BMJ Open

Mapping evidence on the regulations affecting accessibility, availability and management of snake antivenom globally: a scoping review protocol

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To cite: Majeed R, Bester J, Kgarosi K, *et al*. Mapping evidence on the regulations affecting accessibility, availability and management of snake antivenom globally: a scoping review protocol. *BMJ Open* 2024;**14**:e086964. doi:10.1136/bmjopen-2024-086964

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-086964).

Received 28 March 2024
Accepted 21 November 2024

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ABSTRACT

Introduction Snakebite envenomation has been declared a neglected tropical disease by the WHO since 2017. The disease is endemic in affected areas due to the lack of availability and access to antivenom, despite it being the standard treatment for snakebites. This challenge is perpetuated by the shortcomings of the regulatory systems and policies governing the management of antivenoms. This study aims to map the evidence about regulations of snake antivenom globally and identify gaps in the literature. This protocol provides an overview of the methodology and analysis which will be used to conduct the scoping review.

Method and analysis The scoping review follows the guidelines from the Arksey and O'Malley framework for scoping reviews and will be reported using Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews. A search strategy was developed with assistance from a health sciences librarian, and the search was done using six relevant databases. The databases used are PubMed, SCOPUS, ProQuest Central, Africa Wide Web, Academic Search Output and Web of Science. Articles in the English language and between 2009 and 2023 were included. The search results were collated, duplicates were removed and results were exported to Rayyan (https://www.rayyan.ai/) for screening. The initial screening for titles and abstracts is currently in progress, and thereafter the second round of screening will be done for full texts. Data extraction will be done using Google Forms. The results of the review will be synthesised using quantitative and qualitative tools.

Ethics and dissemination This review will provide guidance for studies investigating regulatory gaps globally and inform future policies governing antivenom management. Ethics approval for the complete postgraduate project was obtained from the University of Pretoria Research Ethics Committee. The review will be published in a scientific journal, and findings will also be disseminated using conference presentations.

Trial registration This review has been registered on Open Science Framework (OSF): https://osf.io/54zja.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The review enlisted the assistance from an experienced health sciences librarian, and this collaboration allowed the development of a seamless and comprehensive search strategy.
⇒ The methodology of this review was adopted from the original framework by Arksey and O'Malley, and reporting will be done using Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews, contributing to the rigour of the study.
⇒ The inclusion criteria were limited to studies published between 2009 and 2023, when the policies governing snake antivenoms have existed prior to this time frame.
⇒ Due to the articles in English being an inclusion criterion, there could be an under-representation from the countries where research is published in other languages.
⇒ There are no evaluation tools being used to assess the quality and calibre of the articles chosen for data extraction.

INTRODUCTION

On contact, snakes inject venom into the victim's blood through its modified teeth known as fangs.[1] Snake venom is a complex biological secretion with a varied profile of toxins, and the damage caused to the victim ranges from local tissue injuries to fatal injuries.[1] The biochemical composition of snake venom varies, and usually contains proteins,[2 3] pro-inflammatory factors,[4] minerals and toxins (mycotoxins, cytotoxins, neurotoxins and cardiotoxins).[5]

The clinical symptoms of a snakebite can differ depending on snake species, the composition of venom, bite-size and physiological features of the victim such as age and pre-existing health conditions.[4] Common signs and symptoms include myonecrosis, compromised blood vessel integrity, extravasation, skin, inflammation and pain.[6] Death usually occurs due to shock and organ failure.[4]

Antivenom is the gold standard of therapy for the treatment of snakebite envenomation, backed up by 120 years of history, research

and scientific contributions that led to the development of this life-saving medicine.[7] Albert Calmette has been credited as the founder of antivenom. While researching vaccines for rabies and smallpox in Saigon, he used cobra venom to immunise rabbits, laying a foundation to produce antivenoms in immunised animals.[8] The first successful antivenom was created against *Naja naja*, by administering increasing doses of snake venom in horses at regular intervals.[9] The development of commercial antivenom was further realised by Vital Brazil, who worked on specificity and large-scale production of antivenom.[9 10] Following in Calmette and Brazil's footsteps, other regions acted and began to produce polyclonal antibodies in immunised horses, rabbits, goats and sheep.[11]

Despite the existence of a standard and effective treatment, snakebites remain a significant challenge. The burden of snakebite envenomation falls greatest in Asia, sub-Saharan Africa, South America and Oceania.[1] Since 2023, the cases of snakebites globally have risen to 2.7 million, with 130 000 deaths and 400 000 disabilities.[12] In 2009, snakebite envenomation was first considered a neglected tropical disease by the WHO, which was later removed from the list in 2013. In 2017, the WHO brought it back to the list.[1]

The high mortality from snakebites is seen in low- and middle-income countries (LMICs), more specifically rural communities that are unaware of snakebites and the availability of treatment.[13 14] There is a delay in life-saving treatment due to a lack of education programmes and low rates of literacy.[13] Victims from many destitute and underprivileged areas maintain a mistrust of modern medication and rely heavily on complementary and alternative medicines,[15] especially traditional healers.[16] The lack of awareness regarding snakebite prevention and treatment, poverty, long-distanced healthcare facilities and negative attitude towards antivenom adds to the inaccessibility of treatment.[17]

There is an epidemiological gap between actual morbidity and mortality and the data generated, which downplays the extent of the problem.[18] Poor reporting practices, inadequate report keeping, inaccurate data, reluctance to report and lack of access to healthcare in affected areas exacerbate the problem.[12 19] There is an alarming lack of attention given to snakebites from the healthcare sector. Research funds and finance allocation to antivenom development are scarce.[20] Hence, this has led to overall neglect from the policymakers and health agendas.[20] The meagre resources attributed to the development of snake antivenom are composite consequences of erroneous data and neglect.[20]

Antivenom demand transcends its supply.[21 22] There is a lack of safe, effective and affordable products.[14 23] While data plays a role in undermining manufacturing needs, there is also no budget allocated to the industry.[18] In fact, only a few laboratories manufacture antivenom globally.[18] The production itself is a complex process, involving snake breeding, venom collection, purification and more.[18] The complicated procedure, inadequate resource distribution, privatisation of manufacturing companies, shutdown of laboratories and lack of industrial and pharmaceutical infrastructure have led to serious implications regarding antivenom access in affected countries. Many have now turned to imports.[18 23]

The production of antivenom globally is restricted by regulatory oversight and neglect.[14] Existing products are governed by poor regulatory frameworks, especially in LMICs, hence compromising the quality and safety of antivenom.[14] The demand and supply equation for antivenom can be balanced by contributions and actions of these regulatory organisations towards existing manufacturers, implementation of sound policies and production frameworks.[14 15]

Since there is no investment, costs are high.[24] Even if there is availability of antivenom, most victims are from a rural community and are unable to afford the treatment.[14 24] The WHO attributes the lack of availability, access and poor management of snake antivenoms to inadequate regulatory frameworks.[25] These frameworks provide guidelines, which extend from the initiation of antivenom production until the final product reaches the patient.[25] These parameters include preclinical testing and validation,[26] registration of antivenom,[27] manufacturing practices (including animal breeding and husbandry), formulation and dosage, quality control, product standardisation, reproducibility of protocols, safety and efficacy,[18] stability, labelling and package insert, cost analysis, distribution and procurement, prescribing and dispensing,[27] reporting of adverse reactions,[15] allocation of resources, research and development,[14] regulations for imports[17] and post-market surveillance.[25]

Snakebite envenoming is well documented, but despite being identified as a neglected tropical disease, it remains ignored and no action has been taken to improve the situation.[23] The lack of long-term funding in healthcare, commercial and economic factors all contribute to the crisis. Despite the proven effectiveness of antivenom, the burden of the disease falls disproportionately on communities that cannot access it.[23] There is a need for sound solutions and collaboration between health officials and policymakers.[28]

Despite the WHO providing comprehensive international guidelines on the production, regulation and control of antivenom, the regulatory bodies have failed to adopt them.[16] The WHO has also laid out a roadmap, aimed to halve the burden of snakebite-associated mortality by 2030.[13] The success of this endeavour requires multidisciplinary approaches involving all stakeholders including government organisations and bodies governing antivenom access.[13] Hence, policymakers are instrumental in the improvement of healthcare systems and increasing the affordability of antivenom, inevitably reducing the snakebite burden.[13]

To find feasible solutions geared towards solving the challenge of antivenom access, there is a need to identify the problems plaguing the regulatory systems in regions

burdened by snakebites. This scoping review will allow us to explore the breadth of existing evidence pertaining to the regulations that guide the management of snake antivenom. By scoping the literature, we will be able to discover the systems that work effectively and systems that fail to provide a safe and adequate amount of antivenom to populations that need it direly. We will also be able to compare the regulations governing access to antivenom in LMICs and high-income countries, endemic and non-endemic countries and map out the overall strengths and weaknesses of each. By mapping the evidence in this context, we can then identify the gaps in regulations and guide future policymaking and research.

This scoping review is a component of a postgraduate study, and results will be used in other stages which are primarily focused on sub-Saharan Africa.

METHODS AND ANALYSIS

The scoping review will be used to collect descriptive data on regulations of snake antivenom globally and identify deficiencies thereof. It will allow the researchers to summarise existing literature in this context, explore the regulatory themes and identify gaps in the systems governing access to antivenom to patients.

An evidence synthesis is useful for summarising broad research questions by conducting in-depth literature review.[29] A scoping review identifies gaps in existing literature, maps out key concepts and theories and advises future research.[30] It is a preferred review for qualitative studies that aim to explore complex and heterogeneous topics.[29]

This scoping review has been registered at the Open Science Framework (OSF) and can be found at the following web address: https://osf.io/54zja. The review process was started in October 2023, and the final manuscript is intended to be submitted by March-April 2025.

The review will be performed by three independent reviewers using the original framework for scoping reviews developed by Arksey and O'Malley in 2005.[31] Modifications and improvements from the Joanna Briggs Institute (JBI) guidelines for scoping reviews will be incorporated to provide a workable approach for this context.[32] The framework from Arksey and O'Malley employs a five-stage approach which will be used to perform the review[31]:

- Identification of research question
- Identifying relevant studies
- Study selection
- Charting the data
- Collating, summarising and reporting the results

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) will provide guidance for reporting the results of this scoping review.[33] This will support the adoption of the findings and allow methodological transparency.

Identification of the research question

The starting point of any scientific investigation is a research question. To establish a search strategy, a broad research question is required, which can cover the extent of literature widely.[31] According to the JBI guidelines,[32] a research question is crucial for providing structure to the research study, defining the inclusion and exclusion criteria, and making the overall search effective.

For this study, the research question is:

'What are the regulatory aspects affecting the availability and access of registered snake antivenom products globally?'

Identifying relevant studies

The search strategy for this scoping review was carefully developed as shown in table 1. A population, concept and context (PCC) framework was used to define eligibility criteria and guide the search strategy. The PCC mnemonic promotes consistency between the title, review question and inclusion criteria.[29] It provides a clear approach to creating the search strategy by implementing the focus of the research.[29]

As indicated in table 1, studies on the regulatory aspects of registered snake antivenom products were included. For this study, 'regulatory aspects' are defined as policies

Table 1 The PCC used to develop the search strategy

		Inclusion	Exclusion
Population	Snake antivenom	Snake antivenoms 'in use'. In use: scheduled products, antivenoms registered currently or historically, such as SAVP polyvalent, monovalent and global products	► Spider antivenom ► Scorpion antivenom ► Experimental antivenom ► Unapproved products
Concept	Accessibility	► Regulations (this involves regulatory systems and frameworks) ► Manufacturing ► Quality control ► Procurement ► Supply chain (this involves availability, transport, procurement, storage) ► Prescribing and dispensing	Clinical guidelines related to snakebite treatment
Context	Global	Global	

and structures associated with snake antivenom, from the manufacturing stage, until the product reaches the user.

Studies between the periods of 2009–2023 were used. The WHO first added snakebite envenomation as a neglected tropical disease in 2009. It was later removed from the list and then reinstated in category A neglected tropical disease (NTD) in 2017.[34 35] The choice of this time frame will allow reviewers to explore possible changes and trends in snake antivenom regulations during its removal and then eventual readmission as a priority disease. Only the literature published in the English language was considered, due to lack of translation resources. Peer-reviewed articles published in scientific journals were included, to maintain the quality of the scoping review.

Studies published before 2009 and in a language other than English were not considered. Additionally, correspondence, opinions, conference proceedings and clinical studies on registered or prospective products were excluded from the database searches.

The research question was divided into three themes: snake, antivenom and regulations. These were used to drive the initial broad search. A pilot search on SCOPUS was conducted to mine keywords, using the language and year filters. Title and abstracts were screened for 30 articles, nine publications were selected and the full texts were used to determine relevant keywords. With the assistance of the librarian, a comprehensive search strategy was developed on PubMed using controlled vocabulary, keywords, Medical Subject Headings terms, truncations and Boolean operators (AND) and (OR). The search strategy was tested and finalised. It was then modified and tailored to other databases, depending on syntax requirements.

After the pilot search, practice searches and determination of key terms, the following databases were used to scope the research question; PubMed, SCOPUS, ProQuest Central, Africa Wide Web (via EBSCO), Academic Search Output (via EBSCO) and Web of Science (Core Collection). The complete search strategy can be found in online supplemental table 1).

An initial search was conducted using the above search strategy, search results were imported to EndNote and duplicates were removed. After duplicate removal, 4075 articles were obtained for screening.

The search will be rerun before the completion of the scoping review.

Study selection

The screening is currently underway. The research team is using Rayyan, an online review tool which allows several reviewers to work remotely and form a selection from the search results. This process is divided into two parts:

- Screening 1: title and abstracts
- Screening 2: full texts

A screening brief was created to guide the process and maintain congruence between three independent reviewers. The PCC (table 1) was used to develop an eligibility framework for screeners (table 2). The two tools were used in conjunction to drive the selection process.

The first round of screening consists of articles on Rayyan that are categorised as Include, Exclude and Maybe. All exclusions are supported by one reason, chosen from the following list:

- Wrong language
- Wrong publication type
- Wrong date
- Wrong concept
- Wrong population

The second screening will entail reading full-text articles. The PCC (table 1) and inclusion criteria will apply to the second screening as well.

Any conflicts between the three reviewers will be resolved by discussion, and a consensus will be reached. After the second screening is concluded, Cohen's kappa statistics will be used to determine the degree of agreement between the reviewers. The selection will be reported using the PRISMA flow diagram to provide an outline of studies screened and selected in each stage.

Table 2 The inclusion and exclusion questions developed from the PCC framework

Inclusion	► Does this article present evidence published in the time 2009–2023? ► Does this article present evidence in the English language?
Population	
	► Does this article present evidence on snake antivenom currently in use?
Concept	
	► Does this article present evidence on regulations of antivenom? ► Does this article present evidence on the manufacturing of antivenom? ► Does this article present evidence on the procurement of antivenom? ► Does this article present evidence on the quality control of antivenom? ► Does this article present evidence on the accessibility of antivenom? ► Does this article present evidence on the availability of antivenom? ► Does this article present evidence on the transport of antivenom? ► Does this article present evidence on the storage of antivenom? ► Does this article present evidence on prescribing or dispensing of antivenom?

Table 3 Data will be extracted from selected articles using Google Forms.

Study characteristics	Subcategories
Author and date	
Article title	
Aim	
Key findings	
Study design	
Country	
Income level	► Low- and middle-income ► High-income
Geographic setting	► Rural ► Urban ► Semi-urban
Antivenom in use	
Accessibility indicator	► Articles presenting evidence on **regulatory systems or framework** of antivenom. ► Articles presenting evidence on **manufacturing** of antivenom. ► Articles presenting evidence on **procurement** of antivenom. ► Articles presenting evidence on **quality control** of antivenom. ► Articles presenting evidence on **accessibility or availability** of antivenom. ► Articles presenting evidence on **transport** of antivenom. ► Articles presenting evidence on **storage** of antivenom. ► Articles presenting evidence on **prescribing or dispensing** of antivenom.
Conclusions	

Data charting

The full texts of articles selected from the second screening will be used for extracting data. We will use Google Forms for this process, and a preliminary version can be seen in table 3.

The form in table 3 can be modified and more categories may be added, depending on the studies selected. On the completion of the form, the output will be downloaded as an Excel spreadsheet, and relevant adjustments will be made to the document to support utility.

The independent reviewers will participate in a pilot data extraction activity on 5–10 articles, using the data charting form. Daudt *et al*[36] emphasises the importance of this exercise. It is a valuable tool to ensure consistency between reviewers and the functionality of the data charting form. The data charting trial may result in the emergence of new categories in the form and improve its overall application.

Collating, summarising and reporting the results

After data extraction, the research team will discuss the findings and do a thematic analysis. This will involve an overview of study characteristics (specially the country of publication) and regulatory characteristics governing access of snake antivenoms. The reviewers will employ quantitative and qualitative tools to report results; this includes descriptive statistics and narrative analysis. Results will be presented in forms of tables, graphs, flow diagrams and numerical data where appropriate.

Quantitively, the reviewers expect to present data on the number of policy-related publications from the various regions globally, in line with the incidence of snakebites, as well as the number of regulatory aspects explored in the selected publications. The results will further provide a map of global regulations of snake antivenom, which will allow the research team to identify gaps. The regulations explored in the review will be used to draw comparisons between LMIC and developed countries and endemic and non-endemic countries.

Study status

The scoping review is currently in progress. The team has successfully developed the search strategy, completed the search across the selected databases and completed the first round of screening.

ETHICS AND DISSEMINATION

Due to the qualitative nature of the scoping review, ethics approval is not required. This review is a component of a postgraduate study and ethics approval which was obtained from the University of Pretoria Research Ethics Committee. The review will be published in a peer-reviewed journal, and research will be presented in conferences and other scientific platforms.

Acknowledgements We would like to thank the University of Pretoria Health Sciences Library for their assistance and support as well as Professor Tivani Mashamba-Thompson for her guidance.

Contributors The team of four authors contributed to the development of the protocol. The conceptualisation of this research was led by MS. RM, MS and JB worked on the methodology, research question, eligibility framework and manuscript write-up. KK and RM developed the search strategy, conducted a

preliminary search, tested key terms and conducted a final search across the databases. MS and JB played a supervisory role and provided editorial feedback on the final manuscript. RM is the guarantor of the article.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/disclosure-of-interest/http://www.icmje.org/disclosure-of-interest/ and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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