The timing is right to end snakebite deaths in South Asia

Regional collaboration is crucial to end preventable deaths and disability from snakebites in South Asia, say **Ravikar Ralph and colleagues**

Five million snakebites occur globally each year, causing between 81 000 and 138 000 deaths and nearly 400 000 amputations and other permanent disabilities.¹ South Asia has the highest incidence of venomous snakebites in the world.² Within the region, Bangladesh, India, Nepal, Pakistan, and Sri Lanka together constitute nearly 70% of global snakebite mortality.³

The World Health Organization recognised snakebite as a neglected tropical disease in 2017, giving it high priority for large scale action and research.⁴ A resolution passed in the World Health Assembly in May 2018 urged member states to step up efforts to tackle snakebite.^{5 6} It is important that regional mitigation efforts in South Asia reflect these objectives. In this paper, we explore the determinants of poor clinical outcomes with snakebite in South Asia and propose priority actions for governments to achieve the vision of zero deaths from snakebite.

Disease burden

The region is a biodiversity hotspot for venomous snake species. The sociodemographic and occupational profile of the population contributes to increased risk of snake-human encounters. Snakebites are largely an agrarian occupational hazard in South Asia. Box 1 describes the medically important snake spe-

cies in South Asia and demographic profile of groups commonly affected.

Lack of systematic preventive measures at community and national levels contributes to the high incidence of snakebite. Figure 1 shows snakebite incidence and associated mortality in South Asian countries. These estimates are drawn from extrapolations of hospital records and community surveys, and likely underestimate the problem.^{7 8} Long term complications occur in around 15% of survivors and include musculoskeletal deformities, amputations, visual impairment, chronic kidney disease, and neurological deficits.⁹

High mortality from snakebites

After a venomous snakebite, the management priorities include²¹ first aid to retard the progression of envenoming, rapid transport to a health facility, and antivenom therapy with optimal supportive care.

Deficiencies in these components, as outlined in figure 2, greatly increase

vulnerability to death and adverse outcomes.⁴

Delayed and inappropriate treatment

Delayed treatment can be fatal, especially beyond six hours after the bite.²²⁻²⁵ In many parts of South Asia, only half of patients reach a health centre within six hours of a bite, with the bite-to-treatment delay being as long as 12 to 15 days in some cases.^{13 26 27} As a result, 70-80% of fatalities happen before patients reach the health facility.^{11 22} Nearly 97% of snakebite deaths in India occur in rural areas.¹¹ Sparse distribution of health facilities in rural areas results in patients having to travel long distances for treatment.^{8 28 29} Lack of affordable means of transport, particularly in remote inaccessible regions, compounds the problem.⁸

Communities are rarely aware of simple first aid measures. With poor access to health facilities, they often resort to traditional faith healers, who indulge in practices such as chanting, incisions,

Box 1: Snakebite: the scenario in South Asia

Venomous snake species

- Of 300 different snake species in South Asia, an estimated 70 are venomous¹³
- The “big four” include the common krait (*Bungarus caeruleus*), binocellate cobra (*Naja naja*), Russell’s viper (*Daboia russelii*), and saw scaled viper (*Echis carinatus*). These are distributed across the subcontinent and are largely responsible for deaths and long term complications from snakebite.^{14 15} Around 90% of snakebite deaths in India are from one of these
- Locally prevalent venomous species also contribute to the disease burden¹³⁻¹⁸
 - In Bangladesh, the monocellate cobra (*N kaouthia*) and Wall’s krait (*B walli*) account for a majority of cobra and krait bites respectively
 - Green pit viper bites are more frequent than those by the Russell’s viper in Bangladesh and Nepal. No verified reports of saw scaled vipers exist in these countries
 - Hump nosed pit vipers (*Hypnale sp*) are the commonest cause of snakebite envenoming in Sri Lanka and are now recognised as highly venomous snakes alongside the big four

Populations affected

- With more than 70% of the largely rural South Asian population still dependent on agriculture, hunting, fishing, and forestry for its livelihood, an intersection of these snake biotopes with human dwellings and occupational activities is inevitable¹⁹
- Over half of all snakebites occur in 30-50 year old farmers and in 60-80% of cases involve ankles and feet.¹³ Dependence on non-mechanised, low cost farming techniques and barefoot farming practices place farmers at an increased risk of bites on the extremities.⁸
- Snakebites are more common among the poor.^{8 20} Poor housing conditions and inadequate lighting provide easy access to snakes into living spaces and they are not easily spotted.¹⁸ Open houses, sleeping on the floor, and open defecation are other factors increasing the risk of snake encounters⁸

KEY MESSAGES

- South Asia has the highest burden of snakebite envenoming in the world and contributes to 70% of global snakebite mortality
- Inadequate first aid, delayed treatment access, and suboptimal treatment contribute to poor outcomes
- The global focus on snakebite as a neglected tropical disease provides an opportune time for South Asian countries to strengthen regional cooperation and investment in research on epidemiology, treatment, and prevention

Fig 1 | Distribution of venomous snakebites and related deaths in different South Asian nations.^{1 10-13} Numbers in brackets indicate year of measurement

attempts to suck venom from the bite site, tying tourniquets, or local application of herbs, cow dung, or snakestones.^{10 13 30} These measures can delay treatment^{20 31} and result in increased mortality.^{13 25}

Suboptimal care

Rural health facilities in many parts of South Asia lack the infrastructure and manpower to provide timely and effective treatment.^{5 29 32} Supportive care such as mechanical ventilation, dialysis, and blood transfusion is critical in the management of patients with complications such as

respiratory paralysis, acute kidney injury, and coagulopathy induced haemorrhage. Antivenom therapy alone is insufficient in their care.^{13 21} Most rural health centres and hospitals lack critical care facilities and thereby refer patients elsewhere, resulting in treatment delays.³³

Insufficient knowledge and experience among healthcare providers is also responsible for inadequate treatment. Studies among doctors in primary care and health workers in Bangladesh, India, and Pakistan show gaps in ability to recognise systemic envenoming and

Fig 2 | Determinants of poor snakebite related outcomes in South Asia

administer antivenom.^{5 30 34 35} This may be because snakebite management is not given enough focus in the medical curriculum.³⁶ Health workers in remote settings are also reluctant to treat snakebite because of apprehension about managing antivenom associated adverse reactions.³² This apprehension is not entirely misplaced since up to 80% of those treated develop one or more antivenom associated adverse effects such as anaphylaxis, pyrogenic reactions, or serum sickness.^{13 37}

Most South Asian countries have well formulated snakebite treatment protocols for low resource settings with a tiered referral approach. Yet these are poorly implemented with limited penetration in primary health centres. These protocols are not standardised and numerous conflicting versions exist with differing indications for antivenom administration and dosing.³⁸

Antivenom production and potency

Underproduction and maldistribution of antivenom is a pressing challenge in the region.^{25 32 39} Most South Asian countries import antivenom from Indian manufacturers—with the exception of Pakistan, which, in addition to importing Indian antivenom, also produces indigenous antivenom for domestic consumption.^{39 40} Current production falls short of the requirements of the entire region.^{25 41 42} Several manufacturers and suppliers of Indian antivenom have recently ceased operations citing reasons of price control, poor animal husbandry practices, and venom shortage.^{39 43 44 45} Stringent regulations on snake handling and venom procurement have hindered the establishment of new venom collection centres in India.⁴³

Indian antivenom is produced exclusively against the big four venoms, and it is ineffective against other regionally prevalent species.⁴⁶ Consequently, bites by these species are associated with poorer clinical outcomes despite the administration of large antivenom doses.⁴⁶ Recent studies also reveal significant intra-species variations in the venoms of the big four based on location.⁴⁷⁻⁵¹ Since all major Indian antivenom manufacturers source snake venom from the Irrula cooperative in south India, the available products vary in their neutralisation efficacy and clinical effectiveness against the big four venoms from other parts of South Asia.^{14 43 47 50} A double blind clinical trial comparing Pakistani and Indian antivenoms in 70 snakebite victims in Pakistan with deranged clotting tests and local swelling revealed quicker restoration of coagulopathy at lower doses with the Pakistani antivenom,

suggesting greater specificity against indigenous snake species.⁵²

Indian antivenom is manufactured in two forms—liquid and lyophilised. While lyophilised antivenoms can be stored at room temperature, liquid antivenoms should ideally be transported and stored at 2–8°C, necessitating functional cold chain and cold storage facilities.^{53 54} The lack of an effective cold chain and unreliable refrigeration facilities in rural areas render it ineffective.^{3 55} Non-standard manufacturing practices also result in variable antivenom effectiveness.^{55 56} Stringent measures to contain or withdraw substandard batches are lacking. The government run Central Drugs Laboratory in India screens antivenoms for potency.⁵⁷ These tests cover limited brands, however, and currently batches from only four of the six main antivenom manufacturers are screened.⁵⁸

Why do these problems persist?

Over the years, snakebite mitigation has not had enough attention in the public health agenda of the region. Lack of good quality epidemiological data on snakebites and their impact and affliction of mainly poor and vulnerable populations have contributed to this. Figure 3 summarises these challenges.

Lack of research and innovation

With the exception of Sri Lanka, South Asia has a severe dearth of quality data on snakebite epidemiology, largely because of the skewed reliance by national agencies on hospital based studies.¹³ In a region where a considerable proportion of patients may die before reaching a hospital or preferentially

attend traditional healers, snakebites simply pass unreported and hospital based studies tend to underestimate the problem.⁵⁹ There are few studies on chronic disability burden and socioeconomic impact of snakebites.⁶⁰

There is limited evidence to guide treatment protocols. Most studies on snake distribution, ecology, envenoming profiles, and intra-species venom variation do not encompass all medically important species and are limited in geographical extent.^{10 11 12 22} Studies on preclinical efficacy, pharmacokinetics, clinical effectiveness, and safety of current antivenoms are lacking.^{37 39 56 61} The optimal dose of antivenom is still debated and regional clinical trials offer conflicting evidence. A systematic review of 10 open label randomised controlled trials in the Indian subcontinent on optimal antivenom dose concluded that there is very low quality evidence to guide practice and further research is needed.⁶²

Political and financial barriers

Because of the paucity of data on snakebite epidemiology, socioeconomic impact, and disability burden, most South Asian governments have failed to prioritise snakebite as a matter of national importance needing concerted action and allocation of health resources. Snakebite mitigation strategies are practically non-existent in South Asia and national prevention awareness programmes are largely overlooked.¹³

Snakebite envenoming is also not recognised as a public health problem at the level of the South Asian Association for Regional Co-operation (SAARC). It does not feature in the organisation's

list of priority diseases—which includes leprosy and rabies among others—which benefit from numerous initiatives aimed at setting up integrated networks and nodal centres for regional training, research, disease eradication, and information dissemination.⁶³ This lack of national and regional prioritisation has resulted in the matter being overlooked in the global health agenda, until its recognition as a neglected tropical disease by WHO in 2017.

The way forward

A substantive global target for neglected tropical diseases exists in the form of the Sustainable Development Goal 3.3 to “end the epidemics” of these diseases by 2030.⁴ The recent inclusion of snakebite as a neglected tropical disease should mean greater funding for research and mitigation strategies. We present below key priorities for South Asian countries. Establishing national snake envenoming mitigation programmes in each country can help in effective and centralised execution of these efforts.

Strengthen regional cooperation

A regional collaborative centre for snakebite research and advocacy and nodal training centres for envenoming management must be established along the lines of the SAARC tuberculosis and HIV/AIDS centre.⁶⁴ This would serve as a platform to bring together research and policy experts working on snakebite mitigation from across disciplines. The centre would help collate and monitor data on snakebite incidence in the region; facilitate collaborative research and technology transfers between nations;

Fig 3 | The intricate web of poor outcome determinants interacting with barriers to improvement

and support national snakebite mitigation efforts through policy guidance and technical support.

Improve reporting

Setting up sentinel reporting systems in different parts of each country can help improve the availability of epidemiological information on snakebites. The Big 4 Mapping Project (<http://snakebiteinitiative.in/snake>) under the Global Snakebite Initiative provides an interesting approach to understanding the distribution of snake species across India, with volunteers providing real time information on snake sightings.⁶⁵ Designating snakebite as a notifiable disease would further improve reporting from health facilities. To achieve standardisation, health workers should be encouraged to use the specific international classification of diseases code T63.0 (toxic effect of contact with snake venom) in certification of death in snakebite victims.²¹ In unclear cases of snakebite death, immunological assays can be used to establish the cause.⁶⁶

Increase awareness of preventive measures

The distinctive epidemiology combined with knowledge of snake habitats and periods of activity is important in planning preventive measures. Sleeping under a mosquito net and on a bed above ground level have been protective against krait and cobra bites, in both anecdotal reports and community based observational studies in India, Nepal, and Sri Lanka.^{67 68 69} Protective footwear was distributed among paddy farmers in Myanmar 20 years ago, but its impact in reducing snakebite is unclear.⁷⁰

Lack of awareness and high illiteracy among communities are linked to poor implementation of preventive measures such as keeping domestic areas free of rubbish, rubble, and firewood; controlling rodent populations; constructing snake proof houses; and using protective footwear.^{13 26 71} Snakebite prevention and first aid training programmes targeted towards at-risk populations are essential to reduce snakebites and improve initial response.

Dissuading those bitten by snakes from visiting faith healers can be a challenge since the latter are an integral part of the fabric of many South Asian societies. A non-governmental organisation in eastern India has been trying to engage with faith healers through workshops to promptly refer snakebite victims to health centres.³²

Strengthen rural health services

Ensuring efficient ambulance transport and facilities for dialysis, mechanical ventila-

tion, blood transfusion, and intensive care in rural areas will be vital to prevent deaths from snakebites. A few regional initiatives have attempted to tackle these matters. In Nepal, a network of motorcycle volunteers was organised to transport snakebite victims promptly, on otherwise unpassable trails, to health centres. This simple intervention, along with community education, considerably reduced incidence and fatality from snakebites.⁷² In India, free ambulance services initiated as public-private partnerships have sought to provide rapid access to care.⁷³ The full impact of this initiative is hindered, however, by a shortage of services in rural areas, suboptimal response times or non-attendance of calls, inadequately trained paramedics, and the absence of in-transit antidote therapy and standardised resuscitation protocols.^{73 74}

Healthcare providers, particularly those practising in high burden rural areas, must be trained in using standard treatment guidelines for snakebite management. Hands-on training in airway management and treatment of anaphylaxis must also be included. Nationwide training of health workers and paramedics has been initiated in Nepal, but the impact of this programme is yet to be assessed. Integrating snakebite management in the medical curriculum and organising workshops using locally adaptable training modules based on WHO guidelines will help. Compliance with guidelines must be ensured and an audit of deaths and adverse events must be regularly conducted at the district level.

Enhance production, potency, and safety of antivenom

Measures to revive antivenom manufacturing units that have ceased production, increase snake venom availability, and improve animal husbandry practices will be critical to step up production in the region. Legislative amendments to ease restrictive Indian laws on snake capture and venom extraction need to be considered. Subsidised antivenom should be made available in sufficient quantities in both government and private health facilities and monitored for storage under appropriate conditions. Venom collection must be expanded to multination regional venom cooperatives. Establishing serpentariums for captive husbandry and adherence to WHO recommended standards during venom collection and antivenom manufacture would improve the quality and safety of antivenom. Regulatory bodies for quality control of Indian antivenoms should screen batches from all manufacturers and formulate basic minimum standards for potency and quality based on WHO guidelines.⁷⁵

There is a need to support development of newer antivenoms against locally prevalent snake species. A collaborative initiative between Costa Rica, Sri Lanka, and the US to develop newer antivenoms specific to Sri Lanka's major snake species is an example in this direction.^{76 77} A project initiated in 2018 in Bangladesh aims to establish a geographically representative snake venom production, research, and preclinical testing facility in Chittagong.

Box 2: Recommendations for future research

- Large, representative, community based epidemiological studies to estimate the true burden of snakebite morbidity and mortality, and socioeconomic impact
- Large, well designed clinical trials to establish safety, efficacy, and optimal dose of antivenoms
- Developing and testing preclinical efficacy of new antivenoms involving all medically important snake species across South Asia. These could include different regional antivenoms with specificity against local snake species in addition to the big four, or consist of two separate expanded polyspecific antivenoms against major South Asian viperid and elapid species, respectively
- Studies on envenoming syndromes to establish species-syndrome correlation and aid early identification of snake species. This could help clinicians anticipate complications and initiate appropriate treatment^{78 79}
- Diagnostic tools to identify snake species that screen for species specific venom proteins or amplify and sequence bite site snake DNA. Technical support from countries like Australia, where commercial point-of-care venom detection kits are marketed for indigenous species, could be sought to develop improved kits for South Asian snake species.⁷⁹ DNA aptamers have recently been used in venom based identification of South East Asian krait species⁸⁰
- Clinical evaluation of pharmacological interventions to retard venom transit from bite site to circulation by slowing lymphatic flow and thereby preventing systemic toxicity in animals. These could be a promising adjunct for snakebite first aid measures⁸¹

Research and innovation

The global focus on snakebite provides an opportunity to boost research in this neglected area. Box 2 lists areas for further research. This would help generate critical evidence to inform policy making and more effective, economical, and feasible prevention and treatment measures.

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