLINE (R) and Epub ahead of print, in-process & other non-indexed citations, daily and versions (R) <1946 to December 11, 2020>

Search Strategy:

1. exp Climate Change/or climate change.mp. (44058)
2. (climate adj (resilience or adaption or mediated or vulnerability or induced)).mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (884)
3. exp Snake Bites/(4733)
4. Snakebit*.mp. (2416)
5. ((bite* or envenom*) adj2 Snake*).mp. (5823)
6. exp Snake Venoms/(18504)
7. (snake adj2 venom).mp. (5698)
8. exp Snakes/or snake*.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (28883)
9. 1 or 2 (44363)
10. 3 or 4 or 5 or 6 or 7 or 8 (36989)
11. 9 and 10 (86)

Embase classic + Embase <1947 to 2020 December 11>

Search Strategy:

1. exp Climate Change/or climate change.mp. (54404)
2. (climate adj (resilience or adaption or mediated or vulnerability or induced)).mp. (889)
3. exp Snake Bites/(7037)
4. Snakebit*.mp. (7780)
5. ((bite* or envenom*) adj2 Snake*).mp. (4124)
6. exp Snake Venoms/(28432)
7. (snake adj2 venom).mp. (18087)
8. exp Snakes/or snake*.mp. (38137)
9. 1 or 2 (54688)
10. 3 or 4 or 5 or 6 or 7 or 8 (50011)
11. 9 and 10 (118)
12. limit 11 to exclude medline journals (11)

Global health <1910 to 2020 week 48>

Search Strategy:

1. exp Climate Change/or climate change.mp. (11392)
2. (climate adj (resilience or adaption or mediated or vulnerability or induced)).mp. (133)
3. exp Snake Bites/(3171)
4. Snakebit*.mp. (1775)

5. ((bite* or envenom*) adj2 Snake*).mp. (3823)
6. exp Snake Venoms/(0)
7. (snake adj2 venom).mp. (3522)
8. exp Snakes/or snake*.mp. (13042)
9. 1 or 2 (11436)
10. 3 or 4 or 5 or 6 or 7 or 8 (13042)
11. 9 and 10 (16)

Zoological record < 1978 to November 2020>

Search Strategy:

1. exp Climate Change/or climate change.mp. (25800)
2. (climate adj (resilience or adaption or mediated or vulnerability or induced)).mp. (852)
3. exp Snake Bites/(0)
4. Snakebit*.mp. (222)
5. ((bite* or envenom*) adj2 Snake*).mp. (195)
6. exp Snake Venoms/(0)
7. (snake adj2 venom).mp. (996)
8. exp Snakes/or snake*.mp. (23585)
9. 1 or 2 (26166)
10. 3 or 4 or 5 or 6 or 7 or 8 (23585)
11. 9 and 10 (144)

Environment file (EBSCO host) December 14 2020,

1. (snake or snakebite OR "snake venom" OR "snake anti-venom) AND ("climate change" OR climate resilience" or "Climate adaption" OR "climate mediated" OR "climate vulnerability" OR "climate induced") (217)

Expanders- Apply related words; Apply equivalent subjects

Appendix 2: Reasons for Exclusion of Full Text

This appendix consists of reasons for exclusion at full text level for Bhaumik S *et al.* The impact of climate change on the burden of snakebite: Evidence synthesis and implications for primary healthcare

Study ID	Reason for exclusion
Angarita-Gerlein 2017[1]	Reported relationship between climatic, meteorological or seasonal parameters with snakebite or snakebite risk, with no relation to climate change
da Costa 2019[2]	Reported relationship between climatic, meteorological or seasonal parameters with snakebite or snakebite risk, with no relation to climate change
Ebrahimi 2018[3]	Reported relationship between climatic, meteorological or seasonal parameters with snakebite or snakebite risk, with no relation to climate change
Fry 2018[4]	Wrong study design (Review)
Huber 2009[5]	Study not related to snakebite/snakebite risk
Lawing 2011[6]	Study did not report data on snakebite/snakebite risk
Mukeka 2020[7]	Study did not report data on snakebite/snakebite risk
Na 2014[8]	Reported relationship between climatic, meteorological or seasonal parameters with snakebite or snakebite risk, with no relation to climate change
Sullivan 2014[9]	Study not related to snakebite/snakebite risk
Tauzer 2019[10]	Did not study the impact of climate change on snakebite/snakebite risk
Yañez-Arenas 2014[11]	Reported relationship between climatic, meteorological or seasonal parameters with snakebite or snakebite risk, with no relation to climate change
Yañez-Arenas 2018[12]	Reported relationship between climatic parameters with snakebite or snakebite risk, with no relation to climate change
Yousefi 2020[13]	Reported relationship between climatic, meteorological or seasonal parameters with snakebite or snakebite risk, with no relation to climate change
Ochoa 2020[14]	Wrong study design (review): review did not include any primary study that met inclusion criteria
Longbottom 2018[15]	Reported relationship between climatic, meteorological or seasonal parameters with snakebite or snakebite risk, with no relation to climate change

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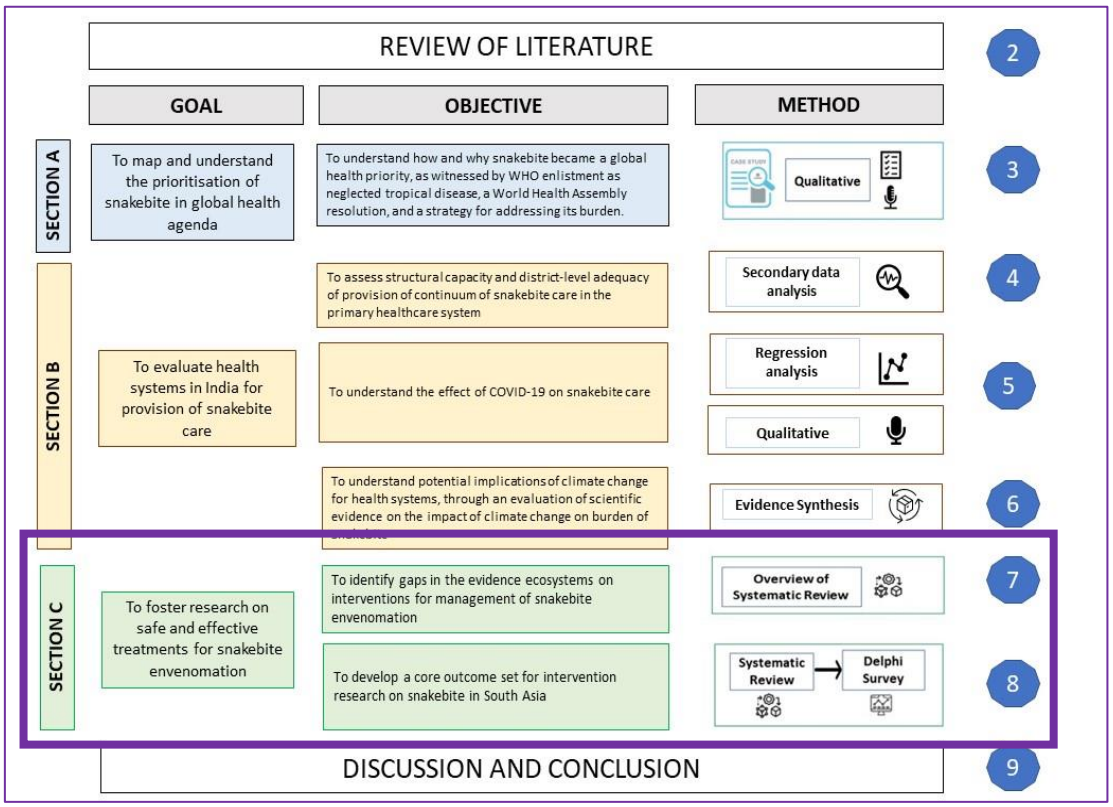
Section C: Fostering research on treatments for snakebite

""Like a snake sheds its skin, we are capable of getting rid of assembled habits, creating space to call matters into question."

~Erik Pevernagie, Belgian Painter

In this section, I conduct "research on research" with the motive to foster future research away from "assembled habits" which impede development of evidence base for snakebite treatments.



7. Identifying gaps in the evidence ecosystem on interventions for the management of snakebite envenoming

7.1. Chapter overview

In this chapter, I conducted an overview of systematic reviews on intervention for the management of snakebite envenoming. It serves the function of identifying key issues, around the evidence base for treatment of snakebite envenoming. The work has its roots in a pre-doctoral work where I evaluated existing WHO guidelines on snakebite, to find recommendations not being informed by systematic reviews, despite WHO standards around it for developing guidelines (Section 1.6). Through the study presented in this chapter, I identified the issue of heterogeneity and lack of standardisation of outcomes preventing meaningful comparison of treatments, as a barrier in the evidence ecosystem around snakebite. Subsequently in Chapter 8, I address this issue by developing a core outcome set for intervention research on snakebite in South Asia.

This chapter is the **published** version of the article in **PloS Neglected Tropical Disease**.

- **Bhaumik S**, Beri D, Lassi ZS, Jagnoor J. Interventions for the management of snakebite envenoming: An overview of systematic reviews. PLoS Negl Trop Dis. 2020 Oct 13;14(10): e0008727. PMID: 33048936; PMCID: PMC7584233. (Link)

The publication is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in the thesis.

7.2. Candidate's contribution to the work

I conceptualised and designed the study which this Chapter contains, with feedback from one co-author. I developed and ran the search strategies, screened the studies, extracted the data, conducted formal analysis, validated the data, and wrote the first draft of the manuscript. A co-author did independent screening and data extraction, with disagreements resolved by consensus. I coordinated and incorporated feedback from co-authors to prepare and submit the manuscript to the journal. I drafted response and amended the manuscript based on the peer-review comments and prepared the final draft which was published.

7.3. Published manuscript

PLOS NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Interventions for the management of snakebite envenoming: An overview of systematic reviews

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Data Availability Statement: The data underlying the results presented in the study is available as appendices for the study.

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Abstract

Introduction

Snakebite is a neglected tropical disease that leads to more than 120,000 deaths every year. In 2019, World Health Organization (WHO) launched a strategy to decrease its global burden by 2030. There is a range of issues around different interventions for the management of snakebite. Decisions around these interventions should be informed by evidence from systematic reviews (SR).

Methods

An overview of SRs was conducted by searching 12 electronic databases, PROSPERO, contacting experts and screening the bibliography of included reviews. Screening, data extraction, and quality assessment (through AMSTAR-2) was done by at least two overview authors independently with discrepancies sorted by consensus. A narrative synthesis was conducted.

Principle findings

The overview found 13 completed SRs that has looked at various aspects of management of snakebite envenomation. There was one SR on first aid, nine on effectiveness and safety of snake anti-venom (SAV), two on drugs to prevent adverse reactions due to SAV therapy, and one on surgical interventions for management of snakebite envenomation. All, except one, SR was appraised to have critically low confidence as per AMSTAR-2 Criteria. Evidence base was restricted to few studies for most interventions.

Discussion

High quality evidence from SRs is required to inform guidelines and health system decisions which can bring down the burden of snakebite. The review indicates the need to fund high-quality SRs, evidence gaps and core outcome sets which can inform guideline recommendations, funding priorities for conduct of future trials. Variation in species distribution as well

Competing interests: The authors have declared no competing interests exist.

as intra-species variation in venom composition implies the need for conduct of region or, nation or state (sub-national) specific randomised controlled trials and SRs on different SAVs and their dosing regimens.

Author summary

Snakebite is a neglected tropical disease which has received priority attention in the global health space with WHO setting a target to decrease death and disability due to snakebite to 50% by 2030. High quality systematic reviews can inform policy and practice. We searched 13 electronic databases and PROSPERO, screened reference lists, and contacted experts. We identified 13 completed systematic reviews which has reviewed effectiveness and safety for first-aid, snake anti-venoms, drugs to prevent adverse reactions and fasciotomy. Evidence for interventions often came from few studies. We judged confidence on the results of the systematic reviews using AMSTAR-2 and all except one review was judged to have critically low confidence. Evidence with respect to specific geographic settings and for many specific anti-venoms is unavailable at the synthesis level and at the primary study level. Evidence related to late adverse reactions, wound-related outcomes, quality of life, duration of hospitalisation, cost, and disability is scarcely reported. Funding evidence gap maps, systematic reviews and development of core-outcome sets based on the results of this overview and subsequent conduct of randomised controlled trials for snakebite envenomation is essential.

Introduction

Snakebite is a neglected tropical disease which leads to more than 120,000 global deaths every year [1]. Disability, social and economic costs of snakebite is not well studied but overall burden of snakebite is understood to be grossly underestimated [2]. Snakebite is global in nature but it mostly affects rural and tribal communities in South Asia, Southeast Asia, and Africa [2]. A modelling study has estimated that inadequate provision of quality healthcare for snakebite affects 146.7 million people adversely [3].

Although 5.4 million snakebites occur annually, only about half of them leads to envenoming (the clinical condition after bite from a venomous snake). Snake venoms are highly complex and diverse, which show inter-species as well as intra-species variation [4–7]. Consequently, snakebite envenomation represents myriad clinical manifestations. These include, but not limited to, local wound, neurotoxic, renal, musculoskeletal, cardiovascular, haemostatic and mental health related manifestations [2, 4]. Management of snake envenomation involves first aid, management of local and systemic effects followed by management of complications and follow-up for addressing any sequalae or disability [4]. Snake anti-venom (SAV) is the only specific intervention that is required, but SAVs are of various types and there is substantial debate on not only its dosage and frequency but also, in its design and suitability in different geographic regions and for different species.

In 2019, the World Health Organization (WHO) has released a comprehensive strategy which aims to decrease the burden of death and disability due to snake envenomation by 50% before 2030 [8]. Ensuring safe and effective treatment is one of the four key pillars which WHO has identified. We have previously analysed existing WHO guidelines for management of snakebites and found poor methodological rigour in its development [9]. The WHO

Guidelines were not based on systematic search, appraisal, and grading of evidence. Using evidence from high-quality systematic reviews (SRs) is crucial for decision-making. An overview of SRs will not only serve as a "single window front-end" on the current evidence but will also help identify gaps at the evidence synthesis level of interventions for management of snakebite envenomation. An overview of SRs is a relatively new approach for evidence synthesis with research methodology and guidance around it evolving [10]. It essentially involves systematically searching, appraising, and synthesising the results of related and relevant SRs on a single topic to support decision making by clinicians, policy makers, and guideline developers.

Methods and analyses

The protocol for the overview was registered prospectively in PROSPERO (CRD42018073048). The PRISMA checklist is provided in **S1 Table**.

Justification of overview of systematic reviews as the right approach for the study

We followed the Cochrane's Comparing Multiple Interventions Methods Group Editorial Decision Tree to establish whether our review would better fit an overview design or an intervention SR design, with or without a network meta-analysis [11]. The overview of SRs is an appropriate study design for our research topic because we did not intend to compare multiple interventions to draw inferences about the comparative effectiveness of the interventions but intended to summarise the available evidence on different interventions for management of snakebite envenoming.

Criteria for considering reviews for inclusion

We included studies which met the following criteria:

- **Study Design:** SR, irrespective of the design of the individual studies included by them, irrespective of whether they have conducted a meta-analysis or not.
- **Population:** SRs that have included studies with patients being treated for snakebite envenoming (irrespective of the snake species and irrespective of the age and sex of the participants or the setting).
- **Interventions:** SRs that have included any kind of medical, surgical or complementary or alternative therapies that can be used as a single intervention or concurrently with others, irrespective of the comparator.
- **Primary Outcomes**

1. All-cause mortality.
2. Any specific type of mortality (including but not limited to death due to neuromuscular paralyses or coagulopathy or cardiovascular shock, acute kidney injury).
3. Early adverse reaction (immediate or anaphylactic reaction and/or early anaphylactoid reaction (archetypal use)- as defined by systematic review authors).
4. Late adverse reactions to snake anti-venoms or serum sickness (as defined by the systematic review authors).
5. Major Complications including but not limited to major haemorrhage, paralysis, muscle loss or kidney failure after snakebite (as defined by the systematic review authors).

6. The proportion of wounds that have healed/are infection free or validated cosmetic outcome scores for wounds.
7. Mental health-related outcomes (as defined by the systematic review authors).

- **Secondary Outcomes**

1. Duration of hospitalization
2. Quality of life
3. Any cost-related outcome
4. Any other wound-related outcome (including but not limited to necrosis)
5. Death or disability as composite outcome (as defined by systematic review authors)

- If there was an update, we included only the latest version.
- We included SRs irrespective of language or date of publication

Search methods for identification of reviews

Electronic database. We searched Ovid MEDLINE(R), Global Health, EMBASE, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Clinical Answers, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Health Technology Assessment, NHS Economic Evaluation Database, APA PsycInfo, CINAHL by EBSCO-Host, and the Campbell Library. We also conducted supplementary search on Scielo (https://www.scielo.org/) for additional coverage of potential Spanish and Portuguese literature from Latin America. Detailed search strategy for all databases (updated 16th May 2020) including the supplementary Search on Scielo (updated 04th August 2020) is provided in **S1 Text**.

Search for grey literature. We contacted experts working in the domain of snakebite. We also searched PROSPERO, and the bibliographies of included SRs (found by other methods), to identify other SRs on the topic.

Selection of reviews

In the first phase, two authors (SB and DB OR ZL) independently screened the studies retrieved based on titles and/or abstracts and marked each record as "exclude" or "needs full text for evaluation". Full texts of all studies marked as "needs full text for evaluation" by either of the two authors were obtained and reviewed independently by two authors for consideration of inclusion based on criteria discussed above. Disagreements were resolved by consensus.

Data extraction and management

Two authors (SB and DB or ZL) independently extracted data. We did not contact the authors of SRs, or authors of individual studies, for any clarification or missing data. Disagreements were resolved by consensus between two authors (SB and DB or ZL). We extracted data using a pre-designed data extraction sheet.

Data synthesis

We narratively synthesised the results of the SRs. No additional quantitative analyses (additional indirect comparisons or network meta-analyses) or critical appraisal of studies included in SRs were conducted.

We provide a narrative description of the summary results from the included SRs. When there was an overlap between two SRs (i.e. had included same studies), we abstracted both the results, compared and contrasted them and reported both. If meta-analysis was conducted, the summary statistics is abstracted and reported, but in absence of meta-analysis, we present the summary results of the included studies. Unless otherwise mentioned all values correspond to 95% confidence interval (CI). We grouped studies for synthesis based on intervention types.

Assessment of methodological quality of included SRs

Quality assessment for included SRs was done independently by two authors (SB and DB or ZL) using the AMSTAR– 2 [12] criteria and discrepancy, if any, was resolved by consensus. AMSTAR-2 is an internationally accepted tool for assessment of quality of SR. The AMSTAR-2 assessment pertains to the conduct of SR and is independent of the quality of included primary studies.

The assessment of quality of included primary studies, if reported in included SRs is presented.

Difference between protocol and actual conduct of overview

As a matter of transparency, we note some protocol deviations during the conduct of the overview. Death or disability as composite outcome and any other wound-related outcome were not a priori outcomes noted in the protocol. These were added to capture additional evidence reported in SRs which could be useful for decision making. We searched 13 electronic databases, much more than originally planned. We had originally planned to search TOXLINE which is no longer a separate subset and relevant records subsumed within PubMed.

Results

Search results

We retrieved 76 records from search in electronic databases, 28 records in PROSPERO and two by citation screening in the original search. We removed duplicates (n = 30) and after screening following titles and abstracts (56 articles excluded) we retrieved 20 full texts from the original search strategy. For the supplementary search for Latin American literature, we retrieved 38 records with no duplicates and after screening, assessed four full texts.

Overall, we evaluated 24 full texts and finally included 13 completed SRs [13–25]. We identified three ongoing SRs which have protocol available in PROSPERO or are published [26–28] which meet our inclusion criteria.

Fig 1 shows the PRISMA flowchart documenting the process. Reasons for exclusion at full-text phase are mentioned in **S2 Table**.

Description of included systematic reviews

The three ongoing SRs study effectiveness of SAV on neuromuscular paralysis [26], interventions for managing thrombotic microangiopathy due to snakebite [27], and the role of therapeutic plasma exchange in acute care (with a planned subgroup analysis for snakebite) [28].

We found 13 completed SRs. Characteristics of included SRs are summarised in Table 1.

The SRs we found looked at the following aspects of management of snakebite envenomation:

- **First-aid for snakebite**: One SR looked comprehensively at all first-aid interventions for management of snakebites that is feasible for laypeople without medical background [21]. The SR had included 14 studies, of which two were randomised controlled trials (RCT), five

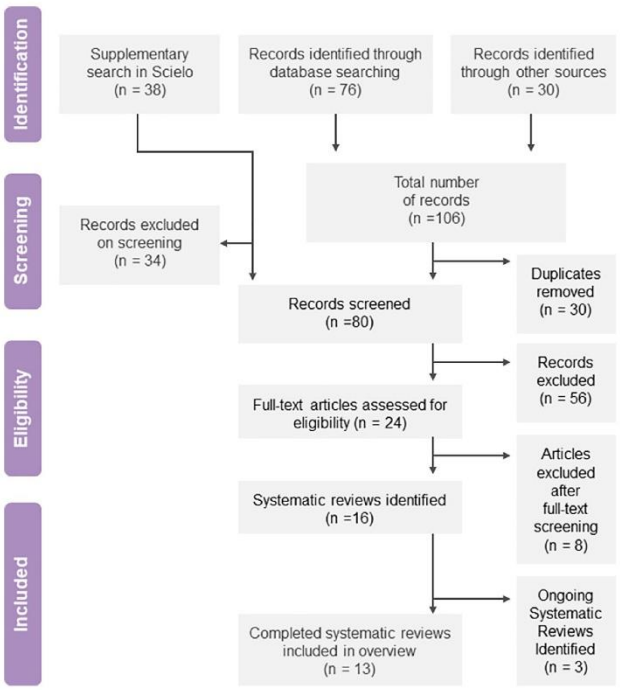

Fig 1. PRISMA flowchart for selection of SRs in the overview.

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were non-randomised intervention studies with control group, four were retrospective cohort studies, and three were prospective cohort design.

- **Effectiveness and safety of SAVs**: Six SRs evaluated different types of SAV for envenoming taking a snake species or genus specific approach [14, 16, 17, 19, 24, 25], while three took a more broad non-species-specific approach [20, 22, 23].

The SRs which took a snake-species specific approach included 81 studies of various designs. Among the studies which took a non-species-specific approach one was an empty review [23], while the other two SRs included 31 studies in total [20, 22].

- **Interventions to prevent adverse reactions due to SAV therapy:** Two SRs looked at interventions for preventing adverse drug reactions due to SAV therapy [13, 15]. Together, these two SRs included nine studies.
- **Other interventions for management of snakebite envenomation**: There was only one SR which evaluated surgical interventions for North American *Crotaline* snake envenomation [18]. It included 42 studies but did not report the total number of participants.

Synthesis of findings from included systematic reviews on interventions

A narrative overview of the findings from the included SRs is presented in a structured manner based on typology of interventions.

Table 1. Characteristics of included systematic reviews.

NAME	Review Objective	Types of Study Design	Population & Setting	Intervention	Types of Comparator	Outcome	Date of Last Search
FIRST AID FOR SNAKEBITE							
Avau 2016	To summarize the best available evidence concerning effective and feasible first aid techniques for snakebite.	1. (quasi or non-) randomized controlled trials, controlled before and after studies or controlled interrupted time series. 2. Observational studies of the following types were also included: cohort and case-control study, controlled before and after study or controlled interrupted time series	Studies concerning people with snakebites or healthy volunteers with "mock" snakebites	Interventions for the first aid management of snakebites that can be applied by laypeople without medical background. Interventions for the management of snakebites that are not feasible to be performed in a first aid setting where laypeople are the first aid providers were excluded.	The interventions to any other first aid intervention or no intervention	(1) survival, functional recovery, pain, complications, time to resumption of usual activity, restoration of the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects) for studies involving snakebite victims, (2) spread of mock venom for studies investigating the efficacy of pressure immobilization and (3) quality of the bandage applied and tension generated for studies investigating the feasibility of pressure immobilization.	March 2016
EFFECTIVENESS AND SAFETY OF SNAKE ANTI-VENOM: SPECIES OR GENUS SPECIFIC SYSTEMATIC REVIEWS							
Johnson 2008	To analyse the literature concerning the utilisation of Crotalidae polyvalent immune fab (ovine; FabAV) in children following Crotalinae envenomation	Human case reports and studies	Paediatric patients less than 18 years of age **Setting:** not specified	Crotalidae polyvalent immune fab	not mentioned	not specified	Feb 2008
Lavonas 2009	To characterize the reported response to FabAV therapy of patients suffering severe crotaline envenomation.	All article types were considered, including prospective clinical trials, cohort and non-cohort case series, single case reports, review articles, editorials, commentaries, published abstracts, and letters-to-the-editor	**Victims of** North American severe crotalid envenomation 1. "severe" envenomation as defined in the US FDA-approved prescribing information for FabAV 2.Snakebite Severity Score (SSS)>7 3. Reviewer defined ""severity of envenomation based on the initial presentation,"	Treatment with FabAV	Not specified	1. "initial control" of a specific venom effect, (specific definition by SR author). 2. initial control of coagulopathy (specific definition by SR author). 3. Initial control of the envenomation syndrome (specific definition by SR author). 4. Persistent severe venom effects 5. Recurrence or delayed onset of severe venom effects 6. Permanent sequelae of envenomation	July 2008
Schaeffer 2012	To evaluate the incidence of immediate hypersensitivity reactions and serum sickness reported in studies of patients treated with FabAV therapy after North American crotaline envenomation.	All prospective and retrospective cohort studies	All patients receiving FabAV therapy for North American crotaline envenomations Setting Not specified	FabAV therapy	NA	Immediate hypersensitivity and serum sickness incidence associated with FabAV administration; rehospitalization or death of a patient as a result of serum sickness	December 2010

(*Continued*)

Table 1. (Continued)

NAME	Review Objective	Types of Study Design	Population & Setting	Intervention	Types of Comparator	Outcome	Date of Last Search
Lavonas 2014	To estimate the proportion of patients with crotaline snake envenomation who are treated with Crotalidae polyvalent immune Fab (ovine) antivenom and who develop medically significant late bleeding	Retrospective observational studies, prospective observational studies, and clinical trials	Crotaline snake envenomation in United States No restriction placed on study setting; therefore, all studies based in EDs, hospital inpatient units, outpatient centers, poison centers, and combinations were considered	FabAV	Not specified	All late bleeding events (specific definition by SR author). Deaths due to late bleeding event	May 2012
Habib 2013	To review and re-analyse all published preclinical and clinical studies on envenoming and antivenom therapy conducted in West Africa to determine the effectiveness of antivenom therapy of carpet viper (Echis ocellatus) envenoming	All observational, interventional and preclinical studies conducted in the region (or on antivenoms derived from the region)	Patients from Sub-Saharan/West African countries with carpet viper bites	Antivenom	Inappropriate or no antivenoms	Effectiveness of antivenoms in resolving features of carpet viper envenoming or curtailing mortality	March 2012
Lamb 2017	Identify all the anti-European Vipera spp antivenoms currently in clinical use and to seek data on comparative effectiveness and safety.	Publications (unspecified) pertaining to clinical outcome, including case reports	Europe Setting not specified	Anti-venom	not specified	Not specified	March 2016
EFFECTIVENESS AND SAFETY OF SNAKE ANTI-VENOM: BROAD NON-SPECIES OR NON-GENUS SPECIFIC SYSTEMATIC REVIEWS							
Das 2015	To evaluate the optimum dose (low vs. high) for snake antivenom (SAV)	RCTs	Patients having evidence of envenomation, irrespective of whether the bite was from a viper, cobra, or krait. Exclusion criteria were, presentation 24 h after the bite, history of any bleeding diathesis or any other previous neurological abnormality, and manifested allergy to the SAV. **Setting:** not mentioned	**Intervention: H**igh dose of SAV (not defined by review authors) **Co-intervention:** as an adjuvant to standard hospital treatment of snake bite. All methods of administration of SAV in all grades of envenomation (mild, moderate or severe) were considered.	low dose **SAV (not defined by review authors)**	**Primary outcome:** Mortality rate. **Secondary outcome:** -Time to normalization of CT; -Neurological complication rate; -Rate of other complications (acute renal failure [ARF], bleeding or disseminated intravascular coagulation [DIC], and shock); -Duration of hospital stay (days); -Adverse-events; -Cost-effectiveness.	August 2014
Maduwage 2015	To assess the effect of snake antivenom as a treatment for venom induced consumption coagulopathy in people with snake bite.	RCTs (with a placebo or no treatment arm)	People of any age with snake envenoming who have already developed snake venom induced consumption coagulopathy	Intravenous administration of snake antivenom regardless of the type of antivenom or the dose.	People not treated with antivenom	**Primary outcomes** •Mortality **Secondary outcomes** • Major haemorrhages •Time to improve clotting studies •Immediate systemic hypersensitivity reactions • Serum sickness	January 2015.
Potet 2019	To systematically collect and analyse the clinical data on all antivenom products now available in markets of sub-Saharan Africa.	All types of clinical data were eligible for inclusion: randomized controlled trials, case-control studies, observational cohort studies, case series, and programmatic data.	Sub-Saharan Africa. All patient populations of all ages were included. Studies reporting less than 10 patients per antivenom product were excluded.	Commercially available antivenom products	not specified	clinical data in terms of safety and effectiveness against the different species and envenoming syndromes.	February 2018
INTERVENTIONS TO MANAGE ADVERSE REACTIONS DUE TO SAV THERAPY							

(*Continued*)

Table 1. (Continued)

NAME	Review Objective	Types of Study Design	Population & Setting	Intervention	Types of Comparator	Outcome	Date of Last Search
Nuchprayoon 2000	To evaluate drugs given to prevent acute adverse reactions to horse serum antivenom, in relation to anaphylaxis and death.	Randomized or quasi-randomized controlled trials.	Patients treated for snake envenoming with horse serum antivenom, irrespective of the snake species.	1. Adrenaline versus no adrenaline. 2. Steroid versus no steroid. 3. Antihistamine versus no antihistamine.	As noted in intervention section	Primary - Death (from any cause). - Symptoms and signs indicating severe anaphylactic reaction (specific definition by SR author). Secondary - Early (anaphylactoid) reactions: urticaria, angioedema, bronchospasm. - Late (serum sickness type) reactions: fever, rash, arthritis, lymphadenopathy more than 5 days after antivenom.	Updated search on 29 March 2004 but newer studies were not included or excluded and original 1999 version of results retained
Habib 2011	To conduct a systematic review and meta-analysis of published data to assess the effect of pre-medication on the risk of EAR (early adverse reactions)	RCT or cohort study designs	Patients with early adverse reaction following antivenom administration in snakebite No regional restriction	antivenoms + pre-medication (for prevention of early adverse reaction)	snake antivenom + placebo/ no pre-medication	Early Adverse Reactions, other outcomes recorded and quality measures (as defined by trial authors)	September 2010
OTHER INTERVENTIONS TO MANAGE SNAKEBITE ENVENOMATION							
Toschlog 2013	To develop best practice guidelines for surgical interventions in the acute management of North American crotaline snake envenomation that are both evidence based and useful to the clinician	Not specified	North America	1. Early excision of tissue near bite site 2. methods for diagnosis of compartment syndrome 3. prophylactic fasciotomy 4. fasciotomy (curative for those with compartment syndrome)	1. standard care alone (including antivenom, if indicated) 2. NA 3. standard care alone (including antivenom, if indicated) 4. standard care alone (including antivenom, if indicated)	All late bleeding events reported in any study (specific definition by SR author).	July 2012

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First-aid for snakebite. The SR on first-aid [21] had a broad scope and included six different types of interventions. It included 1295 participants from 14 studies which were conducted in Australia (n = 4), Brazil (n = 2), India (n = 2), Myanmar (n = 2), Nigeria (n = 2), USA (n = 1) and China (n = 1).

- **Tourniquet**

  The SR identified seven studies on effect of tourniquet on snakebite and found:

  - No significant differences between those treated with a tourniquet (with or without additional incisions in the bite wound) and victims who received no tourniquet or no first aid for death (Relative Risk (RR) 0.77; 95% CI 0.13 to 4.41); and the occurrence of death or disability (Odds Ratio (OR) 4.7; 95% CI 0.58 to 212).
  - No significant difference was seen between those treated with a tourniquet (irrespective of additional wound incisions),in comparison to those patients with snakebite who received no tourniquet or no first aid for the following outcomes: acute renal failure (RR 1.24; 95% CI 0.33 to 4.66) [22], acute respiratory failure (RR 1.4; 95% CI 0.3 to 6.53) [22], occurrence of haemorrhagic syndrome (RR 0.95; 95% CI 0.77 to 1.17) [30], and incidence of multiple organ dysfunction syndrome (RR 1.85; 95% CI 0.56 to 6.15).

- Only a single study included in this SR had studied duration of hospitalisation and found no significant difference in the duration of hospital stay between snakebite victims treated with a tourniquet and those receiving no first aid (MD -0.3 days; 95% CI -1.9 to 1.3), another found a significant increase in the duration of hospital stay between snakebite victims treated with a tourniquet and those receiving no first aid (4.6±2.0 days vs 3.7±2.5 days; MD 0.9, p = 0.04).
- Mixed evidence on wound related outcomes from different studies was found:
  - Increase in local swelling for those treated with a tourniquet (and no local incisions) (RR 1.71; 95% CI 1.49 to 1.96) and those treated with a tourniquet and wound incisions (RR 1.71; 95% CI 1.49 to 1.96), when compared to snakebite victims receiving no first aid.
  - Significantly increased odds for an increased severity of local envenomation in snakebite victims receiving a tourniquet, compared to those not receiving a tourniquet (OR 4.31; 95% CI 1.33 to 13.89).
  - No significant differences were found between snakebite victims treated with a tourniquet (with or without additional incisions in the bite wound) and victims who received no tourniquet or no first aid for tissue necrosis (RR 0.75; 95% CI 0.14 to 4.12) and local oedema (RR 0.98; 95% CI 0.6 to 1.61).

- **Incision of the bite wound**

The SR identified two studies on effect of incision of the bite wound and found:

- No statistically significant difference in the incidence of death or disability (OR 4.3; 95% CI 0.18 to 275) between those whose bite wounds were incised as a part of first-aid and those receiving no first aid.
- No difference in occurrence of haemorrhagic syndrome (RR 1.05; 95% CI 0.71 to 1.53), in comparison to those receiving no first aid.
- Significantly increased incidence of local swelling upon incision (RR 1.66; 95% CI 1.40 to 1.97), in comparison to those receiving no first aid.
- Significant decrease in the duration of hospitalisation in those whose snakebite wound was incised in comparison to those whose bite wound was not incised (2.9±1.6 days vs 4.6 ±2.2 days; MD -1.70 days; p = 0.03)

- **Suction of the bite wound**

The SR identified only one study which looked the effect of suction of bite-would and reported:

- No significant increase in the occurrence of death or disability (RR 1.33; 95% CI 0.07 to 26.98) compared to patients who had not received first aid.
- No significant increase in the duration of hospitalisation (median 6 days vs. 4 days, p = 0.7) compared to those who did not receive suction.

- **Snake stones**

The SR identified two studies on effect of snake stones (animal bones or stones used in folk and indigenous medicine for treatment of snakebite) and found:

- No difference in the occurrence of death or disability between those treated with snake stones in comparison to those receiving no first aid (OR 13; 95% CI 0.39 to 823).
- No significant decrease in duration of hospitalisation in those with snakebite patients who had applied snake stones in comparison to those not receiving any first-aid (MD -0.2; 95% CI -2.57 to 2.17) or in comparison to those not being treated by snake stones (median 2.5 days vs. 4 days; p = 0.09).

- **Traditional medicine and concoctions:**

The SR identified two studies that evaluated the use of traditional medicine and concoctions and found:

- Statistically significant increased odds for death or disability in snakebite patients treated with concoctions applied to the bite wound, compared to those who had not applied concoctions to the wound (OR 15; 95% CI 1.4 to 708).
- Statistically significant increase in odds for death or disability in snakebite patients who had ingested concoctions (6/10), compared to those who did not ingest (OR 20; 95% CI 1.4 to 963).
- No significant decrease in the duration of hospitalisation in those who received traditional medicine, compared to those who did not received no first aid (MD 0.6 days; 95% CI -1.23 to 2.43). There was no difference in the duration of hospitalisation between those who were treated with concoctions applied to the bite wound, in comparison with those on whom no concoction was applied (median 5days vs. 4 days; p = 0.6), those who ingested concoctions, in comparison to those who did not ingest (median about 4 days in both; p = 0.84).

- **Pressure Immobilization**

The SR identified seven studies related to pressure immobilisation on snakebite but none of them reported any outcome of our interest.

Effectiveness and safety of SAVs: species or genus specific systematic reviews. Four SRs looked at evidence with respect to *Crotalidae* polyvalent immune Fab antivenom (FabAV) for *Crotalinae sp (*North American Pit Viper*)* envenomation. One looked specifically at children [24], one on those with severe envenomation [19], one on those who developed medically significant late bleeding [14] and another looked specifically at safety aspects [17]. This apart, two other SR looked at *Echis occelatus* envenomation in West Africa and *Vipera spp* envenomation in Europe [29, 30]. The evidence with these regards is summarised below:

- ***Crotalidae* polyvalent immune fab (FabAV) in children**
  The SR found 10 studies (six case reports, three descriptive reports, and one RCT) with a total of 47 children [24]. When pooled the prevalence of adverse events was found to be in 8.5% of the children (4/47). Of these, three were acute reactions, and one was serum sickness on hospital discharge. All except two studies did not have any recurrent local effects (defined as progression of local injury after initial response to SAV) and late coagulopathy (defined as coagulopathy occurring after initial normal values). One study had 8% (1/12) recurrent local effects and 8% (1/12) late coagulopathy while another study had 75% (3/4) patients who had late coagulopathy.
- **FabAV in those with severe envenomation**
  The SR found 19 studies consisting of 24 people with severe North American Pit Viper

envenomation[19]. Seven cases were described in five cohort studies and 17 cases were described in 14 single patient case reports or non-cohort case series. Persistent severe venom effect (limb swelling, limb pain, soft tissue bleeding, thrombocytopenia, neurotoxicity, or compartment syndrome) was seen in 0% of patients in cohort study but 53% of patients in non-cohort reports. No patient developed systemic bleeding but recurrent and/or delayed-onset severe defibrination syndrome was found in patients.

- **FabAV in those who develop medically significant late bleeding**
  The SR included 19 cohort studies (two cohorts were within the context of RCTs) consisting of 1017 patients. Late bleeding was seen in nine patients (0.9%; 95% CI 0.4% to 2.2%) with five patients developing medically significant late bleeding. (0.5%; 95% CI 0.1% to 1.7%) [14]. Eight of the nine patients who had late bleeding were cases of Rattlesnake envenomation. No deaths or sequalae of any kind was reported.
- ***Safety of* FabAV for North American crotaline snake envenomation**
  The SR included 11 studies (seven retrospective studies, three prospective studies, and one that had both prospective and retrospective data) and included 661 participants [17]. The combined estimate of incidence of early hypersensitivity was 0.08 (95% CI 0.05 to 0.11). The pooled estimate of serum sickness incidence was 0.13 (95% CI 0.07 to 0.21) from amongst the seven studies which reported it.
- **SAV for carpet viper (Echis ocellatus) envenoming in West Africa**
  The SR found 22 studies (four RCTs, 12 observational studies, and six preclinical studies) [16]. Pooled meta-analysis found that the odds of dying decreased by as much as 75% (OR 0.25; 95% CI 0.14 to 0.45) of dying among those treated with a specific antivenom compared to non-specific or no anti-venoms. Mortality rates were more than double when there was stock-out of reliable SAVs (RR 2.33; 95% CI 1.26 to 4.06).
- **Anti-European Vipera spp antivenoms**
  The SR found 40 studies (excepting pre-clinical studies which were included) on various types of anti-European *Vipera spp* antivenoms involving about 2602 participants [25]. There were 14 studies each on Zagreb (n = 1306), and on ViperaTAb (n = 197), 11 studies on ViperFAV (n = 558), three studies on Biomed (n = 43), two studies on Bulbio antivenom (n = 69), and one case-report on Viekvin (n = 1). There were eight studies in the SR which did not specify the antivenom used.
  Deaths were reported only in patients given Zagreb SAV and the rate was 0.2% (n = 5). The median length of hospitalisation in patients who were given ViperFAV or ViperaTAb was significantly less than those being given IM Bulbio or Zagreb antivenoms (1 to 4.8 days versus 2 to 18 days).
  Adverse reactions were reported in 1.5% (37 of 2408 cases including 7 cases of anaphylaxis) 5%) in which SAV was administered. This varied between 0.5 to 2.0% in patients administered with ViperaTAb, Zagreb, and ViperFAV antivenom, 4.7% in those who received Biomed antivenom. No adverse reactions were reported in those administered Bulbio antivenom (n = 67) and in the single patient administered Viekvin antivenom.

Effectiveness and safety of SAVs: broad non -species/genus specific systematic reviews. There were three SRs which took a broad non-species / genus specific approach and investigated the role of SAVs in venom induced consumption coagulopathy in people with snakebite envenomation [23], effectiveness and safety of SAVs available commercially in sub-Saharan Africa [22], and, on different dosing regiments (low vs. high) of SAVs [20].

- **SAVs for managing venom induced consumption coagulopathy**

The SR on RCTs on this issue did not find any studies which met eligibility criteria [23].

- **SAVs available in sub-Saharan Africa**

The SR [22] took a phased approach, wherein the authors first conducted a market analysis to obtain a comprehensive list of SAVs available in the sub-Saharan Africa and then looked systematically for evidence (of any design) for these SAVs specific to the region. This is crucial because there is substantial intra-species variation based on climate and geography. The SR found 26 studies (two RCTs, five non-randomised comparative clinical studies, 11 observational cohort studies, and eight anecdotal clinical reports) on nine SAVs available in the sub-Saharan Africa.

The SR did not find any studies from sub-Saharan Africa on the following seven SAVs, although they were available in the markets:

- ASNA antivenom–D (Bharat Serums and Vaccines)
- Snake Venom Antiserum (PanAfrica) aka Premium-A (Premium Serums)
- Snake Venom Antiserum (Central Africa) aka Premium-CA (Premium Serums)
- Afriven 10, Snake Venom Antiserum (African) aka VINS-A (VINS Bioproducts)
- Anti-Snake Venom Serum Central Africa aka VINS-CA (VINS Bioproducts)
- Snake venom antiserum *Echis ocellatus* (VINS Bioproducts)
- SAIMR-Boomslang (SAVP)
- **EchiTabPlus (ICP) and EchiTabG (Micropharm)–**One RCT and two observational studies were found related to EchiTabPlus and EchiTabG for *Echis ocellatus* envenoming. For the RCT, exact difference in outcomes were not presented though the SR mentioned "ET-Plus was found to be a little more effective than an initial dose of one vial of EchiTabG, and a little less safe"[22]. Very low case-fatality was reported in the two observational studies from Nigeria and Central African Republic on use of EchiTabPlus or EchiTabG for *Echis ocellatus* envenoming. However, an early hypersensitivity reaction was seen in 21 patients (6.9%).
- **Inoserp-Pan African (Inosan)-** The SR found two studies which found case fatality rates of 3.17% in Senegal and 4% and 0.92% in northern Benin and Guinea from a multicentre observational study with 8% of patients in whom adverse events were reported. The multi-country study from Benin and Guinea had many cases of *Echis ocellatus* in Benin. No specific species information was presented in the SR for the study from Senegal. Blood coagulability was found to be restored within 24 hours in 87.5% and 98% of patients in the respective studies.
- **Fav-Afrique aka FAV-A(Sanofi Pasteur)**- FAV-A was studied in eight cohort studies from Cameroon (2/41 had minor adverse event; no death, no serum sickness), Ghana (mortality rate 1.8%), Chad (mortality rate 6.67%), Central African Republic (mortality rate 7.47% in a prospective study and 0.5% in a retrospective study), and Republic of Djibouti (no deaths or adverse events reported in three cohorts). The study in Cameroon and Central African Republic were conducted in an area where *Echis ocellatus was common. The three cohorts from Djibuouti found FAV-A to restore blood coagulability on Echis pyramidum* bites too. Only one patient in a single study from Djibouti which enrolled 31

patients had necrosis. No information about necrosis was reported in the SR for other studies.

- **SAIMR-Polyvalent (SAVP)—**There were six studies on SAIMR-Poly in which a total of 5 deaths were seen in 144 included patients (death rate 3.47%). The SR noted varying rates of adverse events with one showing severe early (anaphylactoid) reaction in 76.47% patients. The adverse event rate across studies was between 10% to 15%.
- **SAIMR Echis ocellatus / Echis Pyramidum (SAVP)—**There were three studies from Nigeria, of which one was an RCT. None of the three studies reported any deaths. The RCT in the SR found that SAIMR-Echis was more effective than SAIME Behringwerke in terms of reversing haematological abnormalities more rapidly (data not specifically reported). The RCT also noted early hypersensitivity in four out of 23 patients while one observational study found adverse reaction in 14 out of 48 patients (one study did not report adverse effects).
- **Antivipmyn-Africa (Instituto Bioclon /Silanes)–**The SR found four studies which reported case fatality rates of 3.11% in Benin, 10% in Central Africa, 18.2% in Guinea, and 15.4% (low dose) and 17.6% (high dose) in another study in Guinea. A low rate of adverse events (between 10% to 15%) was reported across studies on Antivip-A.
- **ASNA antivenom—C (Bharat Serums and Vaccines**)—There was one post-marketing surveillance study from Central Ghana which found 22% mortality and 7.58% anaphylactic shock. Another study included in the SR was from Nigeria and it reported that ASNA-C was ineffective in restoring blood coagulopathy and causing in allergic reactions in many cases. All the studies were conducted in areas where *Echis Occelatus* bites are common.
- Vacsera **POLY-** One retrospective study from Ethiopia reported 17% deaths among 23 patients with prolonged clotting time who were treated with Vacsera Poly.

Different dosing regimens of SAVs. The SR [20] found five RCTs on low versus high dosage regiments of SAV, out of which four were from India and one from Brazil. However, the distinction used between low and high dosage was not specified a priori and as a consequent there were overlaps with low doses ranging from 20–220 ml while high dosage ranged from 40–550 ml. A volume-based classification of dosing regimens as done in this SR might also be inappropriate, because different antivenoms have different protein concentrations leading to differences in the amount of protein administered for the same volume[31].

Four trials reported mortality out of which one did not report any death. Pooled result from other three trails showed no significant difference in death between those with high and low doses of SAVs. (RR 0.69; 95% CI 0.38 to 1.26)

There was no significant difference in rates for neurological complications (RR 0.82; 95% CI 0.23 to 2.94), acute renal failure (RR 0.87; 95% CI 0.62 to 1.21), and bleeding or disseminate intravascular coagulation (RR 0.77; 95% CI 0.46 to 1.29). No significant difference was noted in time to normalisation of clotting time between high dose versus low dose group in one trial (10hours 23 minutes versus 9 hours) while another trial found a significant difference (20.67 ± 9.61 hours in high dose group (regimen I), 16.55 ± 9.84 hours in low dose (regimen II), and 13.4 ± 7.16 hours in low dose (regimen III)).

Adverse SAV reactions (itching, urticaria, and erythema) occurred in eight of 30 patients in the high dose group and 8 out of 60 patients in the low dose group in one trial. The other three trials did not report any major adverse events.

Duration of hospitalisation was reported from two studies and results were pooled to find that low-dose SAV led to 1.27 less days of hospitalisation compared to the high dose group (MD −1.27 days, −2.05 to − 0.5). Another study also reported duration of hospitalisation, but the SR could not pool the data due to non-reporting of standard deviation. It found "no difference in the average hospital stay (days) between the low dose and high dose (8.42 vs. 9.02 days).

The study calculated cost-effectiveness using prices of Indian polyvalent SAV prices. It stated that a low-dose regimen led to savings of INR 500–2000 (USD 10–140) excluding any other expenditures (including expenditure on hospitalisation, and other therapies).

Interventions to prevent adverse reactions due to SAV therapy. Two SR investigated interventions to prevent adverse reactions to SAV administration [13, 15]. The study published earlier [13] included only two RCTs from Brazil and Sri Lanka while Habib 2011 [15] included three RCTs and four cohort studies. The SRs found:

- **Prophylactic medication to prevent early adverse reaction (EAR)**
  The seven studies that Habib et al [15] included had 10 comparisons of adrenaline alone or in combination, hydrocortisone alone, anti-histamine alone or in combination with steroids. The overall pooled RR for any prophylactic pre-medication to no pre-medication for EAR was 0.70 (0.50 to 0.99) but there was high heterogeneity implying different effects of particular types of pre-medications.

- **Prophylactic Adrenaline**
  Nuchpayoon et al [13] included only one trial from Sri Lanka which found that those who received adrenaline had significantly lesser adverse allergic reactions to SAV (Haffkine polyspecific) overall (RR 0.25; 95% CI 0.11 to 0.57) than those receiving placebo. The trial had also noted that severe reactions were many times more in the placebo group over the adrenaline group (RR 0.10; 95% CI 0.01 to 1.77). No death was recorded in either of the groups. No patient developed hypertension (blood pressure >160/100 mmHg), arrhythmia (other than sinus tachycardia), or neurological deficits suggestive of cerebrovascular accidents in either of the groups.
  Habib 2011 [15] had included three studies (including the Sri-Lankan trial which was included in Nuchprayoon) on adrenaline-containing pre-medication (adrenaline alone or with promethazine/hydrocortisone) and found a risk-ratio of 0.32 (95% CI 0.18 to 0.58) with no heterogeneity, when compared to no pre-medication or placebo. The other two studies were a retrospective cohort from Papua New Guinea and nested cohort from Australia with risk-ratio of 0.27 (0.10, 0.79) and 0.78 (0.21, 2.90) respectively for subcutaneous adrenaline-containing pre-medication compared to no pre-medication.

- **Prophylactic Steroid**
  While Nuchprayoon did not find any studies which had looked at the role of steroid alone, Habib found one RCT from Sri Lanka which found no difference for development of EAR between use of hydrocortisone and placebo (RR 0.98; 95% CI 0.70 to 1.39) and the trial was prematurely stopped [15].

- **Prophylactic Anti-Histamine**
  Both SRs found one trial from Brazil on Bothrops envenomation patients to prevent reactions due to *Bothrop* specific SAV (three manufactures: Instituto Butantan, Fundaçao Ezequiel Dias, or Instituto Vital Brazil) and found no difference in acute reactions between those who received promethazine and those who did not (RR 0.98; 95% CI 0.50 to 1.93). One patient from each treatment group suffered severe anaphylaxis. No death was reported in either of the groups.

- **Prophylactic Steroid along with anti-histamine**
  Habib [15]found five studies which had explored several combinations of prophylactic steroid with different anti-histamine and although separate pooled RR for this was not reported, it mentioned that the result was not statistically significant and there were issues with heterogeneity, paucity and quality of data.

Other interventions for management of snakebite envenomation. There was only one SR under this category which was done in the context of consensus-based recommendations being developed for surgical consideration for North American Pit Viper (*Crotalinae*) envenomation [18]. It found evidence on several key issues, one of which pertained to diagnostic accuracy issues and hence not of interest (diagnostic criteria for compartment syndrome) to this overview:

- **Early excision of tissue near bite in *Crotaline spp*. envenomation**
  The SR found two old observational studies (with no comparison group) when early excision along with tourniquet and ice-water immersion but not SAV being administered typically showed worse tissue outcomes (not exactly specified). In the modern context, where SAV administration is the norm, the review found no comparative clinical trials which had examined role of early excision (alone or as an adjunct with SAV). It however, found 16 studies which showed excellent results (outcomes were not explicitly stated) with SAV without incisions or excisions in comparison to just one study which found to the contrary. The SR found no literature in relation to debridement of necrotic tissue or in relation to management of puncture wounds on tendon sheaths for patients with snake envenomation.
- **Prophylactic fasciotomy for preventing compartmental syndrome in Crotaline spp envenomation**
  Prophylactic fasciotomy (done before compartment syndrome develops in *Crotaline spp*) alone or in combination with standard therapy including SAV was found to not improve outcomes. The outcomes were not explicitly specified but are related to "scarring and wound-healing" and "elevated compartment pressure". The quality of evidence was determined to be moderate by the consensus group and was based on two human and one porcine study.
- **Therapeutic Fasciotomy for treating compartmental syndrome in Crotaline spp envenomation**
  It was found that FAb SAV administration decreased myonecrosis and decreased the need for fasciotomy. Therapeutic fasciotomy in those with diagnosed compartmental syndrome for *Crotaline spp* envenomation was found to not decrease intra-compartmental pressure as per a recent evidence-based review included in the SR. However, despite this, the consensus committee mentioned about a "large body of evidence supporting fasciotomy in compartment syndrome caused by fractures, crush injuries, and electrical burns, it is logical that fasciotomy should be performed in cases where aggressive antivenom therapy fails to correct impaired tissue perfusion." The evidence was not cited, while a recommendation was made for therapeutic fasciotomy through an algorithm developed by the consensus panel.

Quality of primary studies included in systematic reviews

Seven included SRs did not conduct any quality appraisal of included studies [14, 18, 19, 22, 24, 25, 30]. The study on low-dose versus high dose of SAV reported that they used the Cochrane tool and reported that the included trials were of "moderate quality" [20]. The study to understand safety of FabAV [17] used the Jadad scale for RCTs, Newcastle-Ottawa Quality Assessment Scale for observational prospective studies, and a chart review tool for retrospective studies. The Jadad score for the included RCT had an Endorsement Frequency of 84.5%,

all the prospective cohort studies had a score of 7 out of 9 (9 being lowest risk of bias) while the retrospective studies had varying quality.

Quality of evidence on different outcomes were reported to be measured by GRADE approach in only two SRs [20, 21] and in both the SRs. the quality of outcomes was found to be low or very low.

Confidence in results of included SRs

We used AMSTAR-2 for assessing the confidence in results of included SRs and found that except for one [23], all were rated to have critically low confidence in results. This implies the SR had more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available primary studies on the topic. We rated Maduwage et al. [23] to have high overall confidence in the results of the SR. AMSTAR-2 ratings for the included SRs are summarised in Fig 2.

Study ID	Nuchprayoon 2000	Johnson 2008	Lavonas 2009	Habib 2011	Schaeffer 2012	Habib 2013	Toschlog 2013	Lavonas 2014	Das 2015	Muduwage 2015	Avau 2016	Lamb 2017	Potet 2019
Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	No	No
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	No	No	No	No	No	No	No	Yes	Yes	No	No	No
Did the review authors explain their selection of the study designs for inclusion in the review?	No	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	No
Did the review authors use a comprehensive literature search strategy?	No	No	Yes	Yes	Yes	Yes	No	Yes	Partial Yes	Yes	Partial Yes	No	Partial Yes
Did the review authors perform study selection in duplicate?	Yes	No	No	No	No	No	No	Yes	Yes	Yes	Yes	No	No
Did the review authors perform data extraction in duplicate?	Yes	No	Yes	No	No	No	No	Yes	Yes	Yes	Yes	No	No
Did the review authors provide a list of excluded studies and justify the exclusions?	No	No	No	Yes	Yes	No	No	No	Yes	Yes	Partial Yes	No	Yes
Did the review authors describe the included studies in adequate detail?	Yes	Partial Yes	No	Yes	Partial Yes	Yes	No	Partial Yes	Yes	Yes	Yes	No	Partial Yes
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? *RCTs or NRSI as applicable*	Partial Yes	No	No	No	Partial Yes	No	No	No	No	Yes	Partial Yes	No	No
Did the review authors report on the sources of funding for the studies included in the review?	Yes	No	Yes	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? RCTS or NRSI as applicable	Yes	No Meta-analysis conducted	No Meta-analysis conducted	Yes	Yes	Yes	No Meta-analysis conducted	Yes	No	Yes	No Meta-analysis conducted	No Meta-analysis conducted	No Meta-analysis conducted
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	No Meta-analysis conducted	No Meta-analysis conducted	No	Yes	Yes	No Meta-analysis conducted	No	No	Yes	No Meta-analysis conducted	No Meta-analysis conducted	No Meta-analysis conducted
Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes	No	No	No	No	Yes	No	No	No	Yes	No	No	No
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	No	No	Yes	Yes	Yes	No	No	No	Yes	No	No	No
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	No Meta-analysis conducted	No	Yes	Yes	Yes	No Meta-analysis conducted	Yes	Yes	Yes	No Meta-analysis conducted	No Meta-analysis conducted	No
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Overall confidence in the results of the review using AMSTAR-2 RATING	Critically low	Critically low	Critically low	Critically low	Critically low	Critically low	Critically low	Critically low	Critically low	High	Critically low	Critically low	Critically low

Fig 2. AMSTAR-2 ratings showing confidence in results of included systematic reviews.

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Discussion

Summary of main results

The available evidence from 13 completed SRs related to management of snakebite envenomation covers a range of interventions (pharmacological and otherwise) and in diverse settings (geographical, species specific, and otherwise). While effect estimates vary, it is evident that there are glaring gaps in terms of availability and quality of evidence. We have summarised the summary evidence for all the interventions at synthesis level in Table 2. Largely we see that high-quality review-level evidence is not available for almost all intervention-outcome pairs. There is no synthesised evidence with regards to quality of life or mental health outcomes across the board and only few SRs [20, 25, 32] had envisaged to understand the effect of interventions to decrease health systems burden (through cost or duration of hospitalisation).

We found that evidence for several key aspects regarding first aid for snakebite envenomation is required. Evidence pertains to only a few studies and with small number of participants [32]. Low quality evidence exists that tourniquet, incision, suction, snake stones and traditional medicines and concoctions are not effective for several outcomes, although evidence on several key outcomes is not available or show no difference compared to their non-application for first aid. There is no evidence on pressure immobilisation related to outcomes of interest.

Evidence with respect to specific geographic settings and for many specific anti-venoms is unavailable at the synthesis level and also at the primary study level (as for example in Africa [22]). Despite SAV being the only life-saving intervention for snakebite dosing regimens and their safety and effectiveness, key clinical issues are studied only in a handful of trials–the evidence base thus being low quality, inconclusive and not providing contextual information [20, 33]. Evidence related to late adverse reactions, wound-related outcomes, quality of life, duration of hospitalisation, costs and disability is scarcely available. Prophylactic medications for preventing adverse reactions for SAV has been studied in only a few RCTs and there is some evidence on the effectiveness and safety of adrenaline for this purpose [13, 15]. There is no evidence suggesting the use of steroids, anti-histamines or their combination for preventing adverse reactions. The SRs on species-specific treatment issues (including SAVs and role of surgical interventions) are mostly restricted to North American Pit Viper (*Crotalidae*) and Carpet Viper (*Echis occelatus*) envenomation [14, 18, 24, 34, 35]. The FabAV antivenom is found to be effective in many studies for children, for those with severe envenomation and for those who develop medically significant late bleeding). It has been found to be safe in several studies. Specific SAV for Carpet Viper envenoming in West Africa is more effective in decreasing mortality compared to non-specific SAVs or no SAVs. There is no synthesised evidence pertaining to envenomation due to other snake species specifically.

Overall completeness and applicability of evidence

All except one SR were rated to have critically low-quality using AMSTAR-2 –this is a major cause of concern for evidence synthesis for snakebite. The only high quality review was an empty review [23], implying high confidence that there is no evidence for effectiveness and safety of SAV for neuromuscular paralysis. Key critical issues in the included SRs were lack of prior registration and/or publication of protocol, non-provision of list of excluded studies at full-text level, and non-usage of appropriate risk of bias tools and/or its usage to interpret results and discussion.

Most SRs did not assess the quality of included primary studies. Critical appraisal of included primary studies is a standard component of systematic reviews as it helps assess the

Table 2. Summary of evidence for interventions for management of snakebite from systematic reviews (SR) (Colour code key at bottom).

BROAD DOMAIN	Intervention Versus Comparator (if available)	No. Of Studies	Summary direction of evidence for Primary Outcome	Summary direction of evidence for secondary outcome
FIRST AID	Tourniquet versus No tourniquet/ first aid	7	• Death–no difference • Acute renal failure–no difference • Acute respiratory failure–no difference • Occurrence of hemorrhagic syndrome–no difference • Incidence of multiple organ dysfunction syndrome–no difference	• Duration of hospital stay–heterogeneity in results • Wound related outcomes • Increase in local swelling–**tourniquet not effective** • increased severity of local envenomation–**tourniquet not effective** • Necrosis–no difference • Local Oedema–no difference • Occurrence of death or disability (composite)- no difference
	Incision of the bite wound versus No first aid/incision	2	Occurrence of haemorrhagic syndrome–no difference	• Duration of hospitalisation–**Incision effective** • Increased incidence of local swelling–**Incision not effective** • Incidence of death or disability (composite)–no difference
	Suction of the bite wound versus No first aid/suction	1	No outcome of interest reported	• Duration of hospitalisation–**suction not effective** • Occurrence of death or disability (composite)–**suction not effective**
	Snake stones versus No first aid/ stone stones	2	No outcome of interest reported	• Duration of hospitalisation–**snake stones not effective** • Occurrence of death or disability (composite)–no difference
	Traditional medicines and concoctions versus No first aid/ concoctions	2	No outcome of interest reported	• Duration of hospitalisation–**traditional medicine and concoctions not effective** • Occurrence of death or disability (composite)–**concoctions not effective**
	Pressure immobilisation	7	No outcome of interest reported	No outcome of interest reported
EFFECTIVENESS AND SAFETY OF SAVS (species or genus specific SRs)	Crotalidae polyvalent immune Fab (FabAV) (in children)	10	• Adverse events (acute reactions, serum sickness)–**FabAV effective** • Late coagulopathy–**FabAV effective**	Recurrent local effects (local injury)–**FabAV effective**
	FabAV (in those with severe envenomation)	19	• Persistent severe venom effect (limb swelling, limb pain, soft tissue bleeding, thrombocytopenia, neurotoxicity, or compartment syndrome)–heterogeneity in study results • Systemic bleeding–**FabAV effective** • Recurrent and/or delayed-onset severe defibrination syndrome–**FabAV not effective**	No outcome of interest reported
	FabAV (in those who develop medically significant late bleeding)	19	• Late bleeding–**FabAV lead to low rates of medically significant late bleeding an** • Specific death—**No deaths or permanent sequale due to bleeding in FAbAV treated**	No outcome of interest reported
	Safety of FabAV (in patients of North American crotaline envenomation)	11	• Early hypersensitivity–**FabAV safe** • Serum sickness—**FabAV safe** • Deaths as a result of serum sickness specifically reported- **FabAV safe**	No outcome of interest reported
	Specific SAV (for carpet viper envenoming in West Africa) Versus non-specific or no anti-venoms	22	• Mortality–**Specific SAV effective**	No outcome of interest reported
	Comparison between different types of Anti-European Vipera spp antivenoms	40	• Death—**Zagreb antivenom not effective** in reducing deaths compared to other anti-European *Vipera spp*• Adverse reactions—**ViperaTAb, Zagreb, and ViperFAV had less** adverse reactions compared to Biomed, Bulbio and Viekvin antivenom.	Duration of hospitalisation—**ViperFAV or ViperaTAb antivenoms more effective** compared to Bulbio or Zagreb antivenoms.

(*Continued*)

Table 2. (Continued)

BROAD DOMAIN	Intervention Versus Comparator (if available)	No. Of Studies	Summary direction of evidence for Primary Outcome	Summary direction of evidence for secondary outcome
EFFECTIVENESS AND SAFETY OF SAVS (broad non -species/genus specific SRs)	SAVs (for managing venom induced consumption coagulopathy)	0	No Evidence Found	No Evidence found
	Comparisons between various types of SAVs available in sub-Saharan Africa	26	• Mortality–**EchiTabPlus or EchiTabG, Inoserp-Pan African (Inosan), SAIMR Echis ocellatus effective** in reducing mortality. Heterogeneity in results on Fav-Afrique aka FAV-A administration. Antivipmyn-Africa antivenom, ASNA antivenom and Vascera POLY ineffective in reducing mortality. • Blood coagulopathy—**ET-Plus effective** in restoring blood coagulopathy compared to ET- G. **Inoserp-Pan African (Inosan) effective while ASNA antivenom–C ineffective** in restoring blood coagulopathy • Adverse events—**ET-Plus a little less safe** than an initial dose of one vial of EchiTabG. **Inoserp-Pan African (Inosan) effective** in reducing adverse events. Rate of adverse events high in SAIMR Polyvalent. Lower rate of adverse reactions was reported by Antivipmyn-Africa antivenom in comparison to SAIMR Echis. The rate of severe adverse events appeared to be high in ASNA antivenom–C. • Haematological abnormalities–**SAIMR-Echis more effective than SAIME Behringwerke antivenom** for reversing haematological abnormalities • Neurotoxicity—Antivipmyn-Africa antivenom showed poor results	No outcome of interest reported
	High dose of SAV versus Low dose of SAV	20	• Mortality–no difference • Neurological complications–no difference • Acute renal failure–no difference • Bleeding or disseminate intravascular coagulation–no difference • Adverse reactions (itching, urticaria, and erythema)–**low dose effective**	• Duration of hospitalisation–heterogeneity of results • Cost-effectiveness–**Low dose more cost effective**
INTERVENTIONS TO PREVENT ADVERSE REACTIONS DUE TO SAV THERAPY	Prophylactic pre-medication Versus No pre-medication	10	Early adverse reactions–**pre-medication effective** (high heterogeneity in implying effects of different pre-medications)	No outcome of interest reported
	Prophylactic Adrenaline versus Placebo/no premedication	4	Early adverse reactions–**Adrenaline effective in prevention**	No outcome of interest reported
	Prophylactic hydrocortisone versus Placebo	1	• Early adverse reactions–no difference	No outcome of interest reported
	Prophylactic promethazine versus No premedication	1	• Early adverse reactions including anaphylaxis–no difference	No outcome of interest reported
	Prophylactic Steroid along with Anti-histamine versus Only Anti-histamine (different types)	5	• Early adverse reactions–no difference	No outcome of interest reported
OTHER INTERVENTIONS	Early excision of tissue near bite (in Crotaline spp. envenomation)	19	No outcome of interest reported	• Worse tissue outcomes—Early excision along with tourniquet and ice-water immersion but not with SAV being administered **not effective**
	Prophylactic fasciotomy (in Crotaline spp envenomation) Versus standard care alone (including antivenom)	3	No outcome of interest reported	• Outcomes related to "scarring and wound-healing" and "elevated compartment pressure"—**Prophylactic fasciotomy not effective**
	Therapeutic Fasciotomy (in Crotaline spp envenomation)	NR	• No outcome of interest reported	No outcome of interest reported

Colour coding based on AMSTAR-2 appraisal–Peach: Critically Low confidence in evidence from SR. Green: High confidence in evidence from SR

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quality of evidence. It enables decision makers to understand the level of confidence one might have in the results of the primary study. Even reviews which used risk of bias tools for critical appraisal of tools did not appropriately report the use of the tools, and the use of risk of bias/

GRADE for drawing conclusions were not appropriate. Potet et al. [22] had planned to use the Newcastle Ottawa Scale to assess quality but abandoned their plan citing that the tool was "not well adapted to the overall very low quality of selected studies" and instead used a study-design based criterion. The Newcastle Ottawa Scale is, in fact, designed to assess quality of non-randomised studies. Several design aspects, beyond study design such as validity of measurements and blinding of outcome assessments, the quality of the conduct of the study (e.g. loss to follow up and success of blinding), absolute and relative size of any effects seen etc. are known to affect the quality of evidence. [36] This means that conclusions drawn from the SRs in terms of some products have "been tested in robust clinical studies and found effective"[22] needs to be cautiously interpreted. Application of risk of bias tool was also inappropriate in Das et al. [20] This review reported quality or risk of bias as "moderate degree as most were open label trials" by using the Cochrane Risk of Bias tool–without providing any further information. The Cochrane tool assessed a trial with ratings for low risk, high risk or uncertain risk for each of the six separate domains without a composite degree of bias being evaluated for individual RCTs. [37] Where quality of reported studies was mentioned, certainty of the effect estimates for different interventions included in the SRs varied but were almost never of high quality. Accounting for the impact of risk of bias of included primary studies in the results of the synthesis and accounting for it while interpreting the results of the SR would enable more informed decision in the future.

The current study also highlights two important aspects with respect to the completeness of the available evidence at the systematic review–there are many important interventions and outcomes on snakebite management on which SRs have not been conducted, and, for when they have been done, apart from quality of SR, there is need to update them. A full discussion on these aspects comprehensively is beyond the scope of the current study and the need for future work to guide this has been discussed subsequently. Broadly, some domains on which primary research evidence exists but no SR available or there is need for update available ones are—wound management, managing psychological impacts, role of antibiotics, interventions for preventing adverse reaction due to SAV and effectiveness of SAVs. [38–43]

Potential biases in the overview process

The overview includes SRs irrespective of study design, recognising the fact that randomised evidence for snakebite envenoming might be difficult to generate. We used a comprehensive search strategy that was implemented in multiple electronic databases. Screening, data extraction and quality assessment using AMSTAR-2 was done by at least two study authors independently with discrepancy being resolved by consensus. As such, high rigor has been maintained in the overview process. The only limitation of our overview is that its broad scope has meant that we had to depend on the findings of SRs on varied topics without any consistent methods of reporting.

Implications for practice, policy and research

With the development of WHO strategy and the goal to reduce death and disability due to snakebite envenomation to half by 2030, accentuated attention. [8] In our previous work, we evaluated WHO guidelines on snakebite envenomation and found limited use of available evidence in formulating recommendations and heavy reliance on expert opinion. [9] The current work highlights the challenges in formulating high quality evidence informed guidelines owing to the lack of high quality SRs. As such, the lack of high-quality SRs on snakebite is a critical gap which needs attention from global health funders. High-quality SRs and other evidence synthesis which can aid clinical and public health decision making and appropriate

Box 1: Key considerations for practice, policy and research

- High quality systematic reviews to inform clinical practice guidelines do not exist. There is no strong evidence to either support or refute many interventions related to snakebite envenomation.
- Investments in "research on research" and evidence synthesis including conduct of high-quality systematic review, development of intervention evidence gap map, and development of core outcome sets on snakebite envenomation might help inform research policy and practice better.
- Systematic reviews on snakebite envenomation should follow high quality standards to enable critical assessment of existing evidence base for development of clinical practice guidelines.
- Systematic reviews on snakebite should extract snake-species specific data whenever reported. Even if species disaggregated outcome data is not reported in the primary studies, sub-group analysis might provide potentially useful information.
- Randomised controlled trials, providing evidence on effectiveness and safety of different snake anti-venoms specific in different geographic settings and for specific snake-species is a gap that needs to be addressed. Such trials should minimally use core-outcome sets to enable wider utility.
- Funding high quality randomised controlled trials addressing existing clinical issues on first-aid, different snake anti-venoms, preventing adverse drug reactions, and wound management for snakebite envenomation is a priority area that needs to be addressed.

investments can guide future primary research too. Given the paucity in primary research evidence, conduct of RCTs and its resourcing is also needed. Developing an evidence gap map of RCTs for snakebite envenomation might be the first step towards this purpose to enable set research priorities. Our overview also indicated the lack of consistency in defining and measuring outcomes for snakebite envenoming. Standardisation on what outcomes are measured and how they are measured will enable comparison between different interventions and ensure relevance for different stakeholders including patients. There is a tremendous need for development of a core outcome set [44] for clinical studies on snakebite. The variation in species distribution as well as intra-species variation in venom composition implies the need for conduct of region, nation or state (sub-national) specific RCTs and SRs on different SAVs and their dosing regimens. The results of this overview can inform priorities for funding and conduct of high-quality SRs and other evidence synthesis on management of snakebite envenomation. Key considerations for practice, policy and research and policy is summarised in **Box 1**.

Conclusion

Ensuring safe, effective treatments which can bring down the burden of snakebite requires conduct of high-quality SRs. The lack of high-quality SRs hampers guideline development as well as informing priorities for primary research on snakebite.

Supporting information

S1 Table. PRISMA Checklist for Interventions for the management of snakebite envenoming: an overview of systematic reviews.
(DOC)

S2 Table. Reasons for exclusion in full-text phase for Interventions for the management of snakebite envenoming: an overview of systematic reviews.
(DOCX)

S1 Text. Search Strategies for Interventions for the management of snakebite envenoming: an overview of systematic reviews.
(DOCX)

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8. Development of a core outcome set for intervention research on snakebite treatments in South Asia

8.1. Chapter overview

In this chapter, I present the development of core outcome set (COS) for intervention research on snakebite envenomation in South Asia (Bangladesh, Bhutan, India, Nepal, Pakistan, and Sri Lanka). The COS is for research on interventions that:

1. prevent adverse reaction to snake anti-venom,
2. are for management of the bitten part,
3. are specific to management of neurotoxic manifestations,
4. are specific to management of the haematological manifestations,
5. act against the snake venom

The chapter contributes to the goal for fostering research on safe and effective treatments for snakebite envenomation in South Asia, by making a minimal list of outcomes, which would be measured in future intervention research in the region with highest burden of snakebite. The COS development process involved three phases:

- Phase 1: systematic review of outcomes, to acquire the long list of outcomes for Phase 2.
- Phase 2: two rounds of Delphi survey, followed by a consensus meeting on what outcomes should be part of the COS.
- Phase 3: online consultation and workshop, to reach consensus on how outcomes part of COS, should be measured.

This chapter contains two manuscripts.

1. The first manuscript (Section 8.3), corresponding to Phase 1 of the COS development, is the **published** version of the article in **F1000 Research**:
   - **Bhaumik S**, Beri D, Tyagi J, Clarke M, Sharma SK, Williamson PR, Jagnoor J. Outcomes in intervention research on snakebite envenomation: a systematic review. F1000Res. 2022 Jun 8;11: 628. PMID: 36300033; PMCID: PMC9579743. (Link)

   The publication is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in the thesis.

2. The second manuscript (Section 8.4), corresponding to Phase 2 and Phase 3 of the COS development, has been **submitted** for peer review.
   - **Bhaumik S**. Beri D, Santra V, Gopalakrishnan M, Faiz MA, Williamson PR, et al. Core outcome set for intervention research on snakebite envenomation in South Asia. Under peer-review in PLoS Neglected Tropical Diseases.

8.2. Candidate's contribution to the work

For the manuscript (Section 8.3), corresponding to Phase 1 of the COS development:

I conceptualised and designed the study. I developed and ran the search strategies, screened the studies, extracted the data, conducted formal analysis, validated the data, and wrote the first draft of the manuscript. Co-authors did independent screening and verified data extraction, with disagreements resolved by consensus. I coordinated and incorporated feedback from co-authors to prepare and submit the manuscript to the

journal. I drafted response and amended the manuscript based on the peer-review comments and prepared the final draft which was published.

For the second manuscript (Section 8.4), corresponding to Phase 2 and Phase 3 of the COS development:

I conceptualised and designed the study, including design and testing of the Delphi survey and platform. I recruited panellists for the Delphi Survey, organised meetings, consultations, and workshops, conducted formal analysis, validated the data, and wrote the first draft of the manuscript. I coordinated and incorporated feedback from co-authors to prepare and submit the manuscript to the journal.

8.3. Manuscript: phase 1 for development of core outcome set for snakebite research in South Asia

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RESEARCH ARTICLE

Outcomes in intervention research on snakebite envenomation: a systematic review [version 1; peer review: 2 approved]

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Abstract

Introduction:
A core outcome set (COS) is a minimal list of consensus outcomes that should be used in all intervention research in a specific domain. COS enhance the ability to undertake meaningful comparisons and to understand the benefits or harms of different treatments. A first step in developing a COS is to identify outcomes that have been used previously. We did this global systematic review to provide the foundation for development of a region-specific COS for snakebite envenomation.

Methods:
We searched 15 electronic databases, eight trial registries, and reference lists of included studies to identify reports of relevant trials, protocols, registry records and systematic reviews. We extracted verbatim data on outcomes, their definitions, measures, and time-points. Outcomes were classified as per an existing outcome taxonomy, and we identified unique outcomes based on similarities in the definition and measurement of the verbatim outcomes.

Results:
We included 107 records for 97 studies which met our inclusion criteria. These reported 538 outcomes, with a wide variety of outcome measures, definitions, and time points for measurement. We consolidated these into 88 unique outcomes, which we classified into core areas of mortality (1, 1.14 %), life impact (6, 6.82%), resource use (15, 17.05%), adverse events (7, 7.95%), physiological/clinical (51, 57.95%), and composite (8, 9.09%) outcomes. The types of outcomes

Open Peer Review

Approval Status ✓ ✓

	1	2
version 1 08 Jun 2022	✓ view	✓ view

1. **Harry Williams**, Toxiven Biotech Private Limited, Coimbatore, India

2. **Julien Potet**, Médecins Sans Frontières, Paris, France

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

varied by the type of intervention, and by geographic region. Only 15 of the 97 trials (17.04%) listed Patient Related Outcome Measures (PROMS).

Conclusion:

Trials evaluating interventions for snakebite demonstrate heterogeneity on outcomes and often omit important information related to outcome measurement (definitions, instruments, and time points). Developing high quality, region-specific COS for snakebite could inform the design of future trials and improve outcome reporting. Measurement of PROMS, resource use and life impact outcomes in trials on snakebite remains a gap.

Keywords

Snakebite, Systematic Review, Clinical Trials, Outcome Assessment, Treatment Outcome, Patient Reported Outcome Measures

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This article is included in the Neglected Tropical Diseases collection.

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Background

Snakebite is a major public health problem in South Asia, Africa, and South America with an estimated 5.4 million people being bitten by snakes annually. It is estimated that snakebite causes up to 138,000 deaths worldwide each year, with three times as many people experiencing permanent disabilities.[1] In 2017, the World Health Organization (WHO) classified snakebite envenoming as a neglected tropical disease and this was followed by the launch of the WHO global strategy to reduce the mortality and morbidity by 50% by 2030.[2] One of the four key pillars of this strategy is to "ensure safe, effective treatment of snakebite".[2] However, clinical practice guidelines, including those from the WHO, have been found to have quality issues, including in the use of evidence to inform recommendations for snakebite management.[3] These issues in guidelines is linked to the poor evidence base for interventions for snakebite management. We had previously found that systematic reviews on snakebite were of critically low quality.[4] Investment in treatments for snakebite, including in the identification of new therapies, has increased in recent years, and this trend is expected to continue.[5] Our earlier overview of systematic reviews on snakebite management has also highlighted the limitation of non-standardised measurement and reporting of outcomes.[4] This non standardisation of outcomes limits the ability of researchers, healthcare providers, decision makers, and patients to undertake meaningful comparisons and understand the potential benefits or harms of different treatment modalities.[6,7] Thus, there is an identified need for a core outcome set (COS)[8] for intervention research on snakebite management including trials and systematic reviews. A COS is a minimal list of consensus outcomes that should be used in all clinical trials and evidence synthesis in a specific area or setting of health or health care.

The objective of this study is to identify what outcomes have been used in intervention research on snakebite through a global systematic review of outcomes. This conduct of a robust and comprehensive systematic review of outcomes is an essential first step in the development of a COS.[8]

Methods

Protocol, registration, and reporting

This systematic review is a part of a larger project to develop a COS for intervention research on snakebite in South Asia. The protocol for the entire project, including the current systematic review was registered *a priori* (https://doi.org/10.17605/OSF.IO/PEKSJ). The COS development was registered *a priori* in the COMET database (https://cometinitiative.org/Studies/Details/1849). A summary of the methods for this systematic review is provided below.

The PRISMA checklist for this report of the review is available in **Extended Dataset: Appendix 1.**[9]

Eligibility criteria

We included studies which met the following criteria:

- **Health condition/Population**: people with snakebite, irrespective of their sex/gender, species of snake, region, or any other factor.
- **Intervention**: any intervention regarding management of snakebite.
- **Comparators**: an active comparator or control group.
- **Outcomes**: the outcomes measured and reported, given the objective of identifying the full range of all outcomes.
- **Study Design**: we included studies with the following designs:
    - Randomised trials.
    - Non-randomised controlled trials.
    - Secondary analysis of randomised or non-randomised controlled trials.
    - Systematic reviews that included randomised or non-randomised controlled trials.

We excluded systematic reviews which solely included non-trial designs. Protocols and trial registry records pertaining to the above were also included.

- **Other criteria**: there were no limits based on date of publication.

Search strategy

We searched 15 electronic databases (PubMed, EMBASE, CINAHL, Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effects, Cochrane Clinical Answers, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Health Technology Assessment, NHS Economic Evaluation Database, Campbell Library, Epistemonikos, Scielo and Open dissertations) on 29th October 2021, with no language restrictions. The search strategies for all databases are presented in **Extended Dataset: Appendix 2.**[9]

We hand-searched nine trial registries (Australia New Zealand Trial Clinical Registry, Brazilian Clinical Trials Registry, Clinical Trial Registry of India, US trial registry (clinicaltrials.gov), Iranian Registry of Clinical Trials, Thai Clinical Trials Registry, Peruvian Clinical Trial Registry, Sri Lanka Clinical Trials Registry, and WHO International Clinical Trial Registry Platform) in November 2021. We also screened the reference lists of included studies and contacted snakebite experts to identify additional eligible studies.

Selection of articles

At least two reviewers (SB and DB or JT) independently screened the records retrieved based on titles and abstracts (where available) in the first phase and subsequently screened the full texts of potentially eligible studies. Disagreements, if any, were resolved by consensus between three reviewers (SB, DB, and JT).

Data collection and management

We extracted data using a standardised data extraction form in REDCap (a secure web application for building and managing online surveys and databases) containing key information pertaining to participant details (number and demographics: age, sex/gender, country and time period of the study), details on the bite (species information), study design, intervention and comparator group, reported outcomes (together with their definitions, measurement instruments and timepoints). The outcomes from trials were supplemented by additional outcomes from systematic reviews. All details pertaining to outcomes were extracted verbatim as recommended by the COMET Handbook.[8]

Data synthesis

We analysed the verbatim information pertaining to reported outcomes. If we found multiple reports for the same study, we included these, but outcomes duplicated across these reports were only counted once. Outcomes which were not reported in the included trials, but which were defined or searched for in systematic reviews were also extracted verbatim. We classified the verbatim outcomes as per a taxonomy structure for outcomes in medical research[10] which has been validated for various health conditions. As such, we mapped outcomes areas (mortality, physiological or clinical, life impact, resource use and adverse events) and sub-domains within these. We had an additional domain for composite outcomes, recognising that their individual elements might not be categorised as "unique" under the other domains so that information on composite outcomes could be used in the next steps in the COS development. We consolidated the outcomes based on similarity of outcome measures and definitions to create a set of the unique outcomes that had been used in intervention studies on snakebite envenomation. We summarized the results using frequencies and percentages for these unique outcomes.

Variation from published protocol

Our protocol envisaged inclusion of studies published from 1990 onwards. However, we searched for studies irrespective of date of publication and removed this time limit. We also searched electronic databases and trial registries that were not listed in our protocol to enhance comprehensiveness. On a post-hoc basis, we included secondary analysis of trials because some outcomes are not reported as a part of the main publication of a trial. This inclusive approach helped capture maximal evidence. We did not separate outcomes by different age-groups and special populations as originally planned because of the lack of studies. The decision to retain composite outcomes was post-hoc.

Ethical approval

No ethical approval is required for this study because it is a systematic review of existing studies and does not include any human or animal participants.

Results

Study selection

We found 3277 records in our search in electronic databases, 69 in trial registries and another two records through hand-searching relevant websites. After removing duplicates, obtaining, and evaluating full texts, 107 records from 97 studies met our eligibility criteria and are included in this review. A detailed PRISMA flowchart showing the inclusion of studies is presented in Figure 1.

Reasons for exclusion of records that were assessed at the full text level are shown in **Extended Dataset: Appendix 3.**[9]

Characteristic of included studies

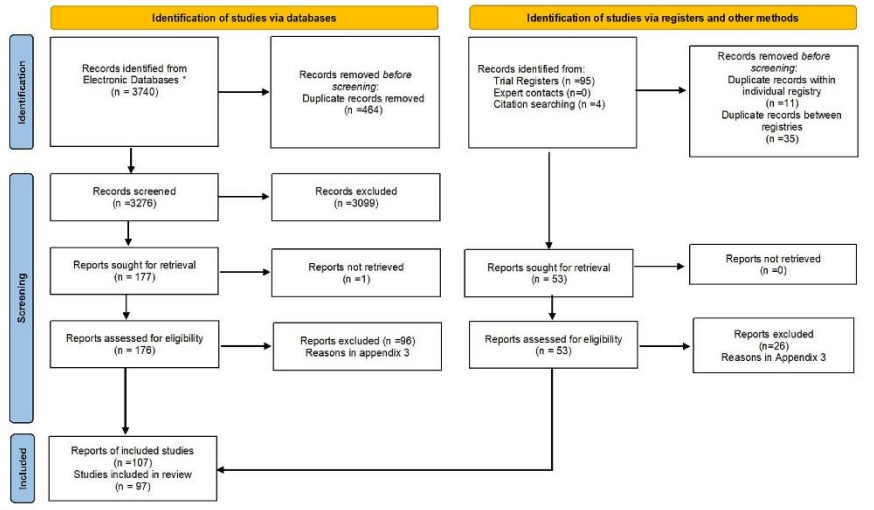
We included nine systematic reviews,[4,11–18] and 88 trials and registry records. Out of the 88 trials and registry records, 84 are randomised trials,[19–98] and 4 are non-randomised controlled trials.[99–102] We found 10 post-hoc or secondary analysis of trials.[103–112] Out of the 84 randomised trials, there was one adaptive,[68] one factorial[67] and one cross-over trial.[66]

The sample size ranged from eight to 1007 participants. Among the included trials, (26, 29.50%) were multicentric.[19–23,26–28,34,41,49,50,55,64,66–68,70,74,81,85,89,90,99,113,114] Three (3.41%) trials were exclusively on children.[23,25,76] Most of the studies (72, 81.8%) had only two arms of comparison. In 16 (18.2%) trials[20,27,30,34,38,41,42,60,67,69,71,80–83,115] with more than two comparison arms, the number of arms ranged from three to eight. A total of 49 (55.7%) trials[19–56,77,78,80,82,85,88,93,98,101,102] were restricted to participants with bites of a specific snake species/genus. Most of the trials started recruitment after the year 2000 (58, 65.91%).

A summary of the characteristics of the included studies is presented in Table 1 below.

Synthesis of outcomes

We extracted verbatim data for 538 outcomes and categorised them into the following core areas: death/mortality (26, 4.83%), life impact (19, 3.53%), resource use (96, 17.84%), adverse events (80, 14.87%), physiological/clinical (288, 53.53%), and composite outcome (29, 5.39%). The proportionate frequency of outcomes by domain and sub-domains of physiological/clinical outcomes varied both by the type of intervention being evaluated and by geographic region (**Extended Dataset: appendix 4**[9]). Trials from South Asia seldom measured life impact outcomes (0.47% of trials in contrast to 17.05% of North American trials which reported on life impact outcomes), but they frequently (29.28%)



*Electronic database hits: PubMed- 2115; EMBASE 829; CINAHL 311; Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effects, Cochrane Clinical Answers, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Health Technology Assessment, NHS Economic Evaluation Database -300 ; Campbell Library – 0;Epistemonikos – 44; Scielo (Spanish version) – 141;Open dissertations- 0.

Figure 1. PRISMA flowchart showing selection of studies in the systematic review.

Table 1. Characteristics of included studies.

Study Designs	• Randomised trials: 84 (and 10 post-hoc or secondary analysis from these) • Non-randomised controlled trials: 4 • Systematic reviews: 9		
Sample Size of trials	• Range is 80 to 1007 (median=80) • 0-50 participants: 24 (27.27%) • 51-100 participants: 27 (30.68%) • 101-200 participants: 26 (29.54%) • >200 participants: 11 (12.50%)		
Decadal Periods (based on start year of recruitment)	• ≤1990:14 • 1991-2000: 13 • 2001-2010: 27 • 2011-2020: 27 • ≥2021: 4 • Unclear/not reported: 3		
Number of centres in trials	• Multicentre: 26 (29.5%) • Single centre: 62 (70.5%)		
Snake species in trials	• Restricted to bites of specific snake species/genus: 49 (55.7%) • Not restricted to bites of specific snake species/genus: 39 (44.3%)		
Country of conduct of trials	**Country**	**Number of trials**	**%**
	Australia	2	2.27
	Brazil	9	10.23
	China	4	4.54
	Colombia	6	6.82
	Ecuador	2	2.27
	India	17	19.32
	Iran	2	2.27
	Malaysia	1	1.14
	Mexico	2	2.27
	Myanmar	3	3.41
	Nepal	1	1.14
	Central African Republic	1	1.14
	Nigeria	6	6.82
	Pakistan	1	1.14
	Papua New Guinea	1	1.14
	Philippines	2	2.27
	Sri Lanka	15	17.04
	Thailand	5	5.68
	United States	7	7.95
	Vietnam	1	1.14

reported resource use outcomes. The focus of trials from South America, Southeast Asia and the rest of Asia is overwhelmingly in physiological/clinical outcomes. Blood and lymphatic system outcomes were proportionately much higher in African trials (64.00%) compared to South Asian (35.63%) trials. South Asian trials measured renal outcomes more (in 18.39% trials) compared to trials in other regions. Reporting of respiratory outcomes were uncommon except in Australia and Papua New Guinea (11.11%) trials.

Only 48 trials (54.54%) specifically identified their primary outcomes, out of which 10 (11.37%)[47,60–62,67,77,84,89,97,98] had adverse events or effects as a primary outcome.

We consolidated the verbatim outcomes into 88 unique outcomes which we categorised as: mortality (1, 1.14%), life impact (6, 6.82%), resource use (15, 17.05%), adverse event (7, 7.95%), physiological/clinical (51, 57.95%), and composite (8, 9.09%).

The long list of the unique outcomes with summary information on their measurement and definitions is provided in Table 2 and discussed below.

Death/mortality outcomes

We found one unique outcome (1.14%) for mortality from 26 verbatim outcomes (4.83%) in 26 trials and five systematic reviews. Time points at which death was measured were until discharge from hospital, 28 days from discharge, 60 days from recruitment/intervention and 90 days from bite.

Table 2. List of unique outcomes identified in systematic review and summary information.

Outcome area	Outcome summary
Mortality	Death was measured as all-cause mortality, survival, or cause-specific mortality
Life Impact Outcome	1. Functional life impact: Patient Specific Functional Scale, and the physical function domain of the SF-36 questionnaire 2. Disability: Sheehan Disability Inventory and American Medical Association (AMA) disability rating score. 3. Quality of life: Patient's Global Impression of Change Scale, Clinical Global Impression - Improvement (CGI-I), and Patient-reported outcome measurement information system physical function-10 score (PROMIS PF-10). 4. Time to functional recovery: defined as time to full functional status recovery as measured by the Patient-Specific Functional Scale, or complete resolution of swelling and ability to run and jump (for lower extremity bites) or equal hand-grip (for upper extremity bites). 5. Lower extremity function: Scores on Lower Extremity Functional Scale, and walking speed. 6. Upper extremity function: Scores on the Disorders of the Arm, Shoulder, and Hand (DASH) and grip strength through a dynamometer.
Resource use outcome	**Hospital** 1. Duration of hospital stay: no clear criterion for discharge except in one study. 2. Duration of Intensive Care Unit (ICU) stay: no clear criterion.
	Need for further intervention 1. Requirement of a blood product (unspecified or any). 2. Requirement of FFP (fresh frozen plasma). 3. Requirement of PRBC (packed red blood cell). 4. Requirement of platelets. 5. Requirement of cryoprecipitate. 6. Requirement of mechanical ventilation. 7. Requirement for non-invasive ventilation or reintubation (Post- extubation). 8. Requirement of antibiotic. 9. Requirement of analgesic. 10. Requirement of dialysis/renal replacement therapy. 11. Requirement of antivenom.
	Economic 1. Cost of antivenom (average compared). 2. Any cost-related outcome.
Adverse event/ effect	1. Adverse event unclassified: proportion and time from antivenom infusion to reaction with or without classification of severity or frequency/proportion of treatment emergent adverse event. 2. Anaphylaxis: incidence and time from antivenom infusion to anaphylaxis with or without classification (Brown 2004 criterion) of severity. 3. Anaphylactoid syndrome: incidence of anaphylactoid syndrome, pyrogenic reaction alone and urticaria alone. 4. Early antivenom reaction (EAR): incidence and time from antivenom infusion to EAR. 5. Late antivenom reaction: incidence. 6. Adverse events specific to FFP: incidence. 7. Capillary leak syndrome: incidence.

Table 2. *Continued*

Outcome area	Outcome summary
Physiological/ Clinical	**Eye** 1. Conjunctival oedema.
	Cardiac 1. Cardiac rhythm abnormalities. 2. Hypotension. 3. Shock.
	Psychiatric 1. Anxiety: Hopkins somatic symptoms checklist. 2. Depression: modified Sinhala version of the Beck depression inventory. 3. Post-Traumatic Stress Disorder: Post-traumatic Stress Symptom Scale-Self Report Scale. 4. Suicidal ideation and behaviour: Columbia-Suicide Severity Rating.
	Respiratory, thoracic and mediastinal 1. Respiratory distress: measured as airway obstruction, respiratory failure, and acute respiratory distress syndrome; no specific definition reported. 2. Negative inspiratory pressure: standard methods. 3. Forced vital capacity: standard methods.
	Neurological 1. Paralysis: proportion or duration; assessed clinically, no clear definition. 2. Ophthalmoplegia/Ptosis: days for resolution of ptosis/ophthalmoplegia, endurance of upward gaze, and proportion of the iris uncovered. 3. Anosmia: as reported by patient. 4. Motor strength: no clear definition. 5. Neurotoxicity overall: incidence/frequency and time to complete resolution of all neuroparalytic features.
	Injury/Poisoning 1. Venom concentration: standard methods. 2. Anti-venom concentration: standard methods. 3. Varisyllabic-methyl levels: standard methods.
	Immunological 1. Immunogenicity profile: standard methods. 2. profile of antibodies: standard methods. 3. COVIP-Plus induced sera: standard methods.
	General 1. Pain: intensity measured by Visual Analogue Scale, time for complete resolution of the local pain with or without induration. 2. Non-specific systemic symptoms: no definition provided.
	Musculoskeletal 1. Myotoxicity as an outcome was measured clinically, levels of creatine kinase, and levels of lactate dehydrogenase, creatine phosphokinase, metalloproteinases.
	Skin and subcutaneous 1. Necrosis: assessed clinically, no clear definition. 2. Blistering: assessed clinically, no clear definition. 3. Oedema: measured as circumference difference between the affected limb and the normal limb; circumference measurements of the affected limb alone; remission time of limb swelling; cessation of local swelling progression; time to swelling resolution; oedema progression; measurement of decrease of oedema-scaled dish. 4. Swelling: measured based on the number of segments affected (extent) and increase in circumference of the bitten limb (intensity); proximal length of swelling from bite site; criteria developed by Warell et al 1977; criteria based on physical appearance of swelling; swelling is confirmed to bitten segment or crosses 1 or 2 joints; and % increase in volume compared to contralateral (non-envenomated) limb. 5. Wound cosmesis: measured by any validated cosmesis score. 6. Any other wound related outcome, including but not limited to cosmesis.
	Infection, Infestation, and Inflammation 1. Abscess. 2. Blister. 3. Cellulitis. 4. Inflammatory markers. 5. Pneumonia. 6. Ventilator associated pneumonia. 7. Wound infection.

Table 2. *Continued*

Outcome area	Outcome summary
	Kidney and Urinary Outcomes 1. Blood urea nitrogen (BUN) and creatinine levels measures in serum. 2. Acute Kidney Injury defined as per Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) Criteria, Kidney Disease Improving Global Outcomes (KDIGO) Criteria, measurement of surrogate markers (Neutrophil gelatinase-associated lipocalin, beta2-microglobulin, Kidney Injury Molecule-1, serum creatinine), estimated glomerular filtration rate and oliguria. 3. Abnormalities in urine: proteinuria or haematuria. 4. Chronic kidney disease: no definition provided. 5. Renal angle tenderness: no definition provided. 6. Ferryl-haem derivatives: detected in urine sample. **Blood and lymphatic system** 1. Blood coagulability -by 20 min whole blood clotting test (WBCT20)/Lee -White method, or standard laboratory measures of international normalized ratio (INR), bleeding time (BT), clotting time (CT), Prothrombin Time (PT), aPTT (activated partial thromboplastin time). 2. Platelet count- standard laboratory measures. 3. Clotting Factors- Clotting factor panel or specific factors like fibrinogen, Factor V, VII, VIII, Fibrinogen degradation products/D-dimer. 4. Bleeding – defined clinically using various criterion. 5. Clot Quality- measures as per a method developed by Reid 6. Other Haematological parameters – complete blood count, packed cell volume. 7. Lymphadenopathy/lymphadenitis – no clear clinical criteria provided.
Composite Outcome	1. Clinical recovery as a composite outcome: seven unique definitions were used. 2. Complications as a composite outcome: four different definitions were used or not clearly reported. 3. Envenoming manifestations: measured compositely as improvement in signs and symptoms of envenoming (systematic alone or together with local). 4. Snakebite Severity Score (SSS): either the complete SSS or the pulmonary, cardiovascular, hematologic symptoms, and nervous system sub scores of the SSS, and as defined in the US FDA-approved information for Crotaline Polyvalent Immune Fab antivenom (FabAV) prescription. 5. Haemolysis: measured using haemolysis markers (visual haemolysis score level and abnormal lactate dehydrogenase - LDH levels). 6. Local Inflammation: Reduction in local inflammatory manifestations such as pain, oedema, and temperature (flushing). 7. Prognosis: no clear definition. 8. Treatment failure: measured as a composite outcome based on clinical features.

More detailed information tabulating this unique outcome, together with measures, definitions and time-points, is reported in **Extended Dataset: Appendix 5**.[9]

Life impact outcomes

We found six unique outcomes (6.82%) from 19(3.53%) verbatim outcomes from six trials and one systematic review. No trials or systematic reviews measured any life impact outcome related to social functioning, emotional functioning/well-being, cognitive functioning, perceived health status, compliance (including withdrawal from treatment), delivery of care or personal circumstances.

A clear definition with clear details on the outcome measurement instruments used was provided for all but one verbatim life impact outcome. Disability outcomes were measured long term (six months from discharge and 12 months from intervention). Serial measurement from baseline through 28 days (from bite) was common. More detailed information about these unique outcomes, together with their measures, definitions and time-points for measurements is provided in **Extended Dataset: Appendix 5**.[9]

Resource use outcomes

We found 15 unique (17.05%) resource use outcomes from 96 verbatim (17.84%) outcomes: two (2.27%) hospital use outcomes from 30 verbatim (5.58%) outcomes in 25 trials; 11 (12.5%) outcomes related to the need for further intervention from 65 verbatim (12.08%) outcomes in 25 trials, and two (2.27%) economic outcomes from two verbatim

outcomes (0.37%) from one trial and one systematic review. No trials or systematic reviews reported on outcomes of societal or carer economic burden.

For almost all the resource use outcomes, the specific clinical criterion associated with the outcome was not reported. For example, none of the outcomes relating to the need for further intervention reported the specific clinical criteria that would lead to further intervention. More detailed information about these unique outcomes together with their measures, definitions and time-points for measurement is provided in **Extended Dataset: Appendix 5**.[9]

Adverse effect/events outcomes

Our synthesis led to seven (7.95%) unique adverse event outcomes from a total of 80 (14.87%) verbatim outcomes from 52 trials and six systematic reviews. There was substantial heterogeneity in the definitions used for these outcomes. Adverse effects and events were almost always measured in the acute setting with no long-term measurement of these outcomes. More detailed information about these unique outcomes together with their measures, definitions and time-points for measurement is provided in **Extended Dataset: Appendix 6**.[9]

Physiological or clinical outcomes

The 288 (53.53%) verbatim physiological/clinical outcomes from trials were consolidated into 51(57.95%) unique physiological/clinical outcomes and were classified as per the taxonomy into the following:

- **Eye**: one unique (1.14%) outcome from one (0.19%) verbatim outcome from one trial. Outcomes were assessed clinically with no clear criteria reported in the trials.

- **Cardiac**: three (3.41%) unique outcomes from seven (1.30%) verbatim outcomes from six trials. Outcomes were assessed clinically with no clear criteria reported in the trials.

- **Psychiatric**: four (4.55%) unique outcomes from four (0.74%) verbatim outcomes from two trials and one systematic review. psychiatric outcomes were measured with validated instruments and had good reporting of time points.

- **Respiratory, thoracic, and mediastinal**: three (3.41%) unique outcomes from four (0.74%) verbatim outcomes from three trials. Two of the outcomes are related to standard spirometry tests while the other was assessed clinically with no clear definition provided.

- **Nervous system:** five (5.68%) unique outcomes from 16(2.97%) verbatim outcomes from 13 trials and one systematic review. Many of the outcomes were measured clinically with no specific criteria mentioned.

- **Injury and poisoning outcomes**: three (3.41%) unique outcomes from 28(5.20%) verbatim outcomes from 20 trials. All the outcomes were laboratory measured.

- **Immune system**: three (3.41%) unique outcomes from three verbatim outcomes from one trial. All were laboratory measures.

- **General:** two (2.27%) unique outcomes from 16 (2.97%) verbatim outcomes from 14 trials. A standardised tool was used for one outcome and a clear definition was not provided for the other. Time points were not clear for both.

- **Musculoskeletal and connective tissue**: one (1.14%) unique outcome from eight (1.49%) verbatim outcomes from seven trials. Clear definitions were provided for the outcome measures and pertained to use of standard laboratory tests.

- **Skin and subcutaneous tissue outcomes**: six (6.82%) unique outcomes from 41 (7.62%) verbatim outcomes from 29 trials and one systematic review. Outcomes were assessed clinically with no clear criteria or time points reported for many outcome measures.

- **Renal and urinary:** six (6.82%) unique outcomes from 26(4.83%) verbatim outcomes from 14 trials and one systematic review. Outcome definitions were clearly reported (except for one outcome) and validated criteria or standard laboratory methods were used.

- **Infection, infestation, and inflammation**: seven (7.95%) unique outcomes from 21(3.90%) verbatim outcomes from 15 trials and 1 systematic review. There was substantial heterogeneity in outcome measures and definition with reporting being poor when clinical assessment was the basis of outcome measurement.

- **Blood and lymphatic system:** seven (7.95%) unique outcomes from 122(22.68%) verbatim outcomes from 49 trials and five systematic reviews. Laboratory tests were the basis of six of these outcomes with clinical assessment being the basis of outcome measurement in the other three.

No trial or systematic review measured endocrine outcomes, ear and labyrinth outcomes, gastrointestinal outcomes, hepatobiliary outcomes, puerperium, and perinatal outcomes, or vascular outcomes. We considered the following taxonomy sub-categories to be not relevant to the snakebite: familial, and genetic outcomes, metabolism and nutrition outcomes, outcomes relating to neoplasms: benign, malignant, and unspecified (including cysts and polyps), reproductive system and breast outcomes.

In general, reporting of time points was poor in many trials. More detailed information about these unique outcomes together with their measures, definitions and time-points for measurement is provided in **Extended Dataset: Appendix 7**.[9]

Composite outcomes

Our synthesis led to eight (9.09%) unique composite outcomes from 29(5.39%) verbatim outcomes from 21 trials and one verbatim outcome from two systematic reviews. There was substantial heterogeneity in outcome definitions as well as in the time points for measurement.

More detailed information on these unique outcomes together with measures, definitions and time-points for measurement is provided in **Extended Dataset: Appendix 8**.[9]

Patient reported outcome measures

Only 15 trials[22,66,78,82,88,90,116] included Patient Reported Outcome Measures (PROMs). The PROMs used in snakebite trials (with related citations on the measurement tools, where relevant) is presented in Table 3.

Table 3. Patient Reported Outcome Measures Reported in Snakebite Trials*.

- Pain related
  - Visual Analog Scale[128]
  - Numeric Pain Rating Scale[128]
- Physical Function/disability related
  - Patient Specific Functional Scale[110,129]
  - Physical function domain of the SF-36 questionnaire[130]
  - Sheehan Disability Inventory[131,132]
  - American Medical Association disability rating score[133]
  - Patient's Global Impression of Change Scale[134]
  - Patient-reported outcome measurement information system physical function-10[135]
  - Lower Extremity Functional Scale[136]
  - Disorders of the Arm, Shoulder, and Hand[137]
  - Anosmia-as reported by patient
- Mental Health related
  - Hopkins somatic symptoms checklist[131,138]
  - Beck depression inventory[131,139](modified Sinhala version)
  - Post-traumatic Stress Symptom Scale-Self Report Scale[131,140]
  - Columbia-Suicide Severity Rating[141]

*Details on PROMS is within different Extended Dataset appendices.

Discussion

This systematic review of outcomes captured a total of 538 verbatim outcomes, which were consolidated into 88 unique outcomes, which had a wide variety of measures, definitions, and time points for their measurement. Outcome definitions and time points were infrequently or poorly reported. Outcomes related to resource use and life impact were included in few trials, with no trials using outcome related, societal or carer burden, social functioning, emotional functioning or well-being, cognitive functioning, perceived health status, compliance, and delivery of care or personal circumstances. The only trial which captured economic outcomes reported the average cost of antivenom without any comprehensive calculation of other direct or indirect costs. No trials had outcomes related to pregnancy. We also found that the primary outcome was explicitly stated in only a few of the trials. Outcome types (by the taxonomy domains) varied for both different geographic regions and different types of intervention being evaluated.

Heterogeneity in outcomes, their measures, definitions, and time points prevents comparison of effectiveness data, thus limiting the usefulness of trials and reviews to clinical practice.[8] The major reason for evidence synthesis specialists not being able to conduct meta-analyses is heterogeneity in the ways in which outcomes are reported and measured.[8,117] This systematic review has shown that this is likely to be a major problem for snakebite research. Therefore, if high-quality trials are to be done to develop a robust evidence base for the management of snakebite,[4] this needs to be preceded by the development of COS for use in intervention research.

The variation in outcomes (by taxonomically domains) across geographic regions and types of intervention indicates the need for development of COS with a focus on specific regions. This is to be expected because the clinical features of envenomation and the consequent choice of type of intervention largely depends on the type of snake and this largely depends on the geographic region. As such, this review has confirmed the appropriateness of our intention to develop a COS with a specific South Asia focus. This is also in keeping with the WHO's work to develop targeted therapeutic profiles for snakebite envenomation therapies on a geographic region basis.[118] The scarce use of PROMs, resource use and life impact outcomes in snakebite research to date is a gap that needs to be filled. These outcomes have high relevance for, for example, patients, clinicians, and hospital administrators. Our systematic review identified several outcome measurements instruments, but their measurement properties (structural validity, internal consistency, cross-cultural validity, and reliability) and the feasibility of using them is unknown. We will address this in future steps of our COS development, which will not only involve public health professionals, social workers, health economists, but also patients and caregivers of people with snakebite. This would enhance the clinical and public health relevance of the COS. To achieve this, the inventory of outcomes from this systematic review will be supplemented by additional outcomes identified by stakeholders participating in the consensus development process in the next steps of COS development.[8]

There is also a need for better reporting of outcome definitions (including outcome measurement instruments) and time points of measurement in clinical trials for snakebite. While the uptake of COS in future trials[119] will address this issue to some extent, there is also a need for funders, trialists, and journal editors to take this into account through the lifecycle of a trial, from its design stage to publication. The lack of specific mention of primary outcomes also needs to be addressed.[120] Trialists should also ensure that their outcome measurement instruments are valid for their own setting or use ones which are validated in their geographic region, such that their cross-cultural validity and feasibility is enhanced.[121] Improvements in trial outcome transparency and reporting should also arise from the forthcoming Outcome extensions for the Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) and CONsolidated Standards of Reporting Trials (CONSORT) statements.[122] Beyond improvements in how outcomes are used in trials, there is also a need to conduct more trials in children, since we identified only three trials exclusively on children.

Strengths of this review include that we searched 15 electronic databases and eight trial registries to comprehensively capture outcomes from as many studies as possible, not only including those trials which have completed but also including trials that are not published, not completed, or were terminated early. We have used standard evidence synthesis methods to maintain quality and used a validated taxonomy to classify outcomes. In keeping with guidance on the use of the taxonomy, this standardised outcome classification system allowed us to remove "inconsistencies due to ambiguity and variation in how outcomes are described across different studies".[10] We acknowledge the limitation that, although we were able to successfully manage records in English and Spanish, we were unable to extract information from five records[123–127] that were available in Portuguese and Chinese.

Conclusion

We have shown that trials evaluating therapies for snakebite envenoming have heterogeneity of outcomes and often omitted key information related to their measurement. Developing high quality region-specific COS for snakebite would facilitate improvements in the design and reporting of future trials and thereby strengthen their ability to have a positive impact on policy, practice, patient care and overall health. Particular attention also needs to be paid to improve the reporting of outcomes, and to include PROMs, resource use and life impact outcomes in trials on snakebite.

Data availability

Underlying data

Figshare. Outcomes in intervention research on snakebite envenomation: a systematic review. DOI: https://doi.org/10.6084/m9.figshare.19777921.v1

This project contains the following underlying data in the extended dataset:

- Data file Appendix 1. PRISMA checklist
- Data file Appendix 2. Search strategies of all databases
- Data file Appendix 3. Reasons for exclusion at full text level
- Data file Appendix 4. Outcome core categories by region and intervention
- Data file Appendix 5. Detailed data on outcomes in categories of death, life impact and resource use
- Data file Appendix 6. Detailed data on outcomes in categories of adverse event
- Data file Appendix 7. Detailed data on outcomes in categories of physiological/clinical
- Data file Appendix 8. Detailed data on composite outcomes

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Open Peer Review

Current Peer Review Status: ✔ ✔

Version 1

Reviewer Report 18 October 2022

https://doi.org/10.5256/f1000research.134062.r153142

✔ **Julien Potet**
Médecins Sans Frontières, Paris, France

The authors have conducted a thorough review of published clinical trial studies and have meticulously listed all the outcomes used in these studies. This review demonstrates heterogeneity on outcomes. This review will be helpful to support efforts to determine a minimal list of consensus outcomes (aka a Core Outcome Set) that should be used in forthcoming trials of interventions against snakebite.

My only criticism is that authors have omitted to mention and discuss a very similar review of existing clinical outcomes for snakebite trials that was published in PLoS-NTD in 2021 (Abouyannis *et al.* 2021)[1]. It would be interesting to compare the results of the authors' review with the results of this other PLoS-NTD review.

Apart from that, I want to commend the authors for this impressive work!

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Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Antivenom development, antivenom access

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.

Author Response 13 Jan 2023

Soumyadeep Bhaumik, University of New South Wales,, Sydney, Australia

We thank the reviewer of the kind comment. We have now taken note of another systematic review for development of a global core outcome set (COS) on snakebite. In our review, as already noted, we used a standard taxonomy for classifying snakebite outcomes [1] which the other review did not. We also included non-randomised trials and systematic reviews. A comparison, when the both the regional and global COS is completed will be valuable, as it will provide methodological insight for future COS development, beyond snakebite.

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Competing Interests: None

Reviewer Report 20 July 2022

https://doi.org/10.5256/f1000research.134062.r144412

Harry Williams
Toxiven Biotech Private Limited, Coimbatore, Tamil Nadu, India

Generally this is a superb review. The authors have carried out an incredibly detailed systematic review and this article meets all the criteria f1000 set for acceptable publications and has hopefully paved the way for their goal of a South Asian Core Outcome Set to be developed. The article is well written with very impressive tables of results and as a precursor to the eventual COS is exemplary

for the methodology to be used in this process. Overall Bhaumik et al. have done a great job at reviewing the vast and varied snakebite literature and I look forward to reading the eventual COS. They have reviewed the literature to identify the full range of outcomes associated with snakebite envenomation. They identify the need to homogenise outcome reports so as to easily compare cases and act fast following the admission of a previously documented outcome. This would enable future clinical trials to be designed more methodically.

Major Points:

1. At no point in their review do they mention any of the snake species involved or any means for diagnosing the bites and ensuring they are indeed snake bites.

2. None of the toxins found within snake venoms are mentioned or attributed to any of the effects seen in these cases. I understand this was not the purpose of the review but it would have added greatly to my personal enjoyment if there was at least some level of discussion surrounding each of the unique outcomes regarding the snakes or toxins to blame.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Not applicable

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Snakebite research, human-wildlife conflict, toxicology

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.

Author Response 13 Jan 2023

Soumyadeep Bhaumik, University of New South Wales,, Sydney, Australia

We thank the reviewer for the kind comments and appreciating the work. We conducted a review of existing trials and systematic reviews on any intervention on outcomes with the

explicit objective to look at outcomes for developing a core outcome set. We did not capture data on diagnosis. We have already noted that 55.7% of studies were restricted to bites of specific snake species/genus in Table 1. We have provided the reference for all studies of this type in the text of Characteristic of included studies section. Since the studies we reviewed were trials or systematic reviews, aiming to clinically evaluate specific therapeutic agents the included studies did not report on the effect of specific toxins within snake venoms.

Competing Interests: No competing interests were disclosed.

8.4. Manuscript: phase 2 and phase 3 for development of core outcome set for snakebite research in South Asia

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Core outcome set for intervention research on snakebite envenomation in South Asia

Soumyadeep Bhaumik [1,2,3*], Deepti Beri [3], Vishal Santra [4], Maya Gopalakrishnan [5], Mohammad Abul Faiz [6], Paula R Williamson [7], Mike Clarke [8], Sanjib Kumar Sharma [9,] Jagnoor Jagnoor [1]

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Abstract

Introduction

The World Health Organization's strategy (2019) to reduce snakebite burden emphasises the need for fostering research on snakebite treatments. Such research should use a relevant core outcome set (COS) and, in 2020, we first highlighted the need for these for snakebite research. A COS is a consensus-derived minimal list of outcomes that should be measured in research on a particular domain, thus improving research efficiency by standardising outcome measurement. We aimed to develop a COS for snakebite management in South Asia, the region with the highest burden.

Methods

We used results from a systematic review to develop an initial list of outcomes for a Delphi survey in which healthcare providers, patients and public, and potential COS users rated these outcomes for importance, for five intervention groups. In the first round of Delphi, participants suggested additional outcomes. We organised a consensus meeting to agree on 'what' outcomes should be part of the COS. We defined the consensus criteria *a priori*. We conducted an online consultation and a workshop to reach final consensus recommendations on 'how' the outcomes in the COS should be measured.

Results

Overall, 72 and 61 people, including patients and public, participated in round I and round II of the Delphi, respectively. Consensus COS, and recommendations on 'how' these outcomes should be measured were developed for interventions that prevent

adverse reaction to snake anti-venom (three outcomes), specifically manage neurotoxic manifestations (five outcomes), specifically manage haematological manifestations (five outcomes), and those that act against snake venom (seven outcomes). No outcomes were included in the COS on interventions for management of bitten part.

Conclusion

The use of these COS in snakebite studies would enable standardisation of outcomes, facilitate meaningful comparisons, and improve research efficiency in South Asia. We also provide methodological insights for future COS development, beyond snakebite.

Author Summary

The burden of snakebite is highest in South Asia. The 2019 World Health Organization strategy (2019) to reduce snakebite burden emphasises on the need for fostering research on snakebite treatments. In 2020, our research group first highlighted the need for developing core outcome set (COS) for future intervention research on snakebite. A COS is a consensus-derived minimal list of outcomes that should be measured in future research. We used data from a systematic review of outcomes to develop a long list of outcomes which were rated in two rounds of online Delphi survey (with the first round having additional round of outcomes) with healthcare providers, patients, and public, and potential COS users to develop a COS for intervention research on snakebite treatments in South Asia for five intervention groups. Subsequently meetings, consultation, and workshop were organised to reach consensus. Consensus COS, with recommendations on ‘how’ these outcomes should be measured were developed for interventions that prevent adverse reaction to snake anti-venom (three outcomes), specifically manage neurotoxic manifestations (five outcomes), specifically manage

haematological manifestations (five outcomes), and those that act against snake venom (seven outcomes). No outcomes were included in the COS on interventions for management of bitten part. The COS contributes to improve research efficiency by standardising outcome measurement in South Asia. It also provides insights for future COS development, beyond snakebite.

Introduction

The Global Burden of Disease study estimates 78,600 snakebite deaths for 2019, with about 80% in India and Pakistan. [1] In 2019, the World Health Organization (WHO), set the target to halve the burden of snakebite by 2030 and recognised the need for fostering research on snakebite treatment as a strategy towards 'ensuring safe, effective treatment of snakebite'. [2] Major funders, such as Wellcome Trust, [3] have committed investments for developing better treatments for snakebite. A 2022 landscape analysis [4] found that, since 2015, 196 candidate therapeutics (drugs and biologics) and 127 available immunoglobulin products (animal plasma/serum derived) had been researched for snakebite treatment. With a pipeline of candidate therapeutics, more intervention research on snakebite is imminent. Interest from snake anti-venom (SAV) manufacturers might also be expected to increase to comply with Target Product Profiles (TPPs) for SAV being developed by the WHO. [5]

In 2020, our research group first identified [6] the issue of non-standardised measurement of outcomes impeding comparison of treatments of snakebite and identified the need for developing a core outcome set (COS) for snakebite. A COS is a consensus-derived, minimal list of outcomes that should be measured in research or practice for a particular health condition. Apart from standardisation, which enables

comparison, a COS also ensures that outcomes which are measured in research are relevant to not only researchers, but also to healthcare workers, patients, and other stakeholders, [7] thus, enabling research efficiency. [8, 9]

We aimed to develop a COS for intervention studies on snakebite management in South Asia (Bangladesh, Bhutan, India, Nepal, Pakistan, and Sri Lanka) for interventions that:

1. prevent adverse reaction to snake anti-venom,
2. are for management of the bitten part,
3. are specific to management of neurotoxic manifestations,
4. are specific to management of haematological manifestations,
5. act against the snake venom.

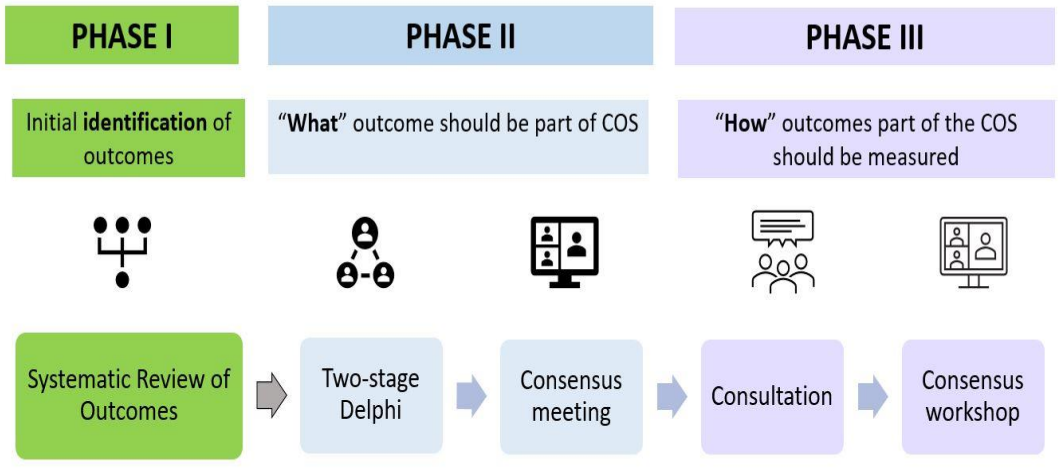
We focused on South Asia because it has the highest burden of snakebites and has similarities in the distribution of medically important snakes, health systems structure and a shared cultural history. [1] Unlike for other health conditions, which are clinically similar globally, snakebite envenomation is a heterogenous clinical condition. The clinical presentation and interventions for its management are dependent on snake species in a particular geographic area. It is for this reason that WHO develops region-specific practice guidelines and TPPs, [5, 10] rather than global ones. By setting the scope of the COS to South Asia, we developed a more contextually relevant and better suited tool for use in future research to facilitate safe and effective treatment in the region. The intervention categorisation is in alignment with WHO- SEARO (South-East Asia Regional Office) guidelines for management of snakebite. [10]

Methods

Study Design

We developed the COS in three phases, in alignment with methods recommended by the COMET (Core Outcome Measures in Effectiveness Trials) Initiative (https://comet-initiative/). In the phase I, we generated a list of initial outcomes for consideration in the COS through a global systematic review of outcomes. [11] In phase II, we conducted a two-round Delphi survey and a consensus meeting to finalise the outcomes to be part of the COS. Phase III comprised of online consultation, followed by a workshop to reach consensus on 'how' the outcomes in the COS should be measured. We present the three phases of the COS development are shown diagrammatically in Figure 1.

Figure 1: Development of Core outcome set for intervention research on snakebite in South Asia



Protocol, registration, and reporting

We registered the study in the COMET database (https://comet-initiative/Studies/Details/1849) and developed the study protocol *a priori*. We report

our compliance with the Core Outcome Set-STAndards for Reporting (COS-STAR) reporting guideline [12] in **Appendix 1.**

Study steering committee

A steering committee for the study included representatives of the COMET Initiative, healthcare workers and researchers from Bangladesh, India, and Nepal and a community practitioner from India, leading snakebite mitigation and prevention programs (See Acknowledgements). This committee members played an advisory role, providing inputs through e-mails and virtual meetings, and the members did not participate in the Delphi survey.

Phase I: Obtaining a list of outcomes for Delphi

We used a global a systematic review of outcomes (separately published [11]) to generate an initial list of outcomes, all categorised as per a standard outcome taxonomy. [13] After the review, we confirmed, with the Steering Committee, the scope of the project to exclude development of a COS for mental health interventions for snakebite, although it is an important area of concern. [14] For the reasons stated, we did not include the following types of outcomes, identified from the review, in the Delphi survey:

- psychiatric outcomes: deemed out of scope,
- immunological or serology related (e.g., venom concentration or antibody measurement): deemed as proxy, not relevant to clinical decision-making, and not feasible, and

- composite outcomes: varied combinations with no validation studies in South Asia, impedes patient and public understanding, and are difficult for healthcare communication.

We reviewed all remaining outcomes and merged those that are sufficiently similar, into a single item. We did this with the intent of limiting survey time to 30 minutes per round and avoiding confusion around similar outcomes (particularly in non-clinician health workers, patients, and public). Survey time is a key factor for participation, completion, and retention in Delphi surveys. Delphi participants could see details of each outcome entity by clicking on it. During the pilot phase, we conducted multiple rounds of testing on the survey tool to avoid ambiguity in language for the outcomes, and to acquire feedback on instructions, presentation, and time of completion (see Acknowledgements).

Phase II: Attaining consensus on 'what' outcomes should be part of the COS

Three groups of participants (18 years and above) participated in the Delphi survey:

i. healthcare providers (clinicians, nurses, community health workers, and social workers) involved in snakebite care.
ii. patients and public (snakebite survivors, family members of a person who has experienced snakebite and representatives of communities affected by snakebite).
iii. potential COS users (researchers including trialists, venom researchers, systematic reviewers, journal editors, research funders and guideline developers).

All participants were from South Asia. For the 'potential COS user' category, those with an international scope of work related to snakebite also participated. The study was designed to be multi-lingual with options in Bangla, English and Hindi, primarily to enable participation of patients and public.

We recruited participants through e-mail (authors of published studies and trial registry records), recruitment posters (for patient and public), e-mail lists of snakebite related organisations/networks and institutional social media accounts. All potential participants were introduced to the COS concept through a plain language summary and a COMET Initiative video. [15] Those who expressed interest were sent the participant information sheet and a link for registering in Delphi Manager, a web-based online system, through which the two-stage electronic Delphi survey was instituted.

In both rounds, participants rated outcomes on a Likert scale of 1–9 (wherein a rating of 1–3 corresponds to "limited importance for decision making"; 4–6 to "important for decision making, but not critical"; and 7–9 to "critical for decision making") for five different modules, corresponding to the five interventions groups for which the COS was developed. During the Delphi voting, intervention modules appeared in random, with no fixed order.

In the first Delphi round, participants could suggest additional outcomes, for consideration of inclusion in the second round. We carried all outcomes from the first round and relevant additional outcomes (reviewed by research team and steering committee member) to the second Delphi round. In the second round, participants saw their own ratings as well as group ratings for the three stakeholder groups and were asked to consider re-scoring the outcomes. We defined consensus for the Delphi *a priori as*:

- Consensus of classification as a core outcome (consensus in): ≥ 70% of participants in all three stakeholder groups give a score between 7-9 (critical for decision making) and ≤ 15% of participants in all three stakeholder groups give a score between 1-3 (of limited importance for decision making).
- Consensus of classification as not being a core outcome (consensus out): ≥ 70% of participants in all three stakeholder groups give a score between 1-3 (of limited importance for decision making) and ≤ 15% of participants in all three stakeholder groups give a score between 7-9 (critical for decision making).
- No consensus: any other scoring.

If a participant skipped rating a particular outcome, we used the actual number of responses for each outcome to calculate the proportions. We invited those who participated in both the rounds of the Delphi to attend an online consensus meeting. For outcomes on which there was "no consensus" after two rounds, the participants deliberated and voted to achieve consensus as per the following *a priori* criteria:

- Consensus in: > 70% of meeting attendees marked it as critical for decision making.
- Consensus out: ≤ 70% meeting attendees marked it as critical for decision making.

Phase III: Developing consensus recommendations on 'how' outcomes in the COS should be measured

We were guided by the principles of the COMET-COSMIN (Consensus-based Standards for the selection of health Measurement Instruments) guidance to develop consensus recommendation on how outcomes in COS should be measured. [16] The minimum criteria for choice were to have good content validity (including face

validity), good internal consistency (if applicable) and be feasible in the South Asian Context. In addition, we also considered reliability, and responsiveness (if applicable).

We listed options for 'how' outcomes in the COS should be measured (including time points) in a tabular manner. For this purpose, we use information from the systematic review conducted in Phase I, and conducted additional focused literature searches, as relevant. We shared the document with participants online, for consultation for 15 days. Subsequently, an online workshop was organised where the COS with measurement recommendations was finalised. We had planned to do voting should there be no consensus, among participants, but this was not necessary.

Ethics and consent

Ethics approval was obtained from The George Institute for Global Health, India (09/2021) and University of New South Wales, Australia (HC210437). Participants provided consent through the online Delphi Manager system.

Result

Study Participants

The Delphi survey took place during August to October 2022. A total of 81 participants registered in the Delphi Manager platform, out of which nine did not participate in the survey (i.e., did not rate any outcome). Overall, 72 participants completed the first round, and 61 participants (84.7% of the 72) completed the second round. In the first round, four (5.5% of 72) participants did not rate outcomes in all five intervention modules. The corresponding number in the second round was two (3.2% of 61). Characteristics of Delphi participants are presented in Table 1.

Table 1: Characteristics of participants in Delphi Survey

Stakeholder Group	ROUND 1 OF DELPHI	ROUND 2 OF DELPHI	Drop-out %
Healthcare provider	34 (Male: 29; Female: 5) •Clinician: 31 •Nurse: 2 •Social worker: 1	30 (Male: 25; Female: 5) •Clinician: 27 •Nurse: 2 •Social worker: 1	88.2 % [a]
Patient or public	12 (Male: 8; Female: 4) •Snakebite Survivor: 5 •Family member: 5 •Community Representative: 2	11 (Male: 8; Female: 3) •Snakebite Survivor: 5 •Family member: 4 •Community Representative: 2	91.7 % [b]

Potential COS user	26 (Male: 18; Female: 8) • Guideline developer: 3 • Journal editor: 1 • Research funder: 1 • Researchers: 21	20 (Male: 13; Female: 7) • Guideline developer: 2 • Journal editor: 1 • Research funder: 0 • Researchers: 17	76.9 % [c]

a. In round 1, country-wise distribution of participants was Bangladesh: 2, Bhutan: 1, India: 29, Nepal: 1, Pakistan: 1, and Sri Lanka: 0. In round 2, 4 participants from India dropped out.
b. All participants from the patient or public representative stakeholder group were from India. In round 2, 1 participant dropped out.
c. In round 1, country-wise distribution of participants was Bangladesh: 2, Bhutan: 0, India: 12, Nepal: 4, Pakistan: 0, Sri Lanka :2, and other countries: 6. In round 2, 1 participant from Bangladesh, 3 from India and 2 from other countries dropped out.

Consensus on 'what' outcomes should be part of COS

After the first round, consensus was achieved on inclusion of one outcome in the intervention specific to neurological manifestations module, and two outcomes in the interventions that target snake venom module. For all other outcomes, no consensus was attained.

We reviewed 16 free text responses from eight participants with regards to additional outcomes and included one for rating in the second round which was - outcomes specific to viper bites (capillary leak syndrome, thrombotic microangiopathy, and adrenal/pituitary insufficiency). Details on suggestions received, and reasons for its inclusion or exclusion in the next round is presented in **Appendix 2**.

After the second Delphi round, a "consensus in" status was obtained for two outcomes in preventing adverse reaction intervention module, four outcomes in intervention specific to neurological manifestations module, two outcomes in intervention specific to haematological manifestations module, and five outcomes in interventions that target snake venom. In both the rounds, no consensus attained "consensus out" status.

The results of the Delphi rounds with scores were sent to all participants who completed both rounds, before the online consensus meeting. A total of 13 (10 male; 3 female) participants from Bhutan (1), India (9), Sri Lanka (1), Malaysia (1) and Australia (1) attended the consensus meeting. No patient or public stakeholder joined the meeting. All outcomes in the 'no consensus' category was discussed and voted on to achieve the final decision regarding inclusion or exclusion for the COS. A summary of different consensus decisions in the two rounds of Delphi and the consensus meeting is presented in Table 2. Detailed scoring is presented in **Appendix 3.**

Table 2: Consensus decision for 'what' outcomes should be part of COS

COS on interventions that prevent adverse reaction to snake anti-venom			
Outcome	**Outcome Decision**		
	Round I	**Round II**	**Consensus meeting**
Anaphylaxis or early antivenom reaction (develops immediately or within hours of administering snake antivenom)	no consensus	Consensus In	Consensus In
Death (all-cause/ cause-specific)	no consensus	Consensus In	Consensus In

Hypotension or shock (sudden fall in blood pressure)	no consensus	no consensus	Consensus Out
Respiratory distress (breathing problem)	no consensus	no consensus	Consensus Out
Requirement of ICU (intensive care unit) admission and/or duration of ICU stay	no consensus	no consensus	Consensus In
Duration of hospital stay	no consensus	no consensus	Consensus Out
Direct cost of treatment (might be measured as cost incurred by the patient or by the provider or both)	no consensus	no consensus	Consensus Out
Late antivenom reaction (develops usually within 1-12 days of administering snake antivenom)	no consensus	no consensus	Consensus Out

COS on interventions for the management of the bitten part

Outcome	**Outcome Decision**		
	Round I	**Round II**	**Consensus Meeting**
Oedema or swelling (localised around the area / extremity in which bite has occurred)	no consensus	no consensus	Consensus Out
Requirement of any surgery	no consensus	no consensus	Consensus Out
Wound infection	no consensus	no consensus	Consensus Out
Wound healing	no consensus	no consensus	Consensus Out
Wound cosmesis (how the wound looks)	no consensus	no consensus	Consensus Out
Pain	no consensus	no consensus	Consensus Out
Impact on life after snakebite (functional impact, disability, quality of life, extremity function, recovery)	no consensus	no consensus	Consensus Out
Duration of hospital stay	no consensus	no consensus	Consensus Out
Direct cost of treatment (might be measured as cost incurred by	no consensus	no consensus	Consensus Out

the patient or by the provider or both)			
Any adverse event due to treatment	no consensus	no consensus	Consensus Out
COS on interventions that are specifically for the management of neurotoxic manifestations			
Outcome	**Outcome Decision**		
	Round I	**Round II**	**Consensus Meeting**
Respiratory distress (breathing problem)	no consensus	Consensus In	Consensus In
Requirement/duration of respiratory support or ventilation	no consensus	Consensus In	Consensus In
Death (all-cause/ cause-specific)	Consensus In	Consensus In	Consensus In
Requirement of ICU (intensive care unit) admission and/or duration of ICU stay	no consensus	Consensus In	Consensus In
Ventilator associated pneumonia (infection of lung associated with patient being on ventilator)	no consensus	no consensus	Consensus Out
Neuro-muscular paralysis	no consensus	no consensus	Consensus In
Amount of antivenom required	no consensus	no consensus	Consensus Out
Any adverse event due to treatment	no consensus	no consensus	Consensus Out
Impact on life after snakebite (functional impact, disability, quality of life, extremity function, recovery)	no consensus	no consensus	Consensus Out
Direct cost of treatment (might be measured as cost incurred by the patient or by the provider or both)	no consensus	no consensus	Consensus Out
Duration of hospital stay	no consensus	no consensus	Consensus Out
Pneumonia (infection of lungs)	no consensus	no consensus	Consensus Out
COS on interventions that are specifically for management of the haematological manifestation			
Outcome	**Outcome Decision**		

	Round I	Round II	Consensus Meeting
Death (all-cause/ cause-specific)	no consensus	Consensus In	Consensus In
Necessity of ICU (intensive care unit) admission and/or duration of ICU stay	no consensus	Consensus In	Consensus In
Blood clotting and blood coagulability	no consensus	Consensus In	Consensus In
Requirement for antivenom	no consensus	no consensus	Consensus Out
Hypotension or shock (sudden fall in blood pressure)	no consensus	no consensus	Consensus Out
Acute kidney failure / injury or requirement of dialysis	no consensus	no consensus	Consensus In
Bleeding	no consensus	no consensus	Consensus In
Duration of hospital stay	no consensus	no consensus	Consensus Out
Requirement of blood product transfusion (any)	no consensus	no consensus	Consensus Out
Chronic kidney disease	no consensus	no consensus	Consensus Out
Any adverse event due to treatment	no consensus	no consensus	Consensus Out
Impact on life after snakebite (functional impact, disability, quality of life, extremity function, recovery)	no consensus	no consensus	Consensus Out
Direct cost of treatment (might be measured as cost incurred by the patient or by the provider or both)	no consensus	no consensus	Consensus Out
Outcomes specific to Viper bites (capillary leak syndrome, thrombotic microangiopathy, and adrenal/pituitary insufficiency).	Not applicable	no consensus	Consensus Out
COS on interventions that act against the snake venom			
Outcome	**Outcome Decision**		
	Round I	**Round II**	**Consensus Meeting**
Respiratory distress (breathing problem)	Consensus In	Consensus In	Consensus In

Requirement/Duration of respiratory support or ventilation	no consensus		Consensus In
Bleeding	no consensus	Consensus In	Consensus In
Blood clotting and blood coagulability	no consensus	Consensus In	Consensus In
Death (all-cause/ cause-specific)	Consensus In	Consensus In	Consensus In
Hypotension or shock (sudden fall in blood pressure)	no consensus	no consensus	Consensus Out
Cardiac (heart) rhythm abnormalities	no consensus	no consensus	Consensus Out
Requirement of blood product transfusion (any)	no consensus	no consensus	Consensus Out
Neuro-muscular paralysis	no consensus	no consensus	Consensus Out
Requirement of ICU (intensive care unit) admission and/or duration of ICU stay	no consensus	no consensus	Consensus Out
Myotoxicity (effect of snake venom on muscles)	no consensus	no consensus	Consensus Out
Acute kidney failure / injury or requirement of dialysis	no consensus	no consensus	Consensus In
Anaphylaxis or early antivenom reaction (develops immediately or within hours of administering snake antivenom)	no consensus	no consensus	Consensus In
Requirement of any surgery	no consensus	no consensus	Consensus Out
Direct cost of treatment (might be measured as cost incurred by the patient or by the provider or both)	no consensus	no consensus	Consensus Out
Impact on life after snakebite (functional impact, disability, quality of life, extremity function, recovery)	no consensus	no consensus	Consensus Out
Duration of hospital stay	no consensus	no consensus	Consensus Out
Pain	no consensus	no consensus	Consensus Out
Oedema or swelling (localised around the area / extremity in which bite has occurred)	no consensus	no consensus	Consensus Out

Any other adverse event due to treatment	no consensus	no consensus	Consensus Out
Chronic kidney disease	no consensus	no consensus	Consensus Out
Pneumonia (infection of lungs			
Late antivenom reaction (develops usually within 1-12 days of administering snake antivenom)	no consensus	no consensus	Consensus Out
Any other adverse event due to treatment	no consensus	no consensus	Consensus Out

Consensus recommendations on 'how' outcomes in the COS should be measured

In this phase of the project, sixteen people (including three who expressed intent to join the consensus meeting on 'what' outcomes should be part of COS but were unable to attend the meeting at the last minute) participated. In the online consultation, the participants reviewed and discussed 'how' the outcomes included in the COS should be measured. Overall, we received 203 responses during this consultation, including suggested edits, notes on agreement and disagreements, discussion on preference parameters, definitions, and time points of measurement. After the online consultation, there was unanimous consensus on outcome definitions for:

- All three outcomes in preventing adverse reaction intervention COS.
- All, but two, outcomes in intervention specific to neurological manifestations COS.
- All five outcomes in intervention specific to haematological manifestations COS.
- All, but one, outcome in interventions that target snake venom COS.

In the final online workshop, the participants discussed all pending issues to arrive at consensus on all aspects of how the core outcomes should be measured in future intervention studies. The final COS for intervention research for different intervention groups, along with recommendations for measurement is presented in Table 3.

Table 3: Core outcome set for intervention research on different intervention types

COS for research on interventions that prevent adverse reaction to snake anti-venom		
Consensus "what" outcomes part of COS	**Consensus recommendation on "how" outcomes part of COS should be measured**	
	Outcome Definition	**Time point**
1. Anaphylaxis or early antivenom reaction (develops immediately or within hours of administering snake antivenom)	**Definition:** Proportion of people with anaphylaxis as defined by World Allergy Organization Anaphylaxis Guidance 2020 [a] **Data Type:** Dichotomous Definition is available in Table 2 / Figure 1 of Cardona V, Ansotegui IJ, Ebisawa M, et al. World allergy organization anaphylaxis guidance 2020. World Allergy Organ J. 2020 Oct 30;13(10):100472.	- 6 hours from randomisation, for randomised controlled trials (RCTs). - 6 hours from intervention, for other non-randomised intervention designs
2. Death (all-cause/ cause-specific)	**Definition:** All-cause mortality **Data Type:** Dichotomous	- 4 weeks (28 days) from randomisation, for RCTs. - 4 weeks (28 days) from intervention, for other non-

		randomised intervention designs
3. Requirement of ICU (intensive care unit) admission and/or duration of ICU stay	**Definition:** Proportion of patients who were admitted to ICU **Data Type:** Dichotomous **Note**: Studies should clearly report the specific criteria used for ICU admission and discharge in trial sites	- 4 weeks (28 days) from randomisation, for RCTs. - 4 weeks (28 days) from intervention, for other non-randomised intervention designs
COS for research on interventions for management of the bitten part		
Consensus was not obtained for any outcome		
COS for research on interventions specific to management of neurotoxic manifestations		
Consensus "what" outcomes part of COS	**Consensus recommendation on "how" outcomes part of COS should be measured**	
	Outcome Definition	**Time point**
1. Death (all-cause/ cause-specific)	**Definition:** All-cause mortality **Data Type:** Dichotomous	- 4 weeks (28 days) from randomisation, for RCTs. - 4 weeks (28 days) from intervention for other non-randomised

		intervention designs
2. Neuro-muscular paralysis	**Definition**: Time taken for complete reversal of paralysis in at least 2 muscle groups (extra-ocular and bulbar) and respiratory paralysis **Data Type:** time-to-event **Note**: Outcome assessors should be mandatorily trained, and a standard operating procedure developed for the purpose.	Not applicable.
3. Respiratory distress (breathing problem):	**Definition:** Proportion of patients with severe respiratory distress, which is defined [b] by, having any one of below i. Talks in words (i.e. in not phrases or sentences) ii. Accessory muscles being used iii. O 2 saturation (on air) <92% iv. RR <12 or >20 /min v. P CO2 >45 vi. Single breath count (number of digits counted in one exhalation) < 25 **Data Type**: Dichotomous	- 24 hours from randomisation, for RCTs - 24 hours from intervention, for other non-randomised intervention designs
4. Duration of respiratory support or ventilation	**Definition:** Time in hours from the onset of intubation to extubating **Data Type:** time-to-event	Not applicable.
5. Duration of ICU stay	**Definition:** Time from admission to discharge from ICU - in hours **Data Type:** time to event	Not applicable.

	Note: Studies should clearly report the specific criteria used for ICU admission and discharge in trial sites.	
COS for research on interventions specific to management of the haematological manifestations		
Consensus "what" outcomes part of COS	**Consensus recommendation on "how" outcomes part of COS should be measured**	
	Outcome Definition	**Time point**
1. Death (all-cause/ cause-specific)	**Definition:** All-cause mortality **Data Type:** Dichotomous	- 4 weeks (28 days) from randomisation, for RCTs. - 4 weeks (28 days) from intervention for other non-randomised intervention designs
2. Duration of ICU stay	**Definition:** Time from admission to discharge from ICU - in hours **Data Type:** time to event **Note:** Studies should clearly report the specific criteria used for ICU admission and discharge in trial sites	**Time point**: not applicable
3. Bleeding	**Definition:** Proportion of people developing major haemorrhage, as defined by the International Society on Thrombosis and Haemostasis as i. fatal bleeding, or	- 24 hours, 48 hours, and 7 days from randomisation, for RCTs. All time points

	ii. symptomatic bleeding in a critical organ (e.g., intracranial haemorrhage), or iii. bleeding resulting in a drop in haemoglobin >20g/L, or iv. requiring blood transfusion. **Data Type:** Dichotomous	should be reported. - 24 hours, 48 hours, and 7 days from intervention for other non-randomised intervention designs. All time points should be reported.
4. Blood clotting and blood coagulability	**Definition**: Proportion of patients with abnormal blood coagulability, assessed by the Whole blood clotting test (20WBCT) [d] **Data Type**: Dichotomous **Note**: Only a single-use clean, dry, glass test tube should be used for the test. There is no clinical evidence indicating validity of the test when plastic containers are used. Outcome assessors should be blinded, trained and a standard operating procedure developed for the purpose.	- 6 hours, 12 hour, 24 hours, and 7 days [c] from randomisation, for RCT. All time points should be reported. - 6 hours, 12 hour, 24 hours, and 7 days [c] from intervention for other non-randomised intervention designs. All time points should be reported.
5. Acute kidney failure /	**Definition**: Proportion of patients who develop AKI, as defined by the Acute	- 4 weeks (28 days) from

injury or requirement of dialysis	Kidney Injury Network (AKIN) OR KDIGO diagnostic criteria should be met (any one of the three): i. An increase in serum creatinine by ≥0.3 mg/dl (≥26.5 μmol/l) within 48 hours i. An increase in serum creatinine to ≥1.5 times baseline within the previous 7 days ii. Urine volume ≤0.5 ml/kg/h for 6 h **Data Type:** Dichotomous	randomisation, for RCTs. - 4 weeks (28 days) from intervention for other non-randomised intervention designs
COS for research on interventions that act against the snake venom		
Consensus "what" outcomes part of COS	**Consensus recommendation on "how" outcomes part of COS should be measured**	
	Outcome Definition	**Time point**
1. Death (all-cause/ cause-specific)	**Definition:** All-cause mortality **Data Type:** Dichotomous	- 4 weeks (28 days) from randomisation, for RCTs. - 4 weeks (28 days) from intervention for other non-randomised intervention designs
2. Anaphylaxis or early antivenom reaction (develops	**Definition:** Proportion of people with anaphylaxis as defined by World Allergy Organization Anaphylaxis Guidance 2020 [a] **Data Type:** Dichotomous	- 6 hours from randomisation, for RCTs. - 6 hours from intervention, for

immediately or within hours of administering snake antivenom)	**Note:** available in Table 2 / Figure 1 of Cardona V, Ansotegui IJ, Ebisawa M, et al. World allergy organization anaphylaxis guidance 2020. World Allergy Organ J. 2020 Oct 30;13(10):100472.	other non-randomised intervention designs
3. Respiratory distress (breathing problem)	**Definition**: Proportion of patients with severe respiratory distress, defined [c] by having any one of below i. Talks in words (i.e. in not phrases or sentences) ii. Accessory muscles being used iii. O 2 saturation (on air) <92% iv. RR <12 or >20 /min v. P CO2 >45 vi. Single breath count (number of digits counted in one exhalation) < 25 **Data Type:** Dichotomous	- 24 hours from randomisation, for RCTs - 24 hours from intervention, for other non-randomised intervention designs
4. Requirement of respiratory support or ventilation	**Definition:** Proportion of patients requiring mechanical ventilation **Data Type:** Dichotomous **Note:** Studies should clearly specify the criteria for deeming a patient requiring mechanical ventilation. This criterion can be used in facilities with no mechanical ventilation too.	- 48 hours from randomisation, for RCTs. - 48 hours from intervention for other non-randomised intervention designs
5. Bleeding	**Definition:** Proportion of people developing major haemorrhage, as defined by the International Society on Thrombosis and Haemostasis as	- 24 hours, 48 hours, and 7 days from randomisation,

	i. fatal bleeding, or ii. symptomatic bleeding in a critical organ (e.g., intracranial haemorrhage), or iii. bleeding resulting in a drop in haemoglobin >20g/L, or iv. requiring blood transfusion. **Data Type:** Dichotomous	for RCTs. All time points should be reported. - 24 hours, 48 hours, and 7 days from intervention for other non-randomised intervention designs. All time points should be reported.
6. Blood clotting and blood coagulability	**Definition:** Proportion of patients with abnormal blood coagulability, assessed by the Whole blood clotting test (20WBCT) [d] **Data Type:** Dichotomous **Note:** Only a single-use clean, dry, glass test tube should be used for the test. There is no clinical evidence indicating validity of the test when plastic containers are used. Outcome assessors should be blinded, trained and a standard operating procedure developed for the purpose.	- 6 hours, 12 hour, and 24 hours, from randomisation, for RCTs. All time points should be reported. - 6 hours, 12 hour and 24 hours, from intervention for other non-randomised intervention designs. All time points should be reported.

7. Acute kidney failure / injury or requirement of dialysis	**Definition:** Proportion of patients who develop AKI, as defined by the Acute Kidney Injury Network (AKIN) OR KDIGO diagnostic criteria should be met (any one of the three) i. An increase in serum creatinine by ≥0.3 mg/dl (≥26.5 μmol/l) within 48 h ii. An increase in serum creatinine to ≥1.5 times baseline within the previous 7 days iii. Urine volume ≤0.5 ml/kg/h for 6 h **Data Type:** Dichotomous	- 4 weeks (28 days) from randomisation, for RCTs. - 4 weeks (28 days) from intervention for other non-randomised intervention designs

a) The World Allergy Organization definition is widely recognised globally, and endorsed by 52 national professional organisations, including in South Asia by the Indian College of Allergy and Applied Immunology, and Pakistan Allergy Asthma and Immunology Society.

b) This is a consensus-derived definition based on review of guidelines of acute respiratory distress (GINA) and snakebite by Ministry of Health and Family Welfare, India, and in alignment with broader principles of respiratory physiology. Respiratory distress (breathing problem) though related to neuro-paralysis was seen as an important outcome for decision making. However, for snakebite, and in South Asia, no robust validated tool is available. The consensus derived criterion included clinical measures, such that evidence generated is in alignment with existing clinical practice in South Asia, and that trials on snakebite ought to be carried out in primary health centres, where advanced equipment might not be available. The criterion is designed, such that it can be used for all patients, irrespective of intubation status.

c) Time point of 7 days is recommended only for specific species, which cause long term or recurrent coagulopathy. An indicative list is provided below:

- *Trimeresurus erythrurus* (Spot tailed/Red tailed green pit viper)
- *Rhabdophis subminiatus* (Red necked keelback)

- *Trimeresurus salazar* (Salazar's pitviper)
- *Naja kaouthia* (Monocle cobra)
- *Naja Naja* (Spectacled cobra)
- *Daboia russelii* (Russell's viper)

d) The 20WBCT was chosen because it is simple to measure, and evidence developed from trials, using it as an outcome would directly translate to practice in the South Asian context. A recent systematic review* found that WBCT20 is highly specific and fairly sensitive bedside test for detecting coagulopathy in snakebite. It should also be noted that a COS is a minimal standard, and trialist might choose other measures (example INR), should resources be available, but such measures do not translate directly for practice in primary health centres and many under-resourced secondary and tertiary hospitals (which do not have 24 X 7 laboratory support), which is where people affected by snakebite present to. Inclusion of WBCT20, in the COS enables conduct of trials in wider types of health facilities.

*Lamb T, Abouyannis M, de Oliveira SS, et al. The 20-minute whole blood clotting test (20WBCT) for snakebite coagulopathy-A systematic review and meta-analysis of diagnostic test accuracy. PLoS Negl Trop Dis. 2021 Aug 10;15(8): e0009657.

Discussion

Summary of key findings

In this study, we developed a COS of what and how a minimum set of outcomes should be measured in future research on snakebite in South Asia on interventions that prevent adverse reaction to SAV (three outcomes), are specifically for the management of neurotoxic manifestations (five outcomes), are specifically for the management of the haematological manifestations (five outcomes) and interventions that act against snake venom (seven outcomes).

Study findings in broader context of snakebite research

Setting the scope for COS for snakebite is challenging. Snakebite is a heterogenous condition, dependent on varying distribution of species geographically and consequent variability in interventions. A very narrow geographical scope of COS would have a very well-defined utility, with few conflicting opinions on what should and should not be part of the COS. However, the relevance of such a COS might be limited to trials in the specific geographic area or population only. On the other hand, a very wide geographical COS would be less contextually relevant and achieving consensus might be challenging (leading to agreement on the inclusion of too many or too few outcomes), thus hampering its utility and applicability. We contend that a regional scope based on similarity in geographic species, health systems and shared socio-cultural history, as was done in our COS, achieves the right balance. For snakebite, another research group has developed a global COS [17]but this is might not be “fit for purpose” in specific regions, such as South Asia. A global COS is conceptually problematic for snakebite, and not in alignment with other ecosystem initiatives that

seek to balance between heterogeneity and standardisation, through a regional basis of work. For example, standards around clinical practice or production of therapeutics is developed on a regional basis by the WHO. [5, 10] Furthermore, in contrast to the global COS, which focuses on therapeutics against snake venom alone, our COS includes several types of interventions, thus enhancing its utility.

In interpreting and using the findings of the COS on interventions for the management of bitten part, it is worthwhile noting that the intervention group consists of three distinct aspects: wound management, bacterial infections and swelling of the limbs. We reflect that this broad scope might have prevented achieving consensus. For the future, we recommend development of separate COS for each of wound management, bacterial infections and swelling of the limb in relation to the bitten part. In the interim, trialists and systematic reviewers working in this area, might consider inclusion of the three outcomes that would have been included if we had lowered the threshold from 70% to 50%. These are oedema or swelling (localised around the area / extremity in which bite has occurred), requirement of any type of surgery, and impact on life after snakebite (functional impact, disability, quality of life, extremity function, recovery).

Strengths and weakness of the study

We followed standard methods of COS development [7] [18] and reported in accordance with the COS-STAR guidelines. [19] Involvement of stakeholders was in alignment with the scope, relevancy of COS for multiple types of interventions, and provision of clear recommendations on how to measure outcomes enhanced the utility of our COS. The number of outcomes in each intervention module in our COS are relevant and reasonable.

We faced considerable challenge in achieving greater involvement of patients and public. We did anticipate the challenge and therefore, designed our study to be multi-lingual, with options to participate in Bangla, English or Hindi. However, despite the multilingual option, extensive promotion through recruitment posters in multiple communities in India (we did not do so in other countries), and social media acceleration, we could recruit only 12 participants in this group, with no participation in phase 3. While the Delphi approach does not depend on statistical power, a minimum number of 10 participants is considered necessary to give reliable results. [20-22] We did achieve this number for all intervention modules except one, which the participation of patient and public group was sub-optimal. Four participants skipped the module on interventions that are specific for management of haematological manifestations, in entirety. Two of these participants had noted that this was because they did not experience haematological manifestations. We believe participation in the patient and public group was impeded overall because of multiple reasons, including absence of lived experience around outcomes or intervention groups, digital nature of the Delphi, and the low levels of education in people who are most affected by snakebite. Four snakebite survivors who expressed interest, could not differentiate between rating for importance of outcomes versus ratings for severity of outcomes. Despite our endeavours, we were unsuccessful in communicating that importance and severity, although related, are not the same. For the future, we recommend methodological research to support and improve patient and public participation in COS development for conditions, such as snakebite, which primarily affect those with little or no education, and people deprived of health literacy.

Other methods that can be tested are - interviewer administered Delphi, use of graphic visual cards and interactive animation with native language audio to support the Delphi survey. There is also need for providing more guidance for the patients and public group on deciding how to measure outcomes, where discussions are highly technical in nature. We tried to mitigate against this by asking a member of our Steering Committee, who is a community practitioner leading a snakebite mitigation and prevention program, to join the consensus meeting.

Methodological insights for future development of COS, beyond snakebite

The COS-STAD [18] sets the minimum standards for COS developers to follow and COS users to evaluate methodological rigour. We suggest that future iterations of COS-STAD should consider adding a standard around geographic region within the scope specification domain. Such a specification is not only important for conditions like snakebite which have clear geographic variation, but also for other health conditions where variation in cultural preferences and health systems is important.

The COS-STAD guideline [18] might also be revised to have more nuanced standards to ensure that COS development happens through meaningful involvement of stakeholders from high burden and endemic nations. A recent systematic review found that only 20% of COS included LMIC participants. [23] It is known that non-involvement or tokenistic involvement of appropriate stakeholders decreases the utility, acceptance, and uptake of COS. [24, 25] Setting a standard for representative participation will fill this gap and contribute towards the larger challenge of poor stakeholder engagement and low uptake of COS in most research areas.

For many neglected tropical diseases and acute medical emergencies (not linked to chronic disease), such as snakebite, there are no organised survivor groups who can support recruitment in COS development. This is also true for many chronic conditions in low- and middle-income countries. The current strategy of the COMET People and Patient Participation, Involvement and Engagement (PoPPIE) Working Group for involvement and engagement is predominantly focused on patient organisations. [26] Guidance and tools for community engagement might be developed by the COMET-POPPIE group to enable future COS development.

Future work on COS and outcomes for snakebite research in South Asia

To enhance uptake of our COS, the core study team will develop a strategy to increase awareness, engage with potential users and promote the adoption of COS in the wider evidence ecosystem, as recent work on the area of COS uptake has suggested. [8, 9, 24, 25]. We will engage with national research funders (such as Bangladesh Medical Research Council, Indian Council of Medical Research, Nepal Health Research Council, Pakistan Health Research Council), professional bodies, medical journals, and clinical trial registries (Indian and Sri Lankan) in South Asia to endorse and promote the uptake of this COS for future intervention research on snakebite. During our Phase III discussions, numerous challenges, and issues around measurement of outcomes in intervention research on snakebite were raised. A by-product of this study is the formulation of an epistemic community of clinicians and COS users, who hope to work together on a position statement noting challenges and a research agenda on outcome measurement for snakebite trials.

Conclusion

The use of our COS in future snakebite research would enable standardisation of outcomes, facilitate meaningful comparisons, and improve efficiency in research in the South-Asian region. Our research has also led to methodological insights, particularly around development standards of COS, and patient and public engagement.

Financial Disclosure Statement

The study did not have any external funding.

Competing interests

PW and MC are members of the Management Team for the COMET Initiative (https://www.comet-initiative.org/). SB joined as a member of the COMET POPPIE Working Group during Phase III of the study. No other conflicts of interests.

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Availability of data

Data relevant to the study are either presented in the paper or in the appendix. Summary of action taken reports in relation to steering committee is available on request from the corresponding author.

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Appendix 1: Compliance with COS-STAR Statement Checklist

SECTION/TOPIC	ITEM No.	CHECKLIST ITEM	REPORTED
TITLE/ABSTRACT			
Title	1a	Identify in the title that the paper reports the development of a COS	✓
Abstract	1b	Provide a structured summary	✓
INTRODUCTION			
Background and Objectives	2a	Describe the background and explain the rationale for developing the COS.	✓
	2b	Describe the specific objectives with reference to developing a COS.	✓
Scope	3a	Describe the health condition(s) and population(s) covered by the COS.	✓
	3b	Describe the intervention(s) covered by the COS.	✓
	3c	Describe the setting(s) in which the COS is to be applied.	✓
METHODS			
Protocol/Registry Entry	4	Indicate where the COS development protocol can be accessed, if available, and/or the study registration details.	✓
Participants	5	Describe the rationale for stakeholder groups involved in the COS development process, eligibility criteria for participants from each group, and a description of how the individuals involved were identified.	✓
Information Sources	6a	Describe the information sources used to identify an initial list of outcomes.	✓
	6b	Describe how outcomes were dropped/combined, with reasons (if applicable).	✓
Consensus Process	7	Describe how the consensus process was undertaken.	✓
Outcome Scoring	8	Describe how outcomes were scored and how scores were summarised.	✓
Consensus Definition	9a	Describe the consensus definition.	✓
	9b	Describe the procedure for determining how outcomes were included or excluded from consideration during the consensus process.	✓
Ethics and Consent	10	Provide a statement regarding the ethics and consent issues for the study.	✓
RESULTS			
Protocol Deviations	11	Describe any changes from the protocol (if applicable), with reasons, and describe what impact these changes have on the results.	✓

Participants	12	Present data on the number and relevant characteristics of the people involved at all stages of COS development.	✓
Outcomes	13a	List all outcomes considered at the start of the consensus process.	✓
	13b	Describe any new outcomes introduced and any outcomes dropped, with reasons, during the consensus process.	✓
COS	14	List the outcomes in the final COS.	✓
DISCUSSION			
Limitations	15	Discuss any limitations in the COS development process.	✓
Conclusions	16	Provide an interpretation of the final COS in the context of other evidence, and implications for future research.	✓
OTHER INFORMATION			
Funding	17	Describe sources of funding/role of funders.	✓
Conflicts of Interest	18	Describe any conflicts of interest within the study team and how these were managed.	✓

From: Kirkham JJ, Gorst S, Altman DG, Blazeby JM, Clarke M, Devane D, et al. (2016) Core Outcome Set–STAndards for Reporting: The COS-STAR Statement. PLoS Med 13(10): e1002148.

Appendix 2: Suggested additional outcome in round I of Delphi: Core outcome set for intervention research on snakebite envenomation in South Asia

Suggested additional outcomes		Action taken for suggested outcome
Interventions that act against the snake venom	Total dose of anti- snake venom given	Not relevant.
Interventions that act against the snake venom	Requirement renal replacement therapy	Already present in the list of outcomes. No action taken
Intervention group not specified	To identify or thinking a possibility of snake bite especially in case of neurolytic snake bites	Not relevant.
Intervention group not specified	Type of blood product used for management of coagulopathy	Already present in the list of outcomes. No action taken
Intervention for management of cardiotoxicity	arrythmia; cardiogenic shock; myocarditis	Already present in the list of outcomes. No action taken
Intervention group not specified	Outcomes specific to Viper bites (capillary leak syndrome; thrombotic microangiopathy; and adrenal/pituitary insufficiency).	Added as a single additional outcome in round 2 of Delphi: outcomes specific to viper bites (capillary leak syndrome, thrombotic microangiopathy, and adrenal/pituitary insufficiency).
Intervention for the management of acute renal injury	thrombotic microangiopathy	
Interventions that act against the snake venom	Capillary leak syndrome:	
Interventions that act against the snake venom	Symptomatic adrenal/pituitary insufficiency:	
Intervention group not specified	Outcomes specific to Viper bites (capillary leak syndrome; thrombotic microangiopathy; and adrenal/pituitary insufficiency).	
Interventions that act against the snake venom	Thrombotic microangiopathy	
interventions to manage haematological manifestations and interventions that act against the snake venom	20-minute whole blood clotting test for	Already present in the list of outcomes. No action taken
Intervention group not specified	Number of days taken to return to the routine work/livelihood after snakebite	Already present in the list of outcomes. No action taken
Use of tourniquet	-	No action taken as it does not pertain to outcome but intervention group. These are already covered.
Immobilization and rest	-	
Role of plasma exchange in management	-	

Appendix 3: Detailed Score of COS for research on snakebite management in South Asia Phase II

Scores for Core outcome set for research on interventions (treatments) that prevent adverse reaction to snake anti-venom

Healthcare provider (clinician, nurse, community health worker) or social worker group is represented by this background colour

Patient or public (a snakebite survivor, family member of a person bitten by snake or representatives of communities affected by snakebite) group is represented by this background colour

Potential COS user (researchers including trialists, venom researchers, systematic reviewers, journal editors, research funders, guideline developer) group is represented by this background colour

Outcome	Not important			Important but not critical			Critical			Outcome Decision		
	Round I	Round II	Consensus meeting	Round I	Round II	Consensus meeting	Round I	Round II	Consensus meeting	Round I	Round II	Consensus meeting
Anaphylaxis or early antivenom reaction (develops immediately or within hours of administering snake antivenom)	0% 0% 0%	0% 0% 0%	NA	0% 44% 0%	7% 30% 5%	NA	100% 56% 100%	93% 70% 95%	NA	Only Patient group does not want IN	Consensus IN	Consensus IN
Death (all-cause/ cause-specific)	6% 0% 0%	3.5% 0% 0%	NA	16% 37% 0%	3.5% 20% 0%	NA	78% 63% 100%	93% 80% 100%	NA	Only Patient group does not want IN	Consensus IN	Consensus IN
Hypotension or shock (sudden fall in blood pressure)	3% 11% 0%	0% 10% 0%	0%	12% 45% 14%	7% 30% 0%	50%	85% 44% 86%	93% 60% 100%	50%	Only Patient group does not want IN	Only Patient group does not want IN	Consensus Out
	3%	0%	0%	16%	14%	38.46%	81%	86%	61.54%			

Respiratory distress (breathing problem) (Reported by patient or measured clinically as airway obstruction, respiratory failure, and acute respiratory distress syndrome)	11% 4%	10% 0%		45% 24%	30% 5%		44% 72%	60% 95%		Only Patient group does not want IN	Only Patient group does not want IN	Consensus Out
Requirement of ICU (intensive care unit) admission and/or duration of ICU stay	7% 24% 0%	3% 0% 0%	0%	27% 38% 15%	14% 50% 10%	30%	66% 38% 85%	83% 50% 90%	70%	Only Patient group does not want IN	Only Patient group does not want IN	Consensus IN
Duration of hospital stay	15% 10% 5%	7% 0% 0%	15.38%	45% 20% 49%	31% 22% 44.44%	61.54%	40% 70% 48%	62% 78% 66.66%	23.08%	Only Patient group wants IN	Only Patient group wants IN	Consensus Out
Direct cost of treatment (this might be measured as cost incurred by the patient or by the provider or both)	12% 22.22% 5%	7% 12.5% 5%	7.69%	45% 33.33% 30%	34% 37.5% 10%	69.23%	43% 44.44% 65%	59% 50% 75%	23.08%	no consensus	no consensus	Consensus Out

Late antivenom reaction (develops usually within 1-12 days of administering snake antivenom)	7% **11%** **0%**	3% **0%** **0%**	33.33% 0% (revote)	42% **67%** **38%**	52% **75%** **32%**	50% 60% (revote)	51% **22%** **62%**	45% **25%** **68%**	16.67% 40% (revote)	no consensus	no consensus	Consensus Out

Scores for Core outcome set for research on interventions (treatment) for management of the bitten part including but not limited to management of wounds, bacterial infections and/or swelling of the limbs (compartment syndrome)

Healthcare provider (clinician, nurse, community health worker) or social worker group is represented by this background colour

Patient or public (a snakebite survivor, family member of a person bitten by snake or representatives of communities affected by snakebite) group is represented by this background colour

Potential COS user (researchers including trialists, venom researchers, systematic reviewers, journal editors, research funders, guideline developer) group is represented by this background colour

Outcome	Not important			Important but not critical			Critical			Outcome Decision		
	Round I	Round II	Consensus Meeting	Round I	Round II	Consensus Meeting	Round I	Round II	Consensus Meeting	Round I	Round II	Consensus Meeting
Oedema or swelling (localised around the area / extremity in which bite has occurred) • Oedema: measured as circumference difference between the affected limb and the normal limb; circumference measurements of the affected limb alone; remission time of limb swelling; cessation of local	16% 27% 4%	7% 27% 0%	8.33%	36% 27% 41%	32% 18% 20%	33.33%	48% 46% 55%	61% 55% 80%	58.33%	no consensus	no consensus but COS Users wants IN	Consensus Out

swelling progression; time to swelling resolution; oedema progression; measurement of decrease of oedema-scaled dish. • Swelling: measured based on the number of segments affected (extent) and increase in circumference of the bitten limb (intensity); proximal length of swelling from bite site; criteria developed by Warell et al 1977; criteria based on physical appearance of swelling; swelling is confirmed to bitten segment or crosses 1 or 2 joints; and % increase in volume compared to contralateral (non-envenomated) limb.												
Requirement of any surgery (Surgery includes but not limited to, incision and drainage, debridement,	22% 12% 0%	11% 11% 0%	0%	24% 33% 42%	21% 33% 20%	33.33%	54% 55% 58%	68% 56% 80%	66.66%	no consensus	no consensus but COS Users wants IN	Consensus Out

fasciotomy, and amputation)												
Wound infection (Defined as cellulitis, swelling and/or abscess/necrosis, diagnosed by a clinician, through laboratory results or patient-reported symptoms or defined as requirement of antibiotic to treat infection)	0% 10% 0%	0% 0% 0%	8.33%	36% 50% 32%	39% 60% 25%	41.67%	64% 40% 68%	61% 40% 75%	50%	no consensus	no consensus but COS Users wants IN	Consensus Out
Wound healing (Diagnosed by a clinician, through laboratory results or patient-reported symptoms)	3% 10% 0%	0% 0% 0%	16.67%	50% 50% 64%	67% 70% 60%	83.33%	47% 40% 36%	33% 30% 40%	0%	no consensus	no consensus	Consensus Out
Wound cosmesis (how the wound looks)	18% 20% 14%	11% 20% 15%	33.33%	58% 50% 68%	71% 60% 70%	58.33%	24% 30% 18%	18% 20% 15%	8.33%	no consensus	no consensus	Consensus Out
Pain (Measured as intensity (through patient reported scales like Visual Analogue Scale or Numeric Pain Rating Scale) or time to complete resolution of the local pain or	12% 27% 5%	7% 27% 0%	8.33%	51% 46% 50%	61% 64% 55%	58.33%	37% 27% 45%	32% 9% 45%	33.33%	no consensus	no consensus	Consensus Out

requirement of analgesic to relieve pain)												
Impact on life after snakebite Might be measured in the following manners: 1. Functional life impact: Patient Specific Functional Scale, and the physical function domain of the SF-36 questionnaire (these are patient reported scoring tools) 2. Disability: Sheehan Disability Inventory and American Medical Association (AMA) disability rating score (these are patient reported scoring tools) 3. Quality of life: Patient's Global Impression of Change Scale, Clinical Global Impression - Improvement (CGI-I), and Patient-reported outcome measurement information system	9% 0% 0%	0% 0% 0%	0%	33% 40% 50%	36% 50% 50%	41.67%	57% 60% 50%	64% 50% 50%	58.33%	no consensus	no consensus	Consensus Out

	physical function-10 score (PROMIS PF-10).(these are patient reported scoring tools))												
4.	Time to functional recovery: defined as time to full functional status recovery as measured by the Patient-Specific Functional Scale, or complete resolution of swelling and ability to run and jump (for lower extremity bites) or equal handgrip (for upper extremity bites).												
5.	Lower extremity function: Scores on Lower Extremity Functional Scale (this is a patient reported scoring tool) and walking speed.												
6.	Upper extremity function: Scores on the Disorders of the Arm, Shoulder, and Hand (DASH)(this is a patient reported scoring tool) and grip strength through a dynamometer												

Duration of hospital stay	4% 10% 5%	0% 0% 0%	0%	45% 18% 57%	43% 27% 42%	63.64%	51% 72% 38%	57% 73% 58%	36.36%	no consensus	no consensus but Patients wants IN	Consensus Out
Direct cost of treatment (this might be measured as cost incurred by the patient or by the provider or both)	4% 10% 10%	0% 0% 5%	0%	45% 30% 32%	29% 40% 26%	66.77%	51% 60% 58%	71% 60% 69%	33.33%	no consensus	no consensus but HCW wants IN	Consensus Out
Any adverse event due to treatment	4% **18%** **0%**	0% **9%** **0%**	0%	33% **64%** **43%**	25% **55%** **26%**	50%	63% **18%** **57%**	75% **36%** **74%**	50%	no consensus	Only Patient group does not want IN	Consensus Out

Scores for Core outcome set for research on interventions (treatments) for management of neurotoxic manifestations (e.g., ventilation-different modalities, neostigmine, edrophonium)

Healthcare provider (clinician, nurse, community health worker) or social worker group is represented by this background colour
Patient or public (a snakebite survivor, family member of a person bitten by snake or representatives of communities affected by snakebite) group is represented by this background colour
Potential COS user (researchers including trialists, venom researchers, systematic reviewers, journal editors, research funders, guideline developer) group is represented by this background colour

Outcome	Not important			Important but not critical			Critical			Outcome Decision		
	Round I	Round II	Consensus Meeting	Round I	Round II	Consensus Meeting	Round I	Round II	Consensus Meeting	Round I	Round II	Consensus Meeting
	3%	0%	NA	3%	0%	NA	94%	100%	NA			

Respiratory distress (breathing problem) (Reported by patient or measured clinically as airway obstruction, respiratory failure, and acute respiratory distress syndrome)	0% 0%	0% 0%		34% 15%	11% 5%		66% 85%	89% 95%		Only Patient group does not want IN	Consensus In	Consensus In
Requirement/duration of respiratory support or ventilation* (Requirement/duration of mechanical ventilation or non-invasive ventilation or re-intubation (post-extubation))	0% 10% 0%	0% 0% 0%	NA	12% 40% 23%	7% 30% 0%	NA	88% 50% 77%	93% 70% 100%	NA	Only Patient group does not want IN	Consensus In	Consensus In
Death (all-cause/ cause-specific)	0% 0% 0%	0% 0% 0%	NA	15% 20% 0%	3% 22% 0%	NA	85% 80% 100%	97% 78% 100%	NA	Consensus In	Consensus In	Consensus In
Requirement of ICU (intensive care unit) admission and/or duration of ICU stay	0% 12% 0%	0% 11% 0%	NA	25% 22% 23%	17% 11% 5%	NA	75% 66% 77%	83% 78% 95%	NA	Only Patient group does not want IN	Consensus In	Consensus IN
Ventilator associated pneumonia (infection of lung associated with patient being on ventilator)	15% 12% 0%	7% 12.5% 0%	25%	16% 38% 40%	13% 50% 15%	50%	69% 50% 60%	80% 37.5% 85%	25%	no consensus	Only Patient group does not want IN	Consensus Out
Neuro-muscular paralysis (Reported by patient or measured clinically as paralysis/ophthalmoplegia/ptosis/motor strength)	7% 12% 0%	0% 0% 0%	9%	12% 44% 10%	3% 44% 5%	15.38%	81% 44% 90%	97% 56% 95%	84.62%	Only Patient group does not want IN	Only Patient group does not want IN	Consensus In

Amount of antivenom required	3% 20% 5%	0% 22.22 % 5%	8%	36% 40% 40%	30% 33.33 % 20%	50%	61% 40% 55%	70% 44.44 % 75%	42%	no consensus	Only Patient group does not want IN	Consensus Out
Any adverse event due to treatment	0% 0% 0%	0% 0% 0%	0%	38% 55% 24%	30% 44% 16%	75%	62% 45% 76%	70% 56% 84%	25%	no consensus	Only Patient group does not want IN	Consensus Out
Impact on life after snakebite Might be measured in the following manners: 1. Functional life impact: Patient Specific Functional Scale, and the physical function domain of the SF-36 questionnaire (these are patient reported scoring tools) 2. Disability: Sheehan Disability Inventory and American Medical Association (AMA) disability rating score (these are patient reported scoring tools) 3. Quality of life: Patient's Global Impression of Change Scale, Clinical Global Impression - Improvement (CGI-I), and Patient-reported outcome measurement information system physical function-10 score (PROMIS PF-10).(these	6% 0% 10%	3% 0% 10%	7%	50% 40% 52%	53% 22% 55%	50%	44% 60% 38%	44% 78% 35%	43%	no consensus	Only patient wants IN	Consensus Out

are patient reported scoring tools)) 4. Time to functional recovery: defined as time to full functional status recovery as measured by the Patient-Specific Functional Scale, or complete resolution of swelling and ability to run and jump (for lower extremity bites) or equal handgrip (for upper extremity bites). 5. Lower extremity function: Scores on Lower Extremity Functional Scale (this is a patient reported scoring tool) and walking speed. 6. Upper extremity function: Scores on the Disorders of the Arm, Shoulder, and Hand (DASH)(this is a patient reported scoring tool) and grip strength through a dynamometer												
Direct cost of treatment (this might be measured as cost incurred by the patient or by the provider or both)	7% 12% 14%	3% 11% 10%	15.38%	53% 22% 43%	40% 33% 40%	69.23%	40% 66% 43%	57% 56% 50%	15.38%	no consensus	no consensus	Consensus Out
Duration of hospital stay	0% 0% 4%	0% 0% 0%	8.33%	43% 27% 67%	53% 40% 55%	58.33%	57% 73% 29%	47% 60% 45%	33.33%	no consensus	no consensus	Consensus Out

Pneumonia (infection of lungs)	18% **22%** **11%**	7% **11%** **0%**	15.38%	34% **56%** **52%**	36.5% **67%** **68%**	69.23%	48% **22%** **37%**	56.5% **22%** **32%**	15.38%	no consensus	no consensus	Consensus Out

Scores for Core outcome set for research on interventions (treatments) for management of the haematological (blood) manifestations (e.g., blood products- different types, plasma exchange, heparin, and recombinant factors)

Healthcare provider (clinician, nurse, community health worker) or social worker group is represented by this background colour

Patient or public (a snakebite survivor, family member of a person bitten by snake or representatives of communities affected by snakebite) group is represented by this background colour

Potential COS user (researchers including trialists, venom researchers, systematic reviewers, journal editors, research funders, guideline developer) group is represented by this background colour

Outcome	Not important			Important but not critical			Critical			Outcome Decision		
	Round I	Round II	Consensus Meeting	Round I	Round II	Consensus Meeting	Round I	Round II	Consensus Meeting	Round I	Round II	Consensus Meeting
Death (all-cause/ cause-specific)	0% 0% 0%	3.5% 0% 0%	NA	15% 33% 0%	3.5% 25% 0%	NA	85% 67% 100%	93% 75% 100%	NA	Only Patient group does not want IN	Consensus IN	Consensus IN
Necessity of ICU (intensive care unit) admission and/or duration of ICU stay	0% 0% 0%	3.5% 0% 0%	NA	28% 33.5% 32%	21% 12% 15%	NA	72% 66.5% 68%	75% 88% 85%	NA	no consensus	Consensus IN	Consensus IN
Blood clotting and blood coagulability	0% 0% 0%	0% 0% 0%	0%	10% 44% 10%	11% 50% 10%	7.69%	90% 56% 90%	89% 50% 90%	92.31%	Only Patient group	Only Patient group	Consensus IN

(Diagnosed by a clinician or patient reported or measured through blood tests, in the laboratory or the bed side) • Blood coagulability - by 20 min whole blood clotting test (WBCT20)/Lee -White method, or standard laboratory measures of international normalized ratio (INR), bleeding time (BT), clotting time (CT), Prothrombin Time (PT), aPTT (activated partial thromboplastin time). • Clotting Factors- Clotting factor panel or specific factors like fibrinogen,										does not want IN	does not want IN	

Factor V, VII, VIII, Fibrinogen degradation products/D-dimer. • Clot Quality- measures as per a method developed by Reid												
Requirement for antivenom	3% 12% 5%	4% 0% 5%	15.38%	25% 33% 0%	14% 37.5% 0%	15.38%	72% 55% 95%	82% 62.5% 95%	69.23%	Only Patient group does not want IN	Only Patient group does not want IN	Consensus Out
Acute kidney failure / injury or requirement of dialysis	4% 0% 0%	4% 0% 0%	0%	12% 44% 10%	7% 37.5% 10%	25%	84% 56% 90%	89% 62.5% 90%	75%	Only Patient group does not want IN	Only Patient group does not want IN	Consensus IN
Bleeding (Diagnosed by a clinician or patient reported or measured through blood tests) Major haemorrhage, defined by the International Society on	0% 0% 0%	0% 0% 0%	0%	15% 44% 19%	11% 50% 10%	15.38%	85% 56% 81%	89% 50% 90%	84.68%	Only Patient group does not want IN	Only Patient group does not want IN	Consensus IN

Thrombosis and Haemostasis criteria OR therapeutic response OR medically significant late bleeding												
Hypotension or shock (sudden fall in blood pressure)	0% 12% 0%	3.5% 12.5% 0%	0%	12% 44% 10%	3.5% 37.5% 10%	50%	88% 44% 90%	93% 50% 90%	50%	Only Patient group does not want IN	Only Patient group does not want IN	Consensus Out
Outcomes specific to Viper bites (capillary leak syndrome, thrombotic microangiopathy, and adrenal/pituitary insufficiency).	NA NA NA	3.5% 0% 0%	0%	NA NA NA	25% 57% 5%	50%	NA NA NA	71.5% 43% 95%	50%	NA	Only Patient group does not want IN	Consensus Out
Duration of hospital stay	9% 0% 0%	0% 0% 0%	8.33%	31% 23% 48%	39% 25% 45%	66.67%	60% 77% 52%	61% 75% 55%	25%	Only patient wants IN	Only patient wants IN	Consensus Out
Requirement of blood product transfusion (any) (Blood product might be whole blood, packed red blood cell, fresh frozen plasma, platelets, cryoprecipitate)	0% 0% 10%	0% 0% 0%	8.33%	37% 44% 34%	32% 37.5% 45%	50%	63% 56% 56%	68% 62.5% 55%	41.67%	no consensus	no consensus	Consensus Out
Chronic kidney disease (Diagnosed clinically or through blood or urine	9% 33.33% 5%	7% 37.5% 5%	25%	32% 33.33% 52%	33% 12.5% 55%	58.33%	59% 33.33% 43%	59% 50% 40%	16.67%	no consensus	no consensus	Consensus Out

tests as requirement ongoing renal replacement therapy)												
Any adverse event due to treatment	0% 0% 5%	3.5% 0% 0%	0%	45% 55% 26%	43% 37.5% 35%	41.67%	55% 45% 69%	53.5% 62.5% 65%	58.33%	no consensus	no consensus	Consensus Out
Impact on life after snakebite Might be measured in the following manners: 1. Functional life impact: Patient Specific Functional Scale, and the physical function domain of the SF-36 questionnaire (these are patient reported scoring tools) 2. Disability: Sheehan Disability Inventory and American Medical Association (AMA) disability rating score (these are	12% 0% 10%	4% 0% 5%	0%	53% 55.5% 38%	68% 62.5% 55%	58.33%	35% 44.5% 52%	29% 37.5% 40%	41.67%	no consensus	no consensus	Consensus Out

patient reported scoring tools) 3. Quality of life: Patient's Global Impression of Change Scale, Clinical Global Impression - Improvement (CGI-I), and Patient-reported outcome measurement information system physical function-10 score (PROMIS PF-10).(these are patient reported scoring tools)) 4. Time to functional recovery: defined as time to full functional status recovery as measured by the Patient-Specific Functional Scale, or complete resolution of swelling and												

ability to run and jump (for lower extremity bites) or equal handgrip (for upper extremity bites). 5. Lower extremity function: Scores on Lower Extremity Functional Scale (this is a patient reported scoring tool) and walking speed. 6. Upper extremity function: Scores on the Disorders of the Arm, Shoulder, and Hand (DASH)(this is a patient reported scoring tool) and grip strength through a dynamometer												

Direct cost of treatment (this might be measured as cost incurred by the patient or by the provider or both)	6% **12%** **5%**	7% **12.5%** **5%**	0%	54% **22%** **38%**	45% **25%** **35%**	81.82%	40% **66%** **57%**	48% **62.5%** **60%**	18.18%	no consensus	no consensus	Consensus Out

Scores for Core Outcome Set for research on interventions (treatments) that act against the snake venom

Healthcare provider (clinician, nurse, community health worker) or social worker group is represented by this background colour Patient or public (a snakebite survivor, family member of a person bitten by snake or representatives of communities affected by snakebite) group is represented by this background colour Potential COS user (researchers including trialists, venom researchers, systematic reviewers, journal editors, research funders, guideline developer) group is represented by this background colour												
Outcome	Not important			Important but not critical			Critical			Outcome Decision		
	Round I	Round II	Consensus Meeting	Round I	Round II	Consensus Meeting	Round I	Round II	Consensus Meeting	Round I	Round II	Consensus Meeting
Respiratory distress (breathing problem) (Reported by patient or measured clinically as airway obstruction, respiratory failure, and acute respiratory distress syndrome)	0% 0% 0%	0% 0% 0%	NA	15% 30% 10%	3% 9% 0%	NA	85% 70% 90%	97% 91% 100%	NA	Consensus IN	Consensus IN	Consensus IN
Requirement/Duration of respiratory support or ventilation (Requirement/duration of mechanical ventilation or non-invasive ventilation or re-intubation (post-extubation))	0% 0% 0%	0% 0% 0%	NA	6% 40% 19%	3% 30% 5%	NA	94% 60% 81%	97% 70% 95%	NA	Only Patient group does not want IN	Consensus IN	Consensus IN
Bleeding	0%	0%	NA	13%	0%	NA	87%	100%	NA			

(Diagnosed by a clinician or patient reported or measured through blood tests) Major haemorrhage, defined by the International Society on Thrombosis and Haemostasis criteria OR therapeutic response OR medically significant late bleeding	18% 0%	0% 0%		28% 20%	20% 10%		54% 80%	80% 90%		Only Patient group does not want IN	Consensus IN	Consensus IN
Blood clotting and blood coagulability (Diagnosed by a clinician or patient reported or measured through blood tests, in the laboratory or the bed side) • Blood coagulability -by 20 min whole blood clotting test (WBCT20)/Lee -White method, or standard laboratory measures of international normalized ratio (INR), bleeding time (BT), clotting time (CT), Prothrombin Time (PT), aPTT (activated partial thromboplastin time). • Clotting Factors- Clotting factor panel or specific factors like fibrinogen,	0% 10% 0%	0% 0% 0%	NA	10% 27% 5%	3% 20% 5%	NA	90% 63% 95%	97% 80% 95%	NA	Only Patient group does not want IN	Consensus IN	Consensus IN

Factor V, VII, VIII, Fibrinogen degradation products/D-dimer. • Clot Quality- measures as per a method developed by Reid												
Death (all-cause/ cause-specific)	6% 0% 0%	4% 0% 0%	NA	10% 25% 0%	0% 27% 0%	NA	84% 75% 100%	96% 73% 100%	NA	Consensus IN	Consensus IN	Consensus IN
Hypotension or shock (sudden fall in blood pressure)	3% 20% 0%	0% 20% 0%	0%	3% 40% 10%	0% 30% 5%	58.33%	94% 40% 90%	100% 50% 95%	41.67%	Only Patient group does not want IN	Only Patient group does not want IN	Consensus Out
Cardiac (heart) rhythm abnormalities	7% 10% 4%	7% 0% 0%	0%	24% 50% 24%	14% 67% 25%	83.33%	69% 40% 72%	79% 33% 75%	16.67%	no consensus	Only Patient group does not want IN	Consensus Out
Requirement of blood product transfusion (any) (Blood product might be whole blood, packed red blood cell, fresh frozen plasma, platelets, cryoprecipitate)	7% 8% 5%	3% 0% 0%	0%	18% 25% 40%	10.5% 27% 47%	66.67%	75% 67% 55%	86% 73% 53%	33.33%	no consensus	Only Potential COS USER does not want IN	Consensus Out
	6%	3%	0%	9%	11%	16.67%	85%	86%	83.33%			

Acute kidney failure / injury or requirement of dialysis	0% 0%	0% 0%		40% 10%	33% 5%		60% 90%	67% 95%		Only Patient group does not want IN	Only Patient group does not want IN	Consensus IN
Anaphylaxis or early antivenom reaction (develops immediately or within hours of administering snake antivenom)	0% 0% 0%	0% 10% 0%	0%	6% 40% 15%	14% 30% 0%	0%	94% 60% 85%	86% 60% 100%	100%	Only Patient group does not want IN	Only Patient group does not want IN	Consensus IN
Neuro-muscular paralysis (Reported by patient or measured clinically as paralysis/ophthalmoplegia/ptosis/motor strength)	0% 0% 0%	0% 0% 0%	0%	6% 60% 5%	3% 45% 0%	33.33%	94% 40% 95%	97% 55% 100%	66.67%	Only Patient group does not want IN	Only Patient group does not want IN	Consensus Out
Requirement of ICU (intensive care unit) admission and/or duration of ICU stay	4% 0% 0%	3% 0% 0%	0%	27% 37% 29%	14% 40% 20%	54.55%	69% 63% 71%	83% 60% 80%	45.45%	no consensus	Only Patient group does not want IN	Consensus Out
Outcomes specific to Viper bites (capillary leak syndrome, thrombotic microangiopathy, and adrenal/pituitary insufficiency).	NA NA NA	3% 0% 0%	0%	NA NA NA	21% 57% 20%	36.36%	NA NA NA	76% 43% 80%	63.64%	NA	Only Patient group does not want IN	Consensus Out
Myotoxicity (effect of snake venom on muscles) (Measured clinically or through blood levels of	4% 10% 5%	0% 0% 5%	0%	30% 50% 10%	21% 50% 5%	81.82%	66% 40% 85%	79% 50% 90%	18.18%	no consensus	Only Patient group	Consensus Out

creatine kinase/creatine phosphokinase/lactate dehydrogenase/ metalloproteinases or through electromyography, or by histology of skeletal muscle)											does not want IN	
Requirement of any surgery (Surgery includes but not limited to, incision and drainage, debridement, fasciotomy, and amputation)	10% 10% 10%	3% 10% 5%	0%	42% 27% 50%	42% 10% 65%	63.64%	48% 63% 40%	55% 80% 30%	36.36%	no consensus	Only patient wants IN	Consensus Out
Direct cost of treatment (this might be measured as cost incurred by the patient or by the provider or both)	6% 18% 5%	3% 10% 0%	10%	54% 18% 43%	42% 20% 40%	70%	40% 64% 52%	55% 70% 60%	20%	no consensus	Only patient wants IN	Consensus Out
Impact on life after snakebite Might be measured in the following manners: 1. Functional life impact: Patient Specific Functional Scale, and the physical function domain of the SF-36 questionnaire (these are patient reported scoring tools) 2. Disability: Sheehan Disability Inventory and American Medical Association (AMA) disability rating score	3% 0% 5%	3% 0% 5%	0%	50% 36% 45%	52% 30% 45%	45.45%	47% 64% 50%	45% 70% 50%	54.55%	no consensus	Only patient wants IN	Consensus Out

(these are patient reported scoring tools) 3. Quality of life: Patient's Global Impression of Change Scale, Clinical Global Impression - Improvement (CGI-I), and Patient-reported outcome measurement information system physical function-10 score (PROMIS PF-10). These are patient reported scoring tools. 4. Time to functional recovery: defined as time to full functional status recovery as measured by the Patient-Specific Functional Scale, or complete resolution of swelling and ability to run and jump (for lower extremity bites) or equal handgrip (for upper extremity bites). 5. Lower extremity function: Scores on Lower Extremity Functional Scale (this is a patient reported scoring tool) and walking speed. 6. Upper extremity function: Scores on the Disorders of the Arm, Shoulder, and Hand												

(DASH)(this is a patient reported scoring tool) and grip strength through a dynamometer												
Duration of hospital stay	4% 0% 10%	3% 0% 0%	9%	46% 25% 57%	41.5% 45% 65%	64%	50% 75% 33%	55.5% 55% 35%	27%	Only patient wants IN	no consensus	Consensus Out
Pain (Measured as intensity (through patient reported scales like Visual Analogue Scale or Numeric Pain Rating Scale) or time to complete resolution of the local pain or requirement of analgesic to relieve pain)	12% 25% 10%	7% 18% 15%	27%	60% 41% 68%	83% 64% 75%	55%	28% 34% 22%	10% 18% 10%	18%	no consensus	no consensus	Consensus Out
Oedema or swelling (localised around the area / extremity in which bite has occurred) • Oedema: measured as circumference difference between the affected limb and the normal limb; circumference measurements of the affected limb alone; remission time of limb swelling; cessation of local swelling progression; time to swelling resolution; oedema progression;	7% 18% 0%	3% 30% 5%	10%	42% 36% 63%	48.5% 20% 40%	70%	51% 46% 37%	48.5% 50% 55%	20%	no consensus	no consensus	Consensus Out

measurement of decrease of oedema-scaled dish. • Swelling: measured based on the number of segments affected (extent) and increase in circumference of the bitten limb (intensity); proximal length of swelling from bite site; criteria developed by Warrell et al 1977; criteria based on physical appearance of swelling; swelling is confirmed to bitten segment or crosses 1 or 2 joints; and % increase in volume compared to contralateral (non-envenomated) limb.												
Any other adverse event due to treatment	0% 18% 5%	3% 10% 0%	0%	34% 46% 40%	31% 50% 50%	54.55%	66% 36% 55%	66% 40% 50%	45.45%	no consensus	no consensus	Consensus Out
Chronic kidney disease (Diagnosed clinically or through blood or urine tests as requirement ongoing renal replacement therapy)	10% 20% 0%	3% 22% 0%	27.27%	42% 70% 65%	69% 67% 78%	54.55%	48% 10% 35%	28% 11% 22%	18.18%	no consensus	no consensus	Consensus Out
Late antivenom reaction (develops usually within 1-12 days of administering snake antivenom)	3% 11% 0%	7% 10% 0%	0%	41% 56% 38%	41% 60% 45%	63.64%	56% 33% 62%	52% 20% 55%	36.36%	no consensus	no consensus	Consensus Out

Pneumonia (infection of lungs)	24% **20%** **21%**	21% **33.33 %** **32%**	45.45%	36% **60%** **42%**	48% **44.44 %** **42%**	45.45	40% **20%** **37%**	31% **22.22 %** **26%**	9.09%	no consensus	no consensus	Consensus Out

9. Discussion and conclusion

9.1. Chapter overview

The concluding chapter of the thesis is structured into the following parts: summary of key findings; strengths and limitations of the research; implication of the thesis findings and critical reflections on the WHO snakebite strategy; implications for policy, practice, and research on snakebite in India; implications for future intervention research on snakebite treatments; and a concluding summary.

Since individual chapters, have their own discussion, I crafted this chapter with a view to discussing the body of work presented in the thesis, considering the overall aim and section goals. Thus, the structure aligns with the thesis goals. I have attempted to avoid repetition and discussed larger issues or aspects which cut across chapters.

Apart from practice and policy relevant knowledge on snakebite, the work in the thesis also provides methodological insights for future work research on the global health agenda setting and COS development, which have been detailed in the discussion sections of the relevant manuscripts (Section 3.3 and Section 8.4).

9.2. Summary of key findings

In the doctoral journey, I sought to generate evidence which can enable strategies, policies, and programs for addressing the burden of snakebite. The key findings, significance, and contribution, considering the section goals, is summarised in Table 1.

Table 1: Key findings, significance, and contributions considering sectional goals of the thesis

Goal A: To map and understand the prioritisation of snakebite in the global health agenda	
Key Findings	**Significance And Contribution**
• Policy prioritisation of snakebite occurred in four crescendos. • Ebbs and flows in establishing legitimacy of the snakebite network, and reluctant acceptance of snakebite within the neglected tropical diseases (NTD) community are identified unaddressed challenges.	• To enhance the legitimacy of network and promote acceptance of snakebite within the NTD community there is a need for inclusion of wider base of proponents, with leadership from endemic nations, and greater investments in community-based programs and strengthening primary health care. • The study indicates the need for an independent commission to review the current criteria for a condition being designated as a NTD, which reinforces biomedical discourse on diseases.
Goal B: To evaluate health systems in India for provision of snakebite care	
• There are limitations in structural capacity and prominent gaps in continuum of snakebite care in the primary health care system of India. Structural capacity for snakebite care was weaker in the systemic domains (physical infrastructure, human resources for health, information systems), in comparison to the snakebite-specific domain(medicines). • The studies provide contextually relevant understanding of how COVID-19 accentuated barriers to care, the interplay of multiple factors which affect snakebite care, and the	• There is a need for integrated strengthening of primary health care, across all domains, and throughout the continuum of care. Piece-meal approaches like training of health workers are unlikely to reduce burden. A nationwide health facility assessment survey focussing on snakebite care is also necessitated. • Multi-faceted community programs, are needed for addressing factors affecting snakebite care, including during disease outbreaks- thus improving health systems resilience. Community programs for increasing formal health service usage, should be accompanied by health systems

need for multi-faceted community-based programs on snakebite. • There is no research on the impact of climate change on snakebite from high-burden areas of South Asia (including India, and Pakistan) and Africa. However limited evidence from other countries indicates possible geographic shift in risk of snakebite.	strengthening, instead of an exclusive focus on awareness against traditional providers. • We identify the immense need for the conduct of transdisciplinary research on the effect of climate change on snakebite in India. Geographic shifts might be expected, and resilience planning can be informed by such research.
Goal C: To foster research on effective and safe treatment of snakebite	
• There is a lack of high-quality systematic reviews on interventions for the management of snakebite. Evidence for interventions often came from few studies. Lack of consistency in defining and measuring outcomes for snakebite envenoming prevents comparison through meta-analysis • A core outcome set (COS), together with consensus measurement recommendations on measurement of was developed for use in research on snakebite in South Asia on interventions that: prevent adverse reaction to snake anti-venom (3 outcomes), are specifically for the management of neurotoxic manifestations (5 outcomes), are specifically for the management of the haematological manifestations (5 outcomes), and act against snake venom (7 outcomes). No outcomes were included in the COS on interventions for the management of bitten part.	• Overall, there is no robust evidence to either support or refute many interventions related to snakebite envenomation, thus necessitating investments in "research on research" and evidence synthesis (including conduct of high-quality systematic reviews, development of intervention evidence gap maps). • The use of our COS in future snakebite research in South Asia would enable standardisation and facilitate meaningful comparisons of relevant outcomes. We also provide methodological insights, for COS development standards, and for public and patient involvement.

9.3. Strength, and limitations of the work done in the thesis

A strength of the research presented in the thesis is that it speaks to three thematic areas and employs a range of "fit for purpose" methods and approaches. I used three broad methodological approaches:

- qualitative: in-depth interview and document analysis,
- quantitative: secondary data analysis, regression analysis, and
- evidence synthesis, overview of systematic review and systematic review of outcomes.

Below, I discuss the strengths and limitations from a methodological perspective. A methodological quality assurance mechanism was in place, which included adhering to standard research methodologies, reporting standards, and development standards, as applicable.

A key issue in qualitative research is loss of nuance and social meanings during translation. [1] I mitigated against it by conducting interviews in the language of participants. The policy case study (Chapter 3) has rich data with extensive document review and participation by a range of stakeholders involved in the process. Language is a limitation, as we interviewed participants who are English speaking only. I posit, however that this would not majorly influence the findings. Majority of people involved in the agenda setting space had the linguistic advantage of English, and information about non-English speaking people involved in the process could be obtained through document analysis.

In the second qualitative study (Chapter 5), I did not need to use translators. I conducted data collection, and analysis in Bangla (my mother tongue), and thus no meaning or nuance was lost. To prevent positionality bias, the initial coding framework was developed in discussion with another researcher who used translated version of the first five transcripts on an independent basis. A key strength of this study is also that it was conducted in two purposively chosen study areas (semi-urban, connected to national highway and rural, hard to reach deltaic area), although from the same state in India. Using a case study design, involving multiple high burden states across India would have enhanced the generalisability, but there were resource limitations.

There are some limitations on the two quantitative studies (Chapter 4 and Chapter 5). As discussed in the individual chapters, these limitations relate to the data source. It is worthwhile mentioning that while the exploratory quantitative study on the effect of COVID-19 was responsive to the situation arising from the pandemic. I made use of data in the constraints of what was feasible. It did not provide any insights on the mechanism for the decreased admission for envenoming cases, we found. I contributed to fill the knowledge gap through the qualitative study (Chapter 5) which looked at access to snakebite care.

We used standard methodologies for evidence synthesis, overview of systematic review and systematic review, and all these three studies, which are published (Chapter 6, Chapter 7, and Chapter 8 are of high rigor. The COS for South Asia (Chapter 8) is developed in accordance with current standards of development. [2] There has been a parallel effort by another group of researchers, who have developed a global COS, which focussed on antivenom therapeutics. [3] The issue around setting a global scope for a COS on snakebite, has been discussed previously (Section 8.4.). The regional COS, I

developed, adheres to standards for development of COS and is reported in accordance with COS-STAR reporting guideline. [2 4]

9.4. Implications of the thesis findings, and critical reflections, on the WHO strategy for addressing the burden of snakebite

The findings from the thesis provide several considerations for global proponents of snakebite, including the WHO, and other advocates for snakebite to consider, as they work towards the goal of reducing the burden of snakebite envenomation to half, by 2030.[5]

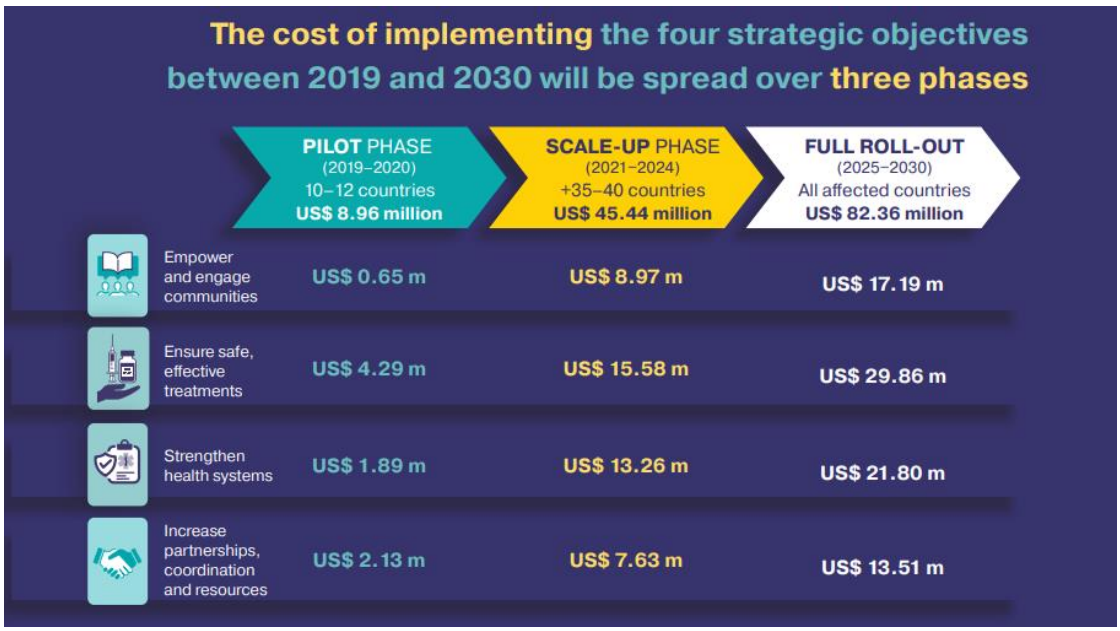
The global policy analysis (Chapter 3), identifies two challenges for sustaining snakebite in the global health agenda. There is a need for the snakebite network to engage and enable leadership from high-burden endemic nations in South Asia and Africa, to enhance legitimacy and the ability of WHO to implement its global strategy. A model where program managers and researchers in high-burden endemic nations take leadership, might be preferred than the current model, wherein they remain passive recipients of technical documents developed by WHO consultants or academics based in non-endemic nations. This phenomenon is not restricted to the snakebite network and is widely prevalent in the global health space. With the decolonising global health movement gaining ground, addressing structural and normative issues, with the explicit aim to enhance legitimacy and ensure redistributive justice (perceived fairness in distribution of resources across group members) within the snakebite community, will reap rich gains. [6-12] The WHO strategy allocates only 54.1% of the budget for countries where snakebite is a public health problem, the remaining being costs for WHO

technical departments (28.8%), and for regional support and collaboration (17.1%).[13] Overall, this implies resource-constrained, low- and middle-income nations, where snakebite is a public health problem, are getting the customary little above half of the budget. Details on how the WHO arrived on budget estimates were arrived at are not available but is unlikely that such top-heavy budgeting (where a huge chunk of money is not for program implementation) will contribute to the target. With COVID-19 triggered economic consequences; countries are facing further fiscal challenges. As such, it is not clear, how countries will resource for implementation of technical documents, strategies, policies, and documents developed by WHO, by spending substantial amounts of donor money and member state contributions. A decentralised management within WHO, wherein the regional offices (WHO-AFRO and WHO-SEARO) engages extensively with national and sub-national governments, might be beneficial. A revision of the budgeting around the mid-term (2024) is perhaps necessitated.

The epistemic injustice reflects in the framing of snakebite (Chapter 3), wherein WHO intends to address snakebite envenoming, and not snakebite [5] is rooted in the prioritisation process; stakeholders were primarily venom researchers and clinicians from high-income nations, and there was a need for them to fit in the norm defining WHO-NTD criteria – as such a path dependency. [14] The framing of the issue being limited to snakebite envenoming, implies a very bio-technical understanding of snakebite, wherein snake anti-venoms are the "magic bullets" akin to chemotherapeutic agents for several NTDs which have elimination or eradication targets. Such medicalisation of health conditions, due to the WHO criteria for a condition being classified as a NTD, has been described by a scholar as an "unwarranted epistemic

privilege frequently afforded to medical institutions and medicalized models of phenomena." [15] Such framing has real world implications and is not a mere change in nomenclature. It reflects on the budget in the WHO strategy (Figure 1), wherein the allocation is prominently for "ensuring safe, effective treatment," whereas other aspects remain, less resourced.

Figure 1: WHO strategy to decrease mortality and disability from snakebite envenoming to 50% by 2030 [5]



(Image used under CC BY-NC-SA 3.0 IGO)

The excessive focus on development of new therapeutics, while required and essential, is misplaced. It is well known that the research and development process for any new therapeutic product, on an average, takes 14 years. [16] There would be additional time required for licensing and post-approval Phase IV trials, prior to scale up and systems-level integration. Given the timelines, even if successful these developments will be too little, and too late for any meaningful contribution towards reducing the burden to half, in an eleven-year plan which targets 2030.

Reframing the issue as snakebite, and not snakebite envenoming, will enable it to find a home within the broader community of public health and "One Health." [17 18] Acceptance within the public health community, might be established through identifying linkages with the agenda on Universal Health Coverage (UHC) and Comprehensive Primary Health Care (CPHC). Re-orienting investments for snakebite towards snakebite prevention (for which One Health is key), health systems strengthening, and community-based programs, instead of an excessive focus on curative approaches will disable epistemic injustice. The results from Section B are limited to the Indian context but reaffirm the need for comprehensive strengthening of primary healthcare, and multi-faceted community-based programs, for addressing the burden of snakebite.

Looking critically at the WHO snakebite strategy, and considering the thesis findings, it is also evident that the section on "strengthening health systems" of the WHO snakebite strategy, [19] is not in cognisant with existing knowledge and understanding of health systems. [20-22] Health systems evaluation and strengthening involves a focus on different blocks of the health system (service delivery, information systems, human resources for health, medicines and technologies, governance, and financing) and the interactions between them, with people being at the heart of it. [20 22] There is a need to apply existing knowledge on health policy and systems research for strengthening snakebite care.

A policy analysis, among key leaders, stakeholders, and funders within the NTD community, globally and in endemic nations, about their perceptions on snakebite, is required to understand the issue better. Such a study would also contribute to understanding aspects of epistemic injustice, arising because of the WHO criteria for designating a condition as a NTD (Chapter 3).There is also a need for policy analysis to

understand the impact of the global prioritisation of snakebite on national and sub-national agendas. Moreover, such an analysis will contribute to the larger literature regarding global health governance, which has primarily focused on agenda setting in the global arena, as well as to future work in the WHO pillar of "increasing partnership, coordination, and resourcing". [23-28]

Lastly, the WHO snakebite strategy has a critical flaw - it does not provide a baseline estimate of the snakebite burden (or lay down the process for it) against which attainment of the target to reduce mortality and morbidity due to snakebite to 50% by 2030 [13] , will be measured. The ambiguity around targets, in the context of population-level estimates and information on disability being absent for almost all high-burden countries, is a huge deterrent to monitoring progress and accountability. In a WHO online seminar on International Snakebite Awareness Day, on 19th of September 2022, WHO staff, in a written response to my query, clarified there is no baseline estimation that has been set and mentioned, “WHO is asking countries to evaluate their own baselines and report these statistics, where they are available. When no data is available WHO’s, role is to encourage countries to begin recording and reporting data.” The response indicates that official data, which is already known to be deficient, might be used to evaluate progress. With the WHO strategy already in the implementation phase, there is an urgent need to establish a baseline, so that commitments made under the World Health Assembly 2018 resolution can be evaluated. [29 30] Development of guidelines, toolkits, and funding to support conduct of robust population-based data collection on snakebite (preferably by the One Health approach, as is being done in Nepal and Cameroon [18 31-34]) in high burden nations must be prioritised.

9.5. Implications of the thesis findings for practice, policy, and future research on snakebite in India

The results from the thesis provide several considerations for public health practitioners, policy makers, health system managers, and other advocates for snakebite in India, and other contextually similar places. Success in decreasing snakebite burden in India, is of critical importance to achieve the global target, since majority of deaths due to snakebite, are in India. [35]

In Section B of the thesis, I identify limitations in structural capacity of the primary healthcare system, and gaps in continuum of care in India (Chapter 4); and acquire insights for health systems resilience by studying the effect of COVID-19 and climate change (Chapter 5 and Chapter 6).

I used the WHO health systems building blocks [22] to design the domains of structural capacity (Chapter 4). The health systems building blocks framework, is ubiquitous in health systems research because of its obvious "simplicity and ability to provide a common language". [36] However, the health system is not just its building block. It is a complex interplay of interactions between the building blocks, the people within and outside it and in the context within which the system operates. [21] Health systems are dynamic, non-linear, path-dependent, self-organizing, tightly linked, counterintuitive, and most importantly governed by stakeholder feedback, and are resistant to change- like any other complex system. [21 37] This is a challenging arena, with almost no work on snakebite available. The work in the thesis just scratches the surface in terms of health systems strengthening for snakebite care. Nevertheless, it provides valuable insights for informing existing strategies and policies in India (and for other snakebite endemic

nations with weak health systems) and lays down the baseline for conducting more resource intensive work in this domain. In 2022, some policy and strategic plans to address snakebite in India came to fruition:

- State governments have appointed nodal officers after a notification to the same effect from the Union Ministry of Health and Family Welfare, Government of India. The process has been completed in October 2022, but details on terms of reference is not available publicly.
- Indian Council of Medical Research, the apex public medical research organisation, has launched two projects (both were envisaged in 2020, but activities postponed due to COVID-19):
    - ICMR project to build capacity of health workers (through periodic short term training programs), develop printed information education and counselling (IEC) material and analyse health facility data retrospectively.
    - ICMR National Task Force project to estimate the burden of snakebite. [38]
- The Mission Steering Group, the apex decision making body for strategy and implementation of the National Health Mission (NHM), in its 7th meeting held in September 2022 accepted the proposal from the Additional Secretary Health, Ministry of Health and Family Welfare, to initiate activities for prevention and control of snakebite within the NHM with an earmarked budget. The meeting minutes reveal acknowledgement in gaps of official data versus what is known from community estimates. It also identified the following programmatic activities:

- training of health professionals on snakebite management and emergency care,
- advocacy meetings,
- surveillance and monitoring, and
- information, education and community (IEC) activities (from existing budget).

This strategy of integrating snakebite activities into the existing broader initiatives of the National Health Mission, rather than developing a separate vertical program on snakebite is commendable since it integrates snakebite within the larger agenda of the Universal Health Coverage (UHC).[39]

However, at the policy and program level, the focus is very much on better understanding of burden, training healthcare workers and traditional IEC activities. It is in this backdrop, that the study assessing structural capacity and continuum of care (Chapter 4) gains relevance, despite the temporal limitation of the underlying data. I identify that poor physical infrastructure in health facilities, availability of health workers and poor health information systems as 'bottlenecks' in terms of structural capacity, in addition to snake anti-venom availability which is sub-optimal. I also identify that continuum of care is severely hampered due to poor connectivity from villages to primary health centres (PHC), and availability of functional transport system for referral from PHC to higher centres of care for management of complications. The analysis thus indicates that piece-meal approaches, like training health workers, although important, is unlikely to address the core health systems issues on snakebite care. The qualitative study (Section 5.4) although in a localised context from India, reaffirms the findings of the quantitative study (Section 5.3) in many ways and provides

further information on the "how" access to snakebite care is hampered. It identifies several factors for addressing snakebite care, including that the decision for preference of traditional care providers is not because of belief systems alone, but related to multiple health system factors. As such, community-based IEC activities or awareness programs alone are unlikely to lead to increased usage of formal health systems. The mapping of factors affecting snakebite care using the three-delay model [40] provides a visualisation of what needs to be addressed to improve access to snakebite care (related to COVID-19 containment measures or not). Physical access to health facility, and costs of transport for reaching formal health facility, was a key factor reported in the qualitative study too. In India, Emergency Response Service/ Patient Transport Service are officially in place but results of studies in Section B indicates significant gaps on this aspect. There is a need for developing a referral transport service model which is available, and affordable by communities affected by snakebite. Previous research in India shows that publicly-financed-privately-delivered patient transport system, had no effect on use of formal obstetric services, [41] but a government-funded-government- run model is efficient. [42] A large fleet of government financed and run ambulances, paired with an additional level of voluntary private vehicles, might be an effective sustainable model which needs to be explored and evaluated. [43]Such strengthening would improve access for all acute medical emergencies, not just snakebites.

While a strong health system is a necessary condition for a resilient one, it need not necessarily imply so. [44] Health systems resilience has been defined as "the ability to prepare for, manage (absorb, adapt and transform) and learn from shocks" [44] and stress. [45] The studies in the thesis (Chapter 5), explores evidence on how snakebite care was affected during health systems shocks due to COVID-19, and on possible stress

(predictable and enduring issues which affect health systems) that might happen due to changing burden of snakebite due to climate change (Chapter 6). The thesis does not cover how health systems can be more resilient for snakebite. This is an area of future work. It is known [46] that to prepare for, manage and learn from shocks and stress, health systems need to develop capacity for:

- trans-disciplinarity, i.e., combining and integrating different forms of information and knowledge,
- building and developing legitimate institutions that are acceptable and contextually relevant,
- anticipating and managing uncertainty,
- interdependence, i.e., effectively managing multiple and cross-scale dynamics.

I discuss each of the four aspects of health systems resilience subsequently.

The need for transdisciplinary approaches for reducing the snakebite burden is being increasingly recognised. [31 33 47-49] The importance of transdisciplinary research is also highlighted in the thesis: there is a need for studying human-environment-snake interface to better understand effect of COVID-19 containment measures (Chapter 5), and ; and undertaking multi-disciplinary modelling accounting for climate change, snake species distribution and human migration to understand change in burden snakebite due to climate change (Chapter 6). Transdisciplinary work on snakebite should also integrate concepts of health systems resilience. Overall, there is a need to develop a transdisciplinary framework, which enables practitioners and researchers from related disciplines to work together and have a shared understanding of the problem of snakebite. Such a framework can also enable practitioners and researchers to

visualise their role in the knowledge translation pathway, and the pathway through which their research or program contributes to addressing the snakebite burden.

The issue of legitimacy, which is relevant for resilience, has also come up in the context of global policy of snakebite (Chapter 3). In India, and for snakebite this would mean strategies and programs for snakebite care and enhancing health systems resilience being adaptable to diverse rural areas and in *Adivasi* (indigenous) people across the nation. Policies and strategies in India should be developed through representatives of all cadres of health workers, *Adivasi* people, and experts form different disciplines , not just clinicians and anti-venom researchers. There is a need for policy and social research in the larger arena of legitimacy with respect to health systems resilience too.. Additionally, implementation research to develop models for co-developing interventions which can be adapted locally for strengthening and developing resilience in health systems are also required.

An important part of anticipating and managing uncertainty is developing capacities for modelling and predictive systems on the impact of several types of stress and shock on different conditions including the burden of, and care delivery for, snakebite. Development of community-based programs for snakebite together with health systems strengthening (Chapter 5) might also improve resilience overall as it contributes to community resilience. A complex adaptive systems analysis of the response to Ebola outbreak in Northern Nigeria in Ebola, suggested addition of community engagement as a seventh block of health systems when focussing on resilience. [50] The analysis concluded that an integrated community engagement approach targeting barriers to first and second delay for emergency maternal health services, enabled establishment of sustainable community response system and promoted accountability of health

providers and managers. Our analysis, much simpler, and for snakebite, indicates similarly on the value of community-based programs for snakebite care. There is a need for more comprehensive studies on other aspects for anticipating and managing uncertainties for health systems overall, including for snakebite.

A comprehensive approach to snakebite requires acknowledging that the issue plays within a larger health system, which in turn is embedded within other complex systems. Issues of critical importance to snakebite care like health infrastructure, lack of, or weak patient transport systems / emergency services, availability of health care workers, affordability of snakebite treatment are all tied to a host of systems- economic, legal, political, social, and ecological. Proponents of snakebite in India are aware of the multitude of health systems challenges and the context around them. [51] However, initiatives continue to be typically restrictive and take a piece-meal approach. Research presented in the thesis contributes to the understanding of some of the larger systems issue which affect snakebite (Chapter 5). Snakebite proponents need to actively engage and make efforts to not only infuse and incorporate snakebite into the agenda for larger initiatives, such as UHC or *Adivasi* development, but also promote systems approach over vertical snakebite initiatives. Engaging with, and for, systems-wide reform would enable greater gains. As for example, training community health workers (called ASHA in India) for snakebite awareness and education, [52] would not reap any benefits, unless grievances of ASHA worker on regularisation, payments and overburdening is addressed. Similarly, snakebite proponents might advocate for regular independent commissioning of district level evaluation of patient transport systems/emergency services, followed by development of district level plans to ensure adequate density and dispersion of ambulances, which are free and available 24*7 (as recommended by

National Health Systems Resource Centre, a decade back [43]) , instead of focussing on transportation of snakebite victims alone. Social network analysis, to understand how social brokers engage with actors, within and outside the health systems, during times of crisis or build relationship to promote inter-sectoral work to manage health systems stress, [46 53 54] with a focus on snakebite might be considered.

9.6. Implications of the thesis findings for future intervention research on snakebite treatments

The research work reported in Section C contributes to increasing value and preventing research waste [55-58] for snakebite treatments by first evaluating the evidence base around snakebite at a systematic-review level and then filling a key gap related to outcome measurement.

In addition to providing modalities for fostering research on safe and effective snakebite treatment, Section C contributes to future intervention research on snakebite in South Asia through its methodological contributions. I identify the need for investment for high quality systematic reviews and meta-analysis of snakebite (Chapter 7). In the subsequent systematic review of outcomes, (Chapter 8) I confirm, that the gap is not just at the systematic review level, but also at the clinical trials level. I identify that there is need for high quality systematic reviews with meta-analysis, and controlled clinical trials, in the following domains:

- Interventions used during first aid for snakebite,
- Interventions for preventing adverse drug reactions,

- Interventions for management of wounds, bacterial infections and or swelling of the limbs,

- Interventions which aim to specifically address haematological manifestations of snakebite, and

- Interventions which aim to specifically address neurotoxic manifestations of snakebite.

To address the scarcity of clinical trials on snakebite, there is a need for fostering research capacity in endemic nations. There is also a need for qualitative research with trialists, health workers and trial participants to understand facilitators and barriers the conduct of controlled clinical trials for snakebite in endemic nations. Such research can inform establishment of snakebite-specific clinical trial networks in high-burden regions and contribute to quickly develop an evidence base for snakebite. Establishment of clinical trial networks has enabled research in other diseases. [59-63]

It is known that existing WHO guidelines on snakebite are not of adequate rigor, with recommendations not being informed by systematic reviews of evidence. [64] As per the WHO standards for guideline development, [65] guidelines should be informed by high quality systematic review with meta-analysis, GRADE tables (which provide information on certainty of evidence) and evidence-to-decision tables (to present practical information for formulation of recommendations) prior to development of any clinical practice guidelines. [65] However, it is not known when updated clinical practice guidelines on snakebite will be developed by WHO. In the absence of high-quality evidence-informed WHO guidelines, national governments of high burden nations,

should commission systematic reviews and develop high quality evidence-informed guidelines, which are in alignment with the WHO standards. [65]

Through the overview of systematic reviews (Chapter 7), I also identified the problem with respect to outcomes in intervention research on snakebite, including the lack of standardization, which prevents comparison and pooling for meta-analysis and evidence synthesis, and relevance of outcomes for decision making. [66] I contribute towards solving this problem through the development of a COS for intervention research on snakebite in South Asia (Chapter 8). In the future, there is, however, a need to work on strategies for fostering their uptake. Strategies for broader uptake of COS in the clinical trials ecosystem in South Asia is also required. Engagement strategies to promote uptake of COS for health conditions, where available, and developed as per acceptable standards, might be targeted towards:

- National and state level academic and professional organisations (medical associations and speciality associations of emergency medicine, primary care physicians/ family medicine, rural doctors) in South Asia.

- Indian Clinical Trial and Education Network (a network of Indian institutions to enable conduct of large multi-centric clinical trials by the Indian Council of Medical Research, Department of Health Research, Government of India).

- Key funders of clinical research in South Asia for mandatory use of COS for intervention research.

- Engagement to promote use of COS through journal editors (example, Indian Association of Medical Journal Editors), and ethics committees (example,

Forum for Ethical Review Committees in the Asian and Western Pacific Region).

9.7. Concluding summary

The findings of the thesis, contribute directly to “increasing partnership, coordination, and resourcing”, “health systems strengthening” and “ensuring safe effective treatment” pillars of the WHO strategy to address snakebite burden and has cross-cutting implications for all pillars of action, and to inform contextually relevant practice and policy at national, sub-national, and program level. The policy analysis documents the process of agenda-setting but more importantly, identifies challenges in sustained attention and action on snakebite. The evaluation of health systems contributes to establishing a baseline understanding of gaps in the Indian health system. The development of COS on snakebite contributes to fostering the evidence ecosystem for developing safe and effective treatments of snakebite in South Asia. Besides snakebite, the global policy analysis and core outcome set work contribute to broader methodological issues.

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“What we call the beginning is often the end

And to make and end is to make a beginning.

The end is where we start from..."

~ T.S. Eliot, English Poet (Little Gidding)