



SYSTEMATIC REVIEW

# The role of antimicrobial prophylaxis in the management of snakebite: a systematic review

[version 1; peer review: 2 approved, 1 approved with reservations]

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## Abstract

### Background

Snakebite, a neglected tropical disease disproportionately affecting lower-income countries, is a significant cause of morbidity and mortality worldwide. Local toxicity and necrosis may result in secondary bacterial infection of bite sites. Despite most guidelines not recommending prophylactic antimicrobials, their use is common in practise. This review aims to systematically assess literature around the use of prophylactic use of antimicrobials in snakebite. We also aim to assess the incidence of secondary infections, types of antimicrobials used, and the aetiology of infections arising from snakebite.

### Methods

Systematic database searches for studies assessing prophylactic antimicrobial use undertaken. Data was assessed by two reviewers and extracted using a standardised proforma. Included studies were assessed for risk of bias and data extracted narratively. The protocol was prospectively registered on PROSPERO database (CRD42023430752).

### Results

492 studies were screened. Four met the inclusion criteria, totaling 696 patients across three countries. No study found a statistically significant benefit for the use of antibiotic prophylaxis, with no effect

## Open Peer Review

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on the number or severity of adverse incidents. There were 114 adverse incidences related to secondary infection, with nineteen positive cultures.

## Conclusions

This review finds little evidence pertaining to the use of antimicrobial prophylaxis. Studies were highly heterogenous with incomplete reporting of standardised processes. Bacteria isolated supports existing observational data implicating bacteria found in snake oral flora (e.g. *M. morgani* and *Enterococcus* spp). This is an important consideration when deciding empirical antimicrobial regimens for suspected superadded infection. International consensus is required to define infection following snakebite and further high-quality research is required to draw definitive conclusions regarding antimicrobial prophylaxis.

## Keywords

Snakebite, envenoming, bacterial infection, antibiotic, antimicrobial, prophylaxis

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## Introduction

Snakebite is classed as a neglected tropical disease (NTD), estimated to cause 81,000–138,000 deaths every year and leaving 400,000 – 2 million surviving victims<sup>1–3</sup>. Low- and middle-income countries shoulder 95% of all cases, with rural areas particularly at risk (commensurate to human interaction and encroachment onto snake habitats)<sup>4</sup>. Without prompt antivenom administration, patients are often left with permanent physical disfigurement: long term disabilities such as amputations, contractures and chronic ulceration are well documented. These also carry a significant socioeconomic impact given the predominance of bites in younger people<sup>5</sup>.

Snake venom is a complex mixture of endo- and polypeptides, metalloproteinases, phospholipases, and endogenous autotoxins (such as histamine, 5-hydroxytryptamine and kinins) and exhibits considerable inter- and intra-species variation<sup>6,7</sup>. While snakebites are known for neurotoxic or coagulopathic sequelae, bite-adjacent tissue damage is the leading cause of morbidity. Myo- and cytotoxins cause local tissue necrosis, exacerbated by tissue ischaemia from local thrombosis<sup>6</sup>. Treatment methods such as tourniquet application can worsen this local toxicity by concentrating the venom in the affected limb<sup>8</sup>.

Distinguishing venom induced cytotoxicity from secondary bacterial infection in bite-adjacent soft tissue is challenging with many clinical features present for both conditions; for example, pain, induration, lymphadenitis and elevated biochemical markers (such as total white cell count and C-reactive protein). Given this diagnostic challenge, it is unsurprising the reported incidence of snakebite infection in literature varies widely (from 0–94%); In one systematic review and meta-analysis of snakebite infection, aggregated prevalence of infection following snakebite was 27.0%, with high heterogeneity ( $I^2 = 99.7%$ )<sup>9</sup>. The lack of accepted case definitions further complicates the identification and comparison of snakebite infection.

The most common pathogens to cause secondary infections post-bite (isolated from wound, abscess or blood cultures) are *Morganella morganii*, *Enterococcus faecalis*, *Staphylococcus aureus*, *Proteus* spp, *Klebsiella* spp, *Aeromonas hydrophilla* and *Pseudomonas aeruginosa*<sup>8,10</sup>. Although most of these pathogens are atypical causes of skin and soft tissue infections, this closely correlates with the oral microbiota of snakes demonstrated in observational studies<sup>11,12</sup>.

In recognition of the unique challenges of diagnosing snakebite associated infection, the World Health Organisation (WHO) recommends antimicrobial prophylaxis in snakebite patients in specific circumstances<sup>13</sup>. Despite some variations national snakebite guidelines are broadly in line with this WHO guidance, noting routine antimicrobial prophylaxis following snakebite is unnecessary<sup>14–16</sup>. Given the diversity in culpable snake species, challenges with microbiological culture and paucity in clinical research, the WHO and national guidelines are largely reliant on expert opinion rather than evidence<sup>7,17</sup>. In practice however, antimicrobials are much more commonly prescribed as

prophylaxis and in some circumstances, administered to all victims of snakebite<sup>18,19</sup>.

Against the backdrop of increasing antimicrobial resistance, the indication for prophylactic antimicrobials is becoming increasingly scrutinized. Antimicrobial resistance in pathogens found in snake oral flora is common including commonly used antimicrobials such as amoxicillin-clavulanate (Co-amoxiclav) and 3rd generation cephalosporins<sup>20,21</sup>. Furthermore, isolates cultured from snakebite wounds and abscesses have been identified as carrying emerging antimicrobial resistance mechanisms- including extended spectrum beta lactamases and carbapenemases<sup>22</sup>.

This systematic review aims to assess available literature around the use of antimicrobial prophylaxis in snakebite. It aims to assess the incidence of secondary infection, the rates and types of antimicrobial prophylaxis used, and the microbiological aetiology of infections arising from snakebites.

## Methods

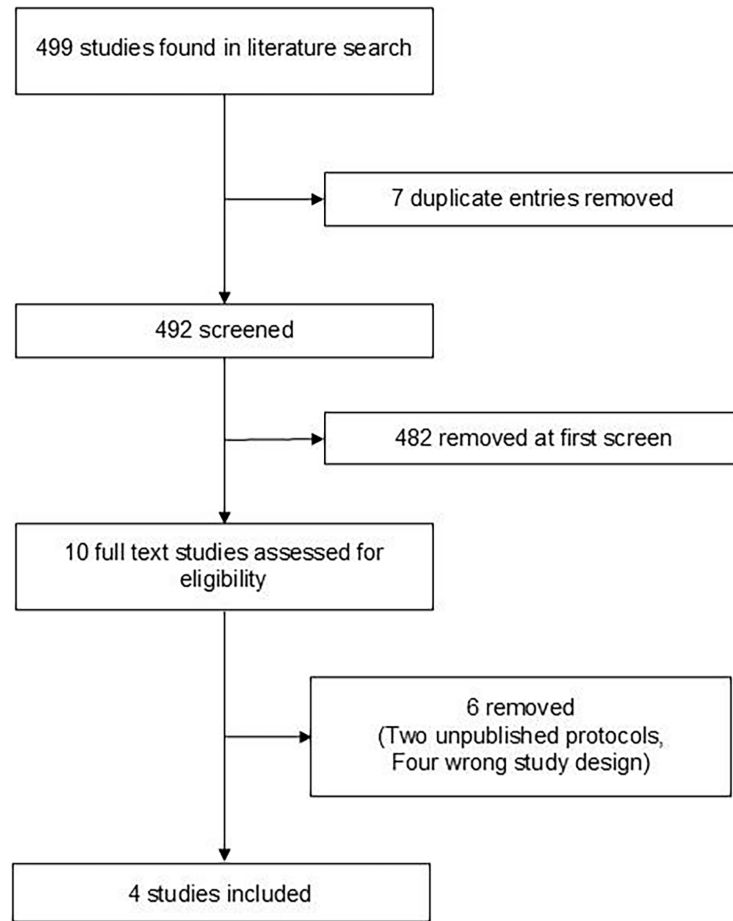
The following bibliographic databases and trial registries were searched by an information specialist (EH) for studies, published from database inception to the search date, to answer the review question: MEDLINE, Embase, and Global Health (via Ovid SP); Scopus; Web of Science Core Collection; WHO Global Index Medicus; the Cochrane Central Register of Controlled Trials; clinicaltrials.gov; and the WHO ICTRP. The databases were searched using relevant thesaurus terms as well as free text terms and synonyms to search the title, abstract or keyword fields, with no limits applied beyond a filter for the study type. Highly sensitive search strategies designed by Cochrane were used to search Ovid MEDLINE and Ovid Embase<sup>23</sup>. The full search strategies can be found in Extended data 1 (online repository)<sup>24</sup>. All references were exported to Covidence systematic review tool.

## Inclusion criteria

The review's inclusion criteria, methodology and outcomes were prospectively registered to the online systematic review platform PROSPERO. Only randomised control trials in humans that compared antimicrobial prophylaxis with placebo following snakebite envenoming were included for review. There were no restrictions on the trial participants (including age, gender, ethnicity, location or health status) or date of publication. Studies were required to have pre-specified their criteria for the diagnosis of infection. Studies were excluded if their full text could not be found.

## Study selection, quality and data extraction

All studies identified were deduplicated and collated using the automated functionality of an online systematic review manager<sup>25</sup>. Each entry was reviewed independently by two reviewers (SM and AB) to determine whether it met the inclusion criteria. Discrepancies in the two reviews were arbitrated by an independent third reviewer (TL). [Figure 1](#) details the PRISMA diagram for the search. Data was extracted using standardised, pre-designed proformas. Included papers were



**Figure 1.** PRISMA diagram of literature search.

assessed for risk of bias using the Revised Cochrane risk-of-bias method (RoB 2)<sup>26</sup>.

## Results

499 articles were screened using the methodology above; of these, 7 were duplicates and were manually removed. 482 entries were unanimously removed on first screening of title and abstract; of the remaining ten, six were removed after full-text screening (two being protocols of unpublished trials and four being of the wrong study design). Four papers met the inclusion criteria. Search outcomes can be found in extended data 2<sup>24,27–30</sup>. Given the search outcome, data is presented narratively.

The four studies were conducted in three countries (Brazil, Ecuador and Sri Lanka). Two studies<sup>27,28</sup>, both in Brazil, exclusively target *Bothrops* (n= 437). Of these, 187 were species-confirmed via enzyme immunoassay, 91 were identified as *B. jararaca* (via physical confirmation) and 160 were a clinical diagnosis. One study assumed all bites to be from Pit vipers (family *Viperidae*, subfamily *Crotalidae*) based on local epidemiology<sup>29</sup>. The final study made no attempt to speciate the snakes in question but does note the four commonest snakes

in their region<sup>30</sup>. The studies included a total of 696 patients: 343 receiving antimicrobial prophylaxis and 353 receiving placebo (or no treatment). The choice, route and duration of prophylactic antimicrobials varied amongst the four included studies. 114 adverse incidents (AI) relating to secondary infection (cellulitis and abscess formation) were recorded; 54 in intervention groups and 60 in control groups. Relevant findings from the included articles are compared in [Table 1](#).

None of these studies found a statistically significant benefit in the use of prophylactic antimicrobials following a snake-bite injury, with their use having no effect on the number or severity of AI's related to infection. There was considerable difference in the incidence of secondary infection across the studies, ranging from 7.9 to 39.6% (one study's reporting methods made calculating infection incidence impossible)<sup>30</sup>. Each study used their own predefined definition of secondary infection.

## Microbiological aetiology

Nineteen positive bacterial cultures (eight from intervention groups, five from control groups and six not disclosed) were

**Table 1. Relevant findings from research included in review.**

First author, year	Sachett, 2017	Jorge, 2004	Kerrigan, 1997	Kularatne, 1997
<b>Country</b>	Brazil	Brazil	Ecuador	Sri Lanka
<b>Trial participants</b>	187 (93 intervention, 94 control)	251 (122 intervention, 129 control)	114 (59 intervention, 55 control)	144 (69 intervention, 75 control)
<b>Antimicrobial intervention</b>	Oral amoxicillin clavulanate 875/125mg, twice daily, seven days	Oral chloramphenicol 500mg, four times a day, five days	IV gentamicin 1mg/kg, three times daily AND IV chloramphenicol 12mg/kg, four times a day, 24 hours	IV benzylpenicillin 2 megaunits, four times a day AND IV metronidazole 500mg, three times a day, five days
<b>Snake species and number identified</b>	<i>Bothrops</i> spp.	<i>Bothrops</i> spp.	Crotalidae	105 'viper', 39 'others'
<b>Method of snake identification</b>	Enzyme immunoassay	91 via physical specimen, 160 on toxidrome	43 identified as <i>Bothrops</i> spp (method not documented). Remaining cases not specified.	Not documented
<b>Adverse incidents related to infection</b>	Cellulitis x64 (28 intervention, 36 control) abscesses x29 (14 intervention, 15 control), in total 74 patients	12 abscesses (6 intervention, 6 control)	9 abscesses (6 intervention, 3 control)	No AIs from infective causes documented
<b>Microbiologically confirmed infections</b>	6	2	11	Not assessed
<b>Bacteria isolated &amp; breakdown by trial group</b>	<i>M.morganii</i> (5), <i>S.aureus</i> (1). Trial group breakdown not documented.	Intervention group: <i>E.coli</i> (1). Control group: <i>M.morganii</i> (1)	Intervention group: <i>E.coli</i> (3), <i>S.aureus</i> (3), <i>Klebsiella</i> spp (1). Control group: <i>Klebsiella</i> spp (1), <i>Enterobacter</i> spp (1), <i>Proteus</i> spp (1), <i>S.aureus</i> (1)	NA
<b>Outcome: benefit of prophylactic antimicrobials</b>	No benefit	No benefit	No benefit	No benefit

AI: Adverse incidents; NA: not applicable.

reported from all 695 participants. One study did not assess microbiological aetiology<sup>30</sup>, and another used aerobic culture only<sup>29</sup>. *M. morganii* was the most frequently identified bacterial pathogen (n=7), followed by *E. coli* (n=4) and *S. aureus* (n=4). Two papers reported bacterial susceptibility data<sup>27,29</sup>.

#### Test of bias (RoB-2)

Two were found to have low risk and two were found to have 'some concerns' of bias (Table 2): One provided no information on their allocation sequence or document a pre-specified analysis plan for their findings (domains 1 & 5)<sup>30</sup>, and the other did not note their data analysis plan (domain 5)<sup>29</sup>. Two studies performed prospective power calculations to estimate sample size<sup>27,30</sup>, of which one study recruited sufficient participants according to this calculation<sup>27</sup>.

#### Discussion

This systematic analysis finds little peer-reviewed evidence concerning the efficacy or utility of routine administration of antimicrobial prophylaxis in snakebite envenomation. All included articles conclude there is no benefit in prophylaxis preventing secondary bacterial infections. Two of the included articles have concerns over risk of bias and there is considerable heterogeneity (including the clinical setting, responsible snake species and definition of snakebite) making them unsuitable for meta-analysis. This is an important finding given the recommendations for prophylaxis by multiple international guidelines. This conclusion is further supported by a recent observational study of rattlesnake (*Crotalus* spp) envenoming in Arizona, USA which identified snakebite associated infection in 20 of 2059 (0.97%) incidences of envenoming<sup>31</sup>.

**Table 2. Summary of Risk-Of-Bias (ROB-2) analysis of articles included in review<sup>25</sup>.**

Study	1. Randomisation process	2. Deviations from intended intervention	3. Missing outcome data	4. Measurement of the outcome	5. Bias in the selection of the reported results	Overall risk of bias
Jorge	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Sachett	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kerrigan	Low risk	Low risk	Low risk	Low risk	Some concerns <sup>1</sup>	Some concerns (domain 5)
Kularantne	Some concerns <sup>2</sup>	Low risk	Low risk	Low risk	Some concerns <sup>1</sup>	Some concerns (domains 1&5)

<sup>1</sup> No information recorded regarding randomisation or concealment of allocation sequence.

<sup>2</sup> No information regarding a pre-specified analysis plan for final data (which should be finalised before unblinding).

Antimicrobial choice is important and must ensure adequate broad-spectrum coverage; we note little consensus on the drugs used here. The antimicrobials used in these four studies (chloramphenicol, co-amoxiclav, combination gentamicin/chloramphenicol and combination benzylpenicillin/metronidazole) were likely selected on the basis of their relative broad-spectrum gram positive, gram negative and anaerobic activity; however, Sachett *et al.* notes the poor efficacy of co-amoxiclav in preventing secondary infections<sup>27</sup>. Although Kerrigan *et al.* notes all gram-negative rods and gram-positive cocci isolated are sensitive to gentamicin<sup>29</sup>, some guidelines advocate against the use of aminoglycosides due to risk of nephrotoxicity or potential exacerbation of the effects of neurotoxic envenoming<sup>16</sup>. Coupled with wider concerns around antimicrobial administration- cost, side-effect risk, and importantly risk of antimicrobial resistance- their routine use becomes harder to justify.

The limited reporting of wound sampling and laboratory procedures makes interpretation difficult and highlights the need for further dedicated research in the area. In one study cultures were only taken from patients with an abscess and only presenting to one study site (which enrolled just 12 of the 251 patients in the study)<sup>28</sup>. The other studies do not report their procedures for taking cultures (or how many were taken), making it impossible to calculate accurate positivity rates. An absence of anaerobic culture capability is also likely to undermine reporting incidence<sup>29</sup> - which is particularly pertinent given the polymicrobial nature of animal-bite associated infections<sup>32</sup>. Future studies should include a clear clinical case definition, document robust sampling methodology and operational procedures for both aerobic and anaerobic cultures.

The bacterial isolates reported in these studies were in keeping with other reports of snakebite associated infection<sup>7</sup>. The lack of anaerobic bacteria identified in the included studies may reflect methodological errors of the included studies.

Although isolates cultured from abscesses and wounds include bacteria from animal oral flora (e.g. *Morganella morganii*), it is uncertain their relative significance in infection pathogenesis<sup>33</sup>.

There are limitations to the evidence found by this review. The search methodology limited included studies to English-language texts only, risking missing research not reported in English. The heterogeneity of included studies also suggests a wider lack of term definitions, possibly obfuscating systematic search findings. We are also unable to draw broader conclusions about snakebite from the studies reported here. Only one subfamily of vipers – Crotalinae – have been reported, with no other species positively identified. The included data therefore excludes snake genera such as *Naja* spp. that is more commonly associated with snakebite associated infection. Furthermore, snake oral flora is unique, containing bacterial organisms not commonly observed in routine soft tissue infections (coupled with a mechanism for deep inoculation and concomitant tissue inflammation); more research is required around both species and geography. Consensus in case definition for snakebite associated infection, and comprehensive yet pragmatic laboratory procedures, would increase the external validity of future studies. Details of polymicrobial infections and antimicrobial susceptibility patterns to aid empirical antimicrobial decision making is increasingly important and should be considered in future research design.

While this review was being prepared for publication, a further non-inferiority trial was published comparing routine vs. clinically directed use of co-amoxiclav in snakebite in southern India<sup>34</sup>. The study randomized 66 patients, with those in the clinically directed arm (n=34) being assessed daily and receiving antimicrobials if they were found to have any of several pre-determined clinical or biochemical complications. It speciated 26 (39.4%) bites; 21 as Russell's viper and 5 as

saw-scaled vipers. Importantly, these are both from a subfamily of vipers (Viperinae) not described in the studies included in this review.

The trial was stopped prematurely due to the Covid-19 pandemic. Non-inferiority of clinically directed antibiotics use was not demonstrated. Total antibiotics consumption was significantly lower in the directed arm vs the prophylactic arm. There was one death recorded in each group. This research denotes the importance of the subject, as well as being a topic worthy of further investigation worldwide (this is the first research, to our knowledge, undertaken in India). It also adds to the body of research concluding there is no evidence in the use of prophylactic antimicrobials.

## Conclusion

We find a paucity of quality research concerning the role of antimicrobial prophylaxis in snakebite. Of the evidence found, there is no evidence for the routine administration of antimicrobial prophylaxis following snakebite at reducing bacterial superinfection. Coupled with the global efforts to reduce antimicrobial administration (and its effects on antimicrobial sensitivity), the routine administration of prophylactic antimicrobials following snakebite should not be recommended. More research is required to build up a more inclusive picture of secondary infection rates, and if antimicrobial prophylaxis is effective in reducing this number. While such research is challenging given the wide heterogeneity of both snake species and their oral microbiota, ongoing and recently published research is a signal that this topic remains worthy of both investment and investigation.

## Transparency declaration

The authors affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained. The authors declare no conflicts of interest.

## Data availability statement

Zenodo: Extended data: The role of antimicrobial prophylaxis in the treatment of snakebite: a systematic review, <https://doi.org/10.5281/zenodo.17171619> (Moody 2025).

This project contains the following underlying data:

- Extended\_data\_1 (search strategies)
- Extended\_data\_2 (Search outcome data)
- PRISMA\_2020\_Main\_Checklist (PRISMA checklist)
- PRISMA\_2020\_Abstract\_Checklist (PRISMA abstract checklist).

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

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  34. Gautam A, Mayalil BI, Bhardwaj A, *et al.*: **Clinically directed initiation versus routine use of amoxicillin-clavulanate and the risk of complications among patients with haemotoxic snakebite envenomation treated at a teaching hospital in southern India: a randomised, non-inferiority trial.** *BMJ Open*. 2025; **15**(6): e094409.  
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# Open Peer Review

Current Peer Review Status:



## Version 1

Reviewer Report 22 November 2025

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**Jaideep Menon** 

Amrita Institute of Medical Sciences, Kochi, Kerala, India

I read with interest the manuscript authored by Moody and colleagues titled 'The role of antimicrobial prophylaxis in the management of snakebite: a systematic review', and have the following observations to make

The topic is relevant as National Guidelines vary substantially on advocacy towards the use of antimicrobials and drug.

Given the pro-inflammatory nature of certain snake venom components, it becomes particularly difficult to diagnose underlying infection, given that whole blood counts, neutrophilia and raised acute phase reactants are associated with snakebite envenoming.

Additionally significant local bite site inflammation made it difficult to diagnose superadded infection other than from a culture.

All these together make it difficult to diagnose superadded infection with snakebite envenoming. The Systematic Review though not powered by great numbers does shed some light on this issue. I would like the authors to touch on a few of these points for greater clarity in the context of SBE. I opine that the manuscript is well written and finds my approval for indexing.

**Are the rationale for, and objectives of, the Systematic Review clearly stated?**

Yes

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

Yes

**Is the statistical analysis and its interpretation appropriate?**

Yes

**Are the conclusions drawn adequately supported by the results presented in the review?**

Yes

**If this is a Living Systematic Review, is the 'living' method appropriate and is the search**

**schedule clearly defined and justified? ('Living Systematic Review' or a variation of this term should be included in the title.)**

No

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Clinical aspects and epidemiology of snakebite envenoming in India

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

Reviewer Report 10 November 2025

<https://doi.org/10.21956/wellcomeopenres.27217.r137361>

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**Joseph J Erinjery** 

Kannur University, Mananthavady Campus, Mananthavady, Kerala, India

Snakebite is considered a neglected tropical disease, and it affects millions of lives and livelihoods around the world. The current systematic review assesses the efficacy of prophylactic antimicrobials for the treatment of secondary infections at bite sites. As the authors noted, only a few existing studies were available for the review, and some of those selected were biased. Based on these studies, the authors do not recommend using antimicrobials at bite sites. The article is well written, and I only have a few minor comments.

- The study could have used some meta-analysis methods for analysis
- Italics for species names in the Microbiological aetiology section.

**Are the rationale for, and objectives of, the Systematic Review clearly stated?**

Yes

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

Yes

**Is the statistical analysis and its interpretation appropriate?**

Partly

**Are the conclusions drawn adequately supported by the results presented in the review?**

Yes

**If this is a Living Systematic Review, is the 'living' method appropriate and is the search schedule clearly defined and justified? ('Living Systematic Review' or a variation of this term should be included in the title.)**

Not applicable

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Disease prevalence; snake bite prevalence;

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

Reviewer Report 17 October 2025

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**Nicholas Amani Hamman** 

Community Medicine and Public Health, Gombe State University, Gombe, Nigeria

#### REVIEW REPORT

**Manuscript title: The role of antimicrobial prophylaxis in the management of snakebite: a systematic review**

#### General summary

This manuscript presents a systematic review assessing the efficacy of prophylactic antimicrobial use following snakebite envenomation. The authors registered their protocol on PROSPERO, searched multiple databases and identified four randomized controlled trials (RCTs) totaling 696 participants. Their main finding is that prophylactic antibiotic administration does not significantly reduce the incidence or severity of secondary bacterial infection after snakebite.

The topic is highly relevant especially for low- and middle-income countries where snakebite burden and antimicrobial misuse are common. However, despite the relevance, the manuscript has methodological, structural and interpretative weaknesses that limit its current scientific robustness. While the authors have followed several PRISMA principles(1), key details necessary for reproducibility, critical appraisal and transparency are either underreported, briefly summarized or insufficiently detailed

Major Comments

#### Search strategy transparency and comprehensiveness

The manuscript describes an extensive database search but crucial methodological details are missing:

1. The full search strategy is said to be available as "Extended Data 1" yet no summary or example query is included in the main text.
2. There is no date for the last search, which violates PRISMA 2020(1) reporting standards.
3. No mention of grey literature sources, regional databases (e.g., LILACS, African Index Medicus) or manual reference checks which are essential given the geographical burden of snakebite (South Asia, sub-Saharan Africa).
4. Limiting inclusion to English-language studies introduces a potential language bias especially as snakebite trials are often published in Portuguese, Spanish, Hindi or Thai.

**Recommendation:**

Include the complete search syntax in an appendix or supplement. Specify the exact final search date. The authors acknowledge the English only limitation in the discussion but they should also explain its rationale and possible implication for the comprehensiveness of the review

**Inclusion/exclusion criteria**

Restricting inclusion to RCTs is excessively stringent for this field where RCTs are rare due to ethical and logistical barriers. This restriction results in only four included studies which undermines the generalizability of findings and may distort the real-world clinical picture. While methodological purity is admirable, excluding high-quality observational or quasi-experimental studies leads to a narrow and potentially unrepresentative evidence based that may not reflect clinical practice

**Recommendation:**

Authors should justify this decision explicitly in the Methods or preferably consider a sensitive analysis or expanded literature review including a well design cohort or prospective studies to increase the breath and relevance of evidence

**Data extraction and risk-of-bias evaluation**

The manuscript claims to use standardized proformas and independent reviewers but:

1. There is no mention of inter-rater reliability (e.g., kappa coefficient or percentage agreement).
2. The RoB 2 summary table lacks supporting narrative justifications as the text merely reproduces domain ratings without explaining the reasoning behind each risk judgment.
3. There is no discussion of publication bias assessment (e.g., funnel plot, Egger's test) even if meta-analysis was not feasible, narrative bias assessment is expected.

**Recommendation:**

Include detailed rationale for each RoB 2 domain judgment in supplementary material. If a quantitative assessment was not possible add a short narrative discussion of potential publication bias

**Handling of heterogeneity and justification for narrative synthesis**

The authors state that "data are presented narratively" due to high heterogeneity, but this is not quantified. The decision not to attempt a quantitative synthesis should be justified more explicitly using at least descriptive commentary or visual comparison across studies.

Moreover:

1. There is no clear definition of what dimensions (population, intervention, outcome definitions or snake species) contributed to heterogeneity.
2. No attempt was made at subgroup analysis (e.g., by snake genus or antibiotic type), even though limited exploratory comparisons could have been informative

**Recommendation:**

Provide explicit justification for narrative synthesis and summarize the main sources of heterogeneity in tabular or narrative form. If possible, include exploratory subgroup analyses or at least tabular comparisons of infection incidence and relative risk.

**Incomplete data presentation**

Several crucial data points are omitted:

1. Infection definitions vary between studies but these definitions are not summarized in the Results.
2. There is no unified table summarizing infection incidence (in %), relative risks or confidence intervals for each included trial.
3. No information on adverse events from antibiotic use (e.g., gastrointestinal symptoms, allergic reactions), which is relevant when weighing prophylactic risk-benefit balance.

**Recommendation:**

Reformat Table 1 or create an additional summary table including:

1. Definition of infection used per study.
2. Infection incidence per arm.
3. Relative risk or risk difference.
4. Adverse event rates.

This will improve interpretability and transparency.

**Discussion**

While the discussion is generally cautious, there are several issues:

1. The authors extrapolate findings from four small, geographically limited trials (Brazil, Ecuador, Sri Lanka) to all snakebite contexts globally, which is overly broad given ecological and microbiological diversity.
2. The mention of “recent observational data” and “new trials in India” is helpful but not systematically integrated i.e. the Indian trial (ref 34) should be more critically compared to the included studies rather than discussed in isolation
3. The discussion on antimicrobial resistance (AMR) is conceptually important but not well linked to the actual evidence extracted from the included trials (none of which investigated resistance profiles comprehensively).

**Recommendation:**

Tighten the discussion by explicitly separating evidence derived from included studies vs. contextual or theoretical considerations. Avoid generalizing findings beyond the included snake species or settings.

**Limitations section**

While the limitations are mentioned, several important points are not sufficiently expanded:

1. Exclusion of grey literature and non-English publications.
2. Lack of standard case definition for infection across trials.
3. Absence of anaerobic cultures and incomplete microbiological reporting.
4. Small sample size and low event rate reducing statistical power.

**Recommendation:**

Expand the limitations to reflect these methodological constraints and explicitly note that these factors reduce the certainty and generalizability of the conclusions

**Conclusions and implications**

The conclusion that “routine antimicrobial prophylaxis should not be recommended” is too definitive given the evidence base. The absence of evidence for benefit is not evidence of absence of benefit, especially with only four small, heterogeneous RCTs.

**Recommendation:**

Rephrase to reflect uncertainty:

“Current randomized evidence does not demonstrate a significant benefit from routine antimicrobial prophylaxis after snakebite; however, the available studies are small and heterogeneous. Larger, geographically diverse trials using standardized infection definitions are required before definitive clinical recommendations can be made.”

**Minor Comments****Writing and structure**

1. Some sentences in the introduction are overly long and densely referenced. Consider tightening prose for readability.
2. Ensure all abbreviations (e.g., AI, RoB, PROSPERO) are defined at first use.

**Tables and figures**

1. Table 1 should include column totals for clarity.
2. . include the date of the search.

**Referencing**

1. Verify reference numbering consistency; some citations (e.g., 24, 27–30) appear misplaced or duplicated.
2. The recent Indian non-inferiority trial (ref 34) should include full citation details and journal reference if available

**Formatting**

1. Ensure all bacterial species names are italicized (e.g., *Morganella morganii*).
2. Use consistent formatting for antimicrobial agents (generic names only, lowercase)

**Supplementary material**

1. Extended data references should include working links or DOI numbers to ensure reproducibility.

**Conclusion**

Major revision

While the manuscript addresses an important and underexplored clinical question, clarifications and expansions in methodology, data presentation and conclusion phrasing are needed before it can be considered for publication. Specifically:

1. Provide full search transparency and clarify inclusion rationale.
2. Expand data presentation with infection incidence and risk estimates.
3. Refine conclusions to match evidence strength.

**References**

1. Page M, McKenzie J, Bossuyt P, Boutron I, et al.: The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *Journal of Clinical Epidemiology*. 2021; **134**: 178-189  
[Publisher Full Text](#)

**Are the rationale for, and objectives of, the Systematic Review clearly stated?**

Yes

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

Yes

**Is the statistical analysis and its interpretation appropriate?**

Partly

**Are the conclusions drawn adequately supported by the results presented in the review?**

Partly

**If this is a Living Systematic Review, is the 'living' method appropriate and is the search schedule clearly defined and justified? ('Living Systematic Review' or a variation of this term should be included in the title.)**

Not applicable

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Epidemiology and control of Snakebite Envenoming; Maternal and Child Health

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

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