Paediatric snakebite envenoming: the world's most neglected 'Neglected Tropical Disease'?

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ABSTRACT

Snakebite disproportionally affects children living in impoverished rural communities. The WHO has recently reinstated snakebites on its list of Neglected Tropical Diseases and launched a comprehensive Strategy for the Prevention and Control of Snakebite Envenoming. In the first of a two paper series, we describe the epidemiology, socioeconomic impact and key prevention strategies. We also explore current challenges and priorities including the production and distribution of safe and effective antivenom.

What is known about this topic?

- The WHO has recently reinstated snake envenomation on the list of Neglected Tropical Diseases and launched a Strategy for Prevention and Control of Snakebite Envenoming.
- Most deaths and serious sequelae related to paediatric snakebites are preventable.

What this study adds?

- Snakebite disproportionally affects children living in impoverished rural communities.
- Prevention strategies are needed that focus on children.
- Discussion on current global challenges in providing antivenom including production, supply and distribution.

INTRODUCTION

In 2017, snakebite envenoming was reinstated within the list of Neglected Tropical Diseases (NTDs) of the World Health Organization (WHO).[1] Snakebite's annual morbidity and mortality is among the highest of the NTDs.[2] A resolution on snakebite envenoming was subsequently adopted by the World Health Assembly in 2018, and a strategy for the prevention and control of this disease was launched by the WHO in 2019.[3] This recent attention is crucial and long-awaited.

The estimated global burden of snakebites is 5 million people per annum with 1.8–2.7 million envenomings. Between 81 000 and 138 000 people die each year, and about three times that many have permanent physical and psychological sequelae.[4] The burden of snakebites disproportionately falls on the world's poorest people in rural communities.[5] Ninety-five per cent of snakebites occur in Africa, Asia and Latin America (see figure 1), with India having the highest reported death toll (exceeding 45 000 deaths per annum).[6] The impact of snakebite envenomings becomes even more evident when analysed in terms of disability adjusted life years lost.[7]

Snakebites mainly affect young people of economically productive age. Children are often bitten when participating in agricultural work or while playing or walking close to their homes. For example, in sub-Saharan Africa, 30.5% of envenomings occur in children.[8] Envenomings in children can be more severe than in adults.[9] Paediatric cases are particularly challenging to manage clinically due to the lower volume of distribution of venom, and the potential for life long permanent sequelae from tissue damage and necrosis, in addition to psychological sequelae. The long-term effects of amputations and post-traumatic stress disorder account for a significant part of the burden of snakebite envenoming in children.[10]

Snakebite envenomings share the features that characterise NTDs, such as: (a) They affect predominantly impoverished rural populations whose people often lack a political voice. (b) By causing significant rates of mortality, morbidity and physical and psychological sequelae, snakebite envenomings exert drastic economic and social impacts and foster a vicious cycle of poverty. (c) Generally, envenomings represent much less of a health risk for high-income countries, an issue that contributes to the lack of development of treatments and preventative strategies. (d) They cause stigma and discrimination, especially in people suffering from sequelae. (e) Snakebite envenomings have received little attention by research agendas and pharmaceutical development.[11]

Which snakes are the most dangerous?

There are more than 2500 species of snakes classified in the superfamily Colubroidea. Snakes belonging to the families Viperidae (eg, true vipers and pit vipers) and Elapidae (subfamily Elapinae) (eg, cobras, mambas, kraits) exert the heaviest toll of envenomings.[1] Along with these, some species in the non-front fanged colubroid snakes (eg, boomslangs, vine snakes, red-necked keelbacks) can cause fatalities, as can the Atractaspidinae (eg, mole vipers) and several species of Hydrophiinae (eg, sea snakes).[4] The most relevant species vary depending on the region (see figure 2).

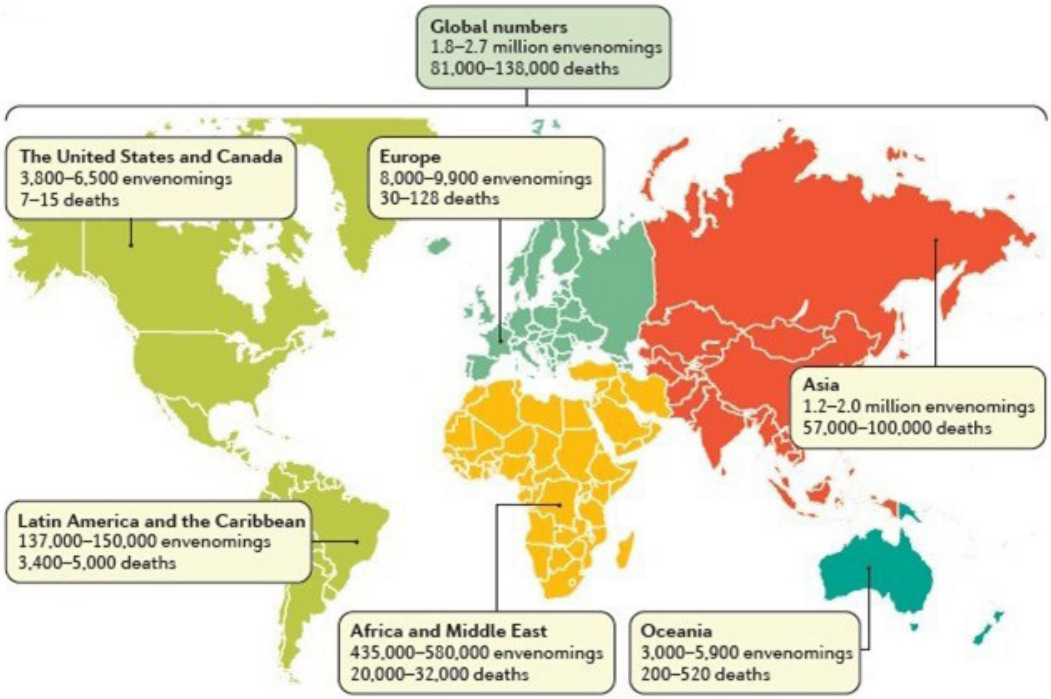

Figure 1 Geographical distribution of the estimated number of snakebite envenomings and deaths. With permission from Gutierrez *et al*, Snakebite envenoming. *Nat Rev Dis Primers* 2017;3:170763.

In sub-Saharan Africa, the carpet vipers (*Echis* spp), puff adders (*Bitis* spp), a number of neurotoxic elapids including cobras and mambas (*Naja* spp and *Dendroaspis* spp) and the spitting cobras (*Naja* spp) cause the majority of bites and deaths.[13] In Asia, the most dangerous viperids are the Russell's viper (*Daboia russelii* and *D. siamensis*), saw scaled viper (*Echis* spp), hump-nosed viper (*hypnale* spp), green pit vipers and their relatives (*Trimeresurus* spp), Habu pit vipers (*Protobothrops* spp) and the Malayan pit viper (*Calloselasma rhodostoma*).[14] Among elapids, the cobras (*Naja* spp) and kraits (*Bungarus* spp) play a leading role.[15] In the Americas, viperids are responsible for the vast majority of cases, particularly rattlesnakes (*Crotalus* spp) in North America and lance-head vipers (*Bothrops* spp) in Central and South America.[16] In Australia and Papua New Guinea, the only terrestrial venomous snakes of medical importance are species from several genera of the subfamily Elapinae, including taipans (*Oxyuranus* spp), brown snakes (*Pseudonaja* spp) and tiger snakes (*Notechis* spp),[17] while in Europe, most envenomings are caused by species of the genus *Vipera*.[18] Dangerously venomous species from the subfamily Hydrophiinae (eg, true sea snakes and sea kraits) are distributed in tropical and subtropical waters of the Indian and Pacific oceans. Several species of mole vipers (Atractaspidinae) are found in Africa and Middle-East. Venomous non-front fanged colubroid species are found in Africa (boomslangs, vine snakes), Asia (Yamakagashi, red-necked keelbacks) and Latin America.

Figure 2 Some snake species having a medical impact in various regions of the world. Asia: (A) *Naja kaouthia*, (B) *Daboia russelii*. The Americas: (C) *Bothrops asper*, (D) *Crotalus durissus*. Africa: (E) *Naja nigricollis*, (F) *Bitis arietans*, (G) *Echis ocellatus*. Oceania: (H) *Oxyuranus scutellatus*. Photos A, B, D, E, F, G and H by David J. Williams. Photo C by Alejandro Solórzano.

Epidemiological trends of snakebite envenoming

Snakebite envenoming disproportionately affects people living in rural communities of sub-Saharan Africa, Asia and Latin America,[4] particularly in impoverished agricultural and pastoral settings. The majority of snake bites occur on the feet, since people often work barefoot, and the hands. Changes in the use of land, associated with deforestation or mining activities, have also brought human populations in closer contact with snakes, increasing the likelihood of accidents. Incidence of snakebites is also affected by weather fluctuations,[19] and by natural disasters, such as floods.[20] A higher incidence of bites is observed at the beginning of rainfall and during harvest period reflecting seasonal agricultural activities. In India, the greatest number of fatalities is recorded in the postmonsoon months between September and November.[6]

Rural areas tend to have a higher incidence than urban areas. Thus, there is significant variation in the incidence of snakebites between regions in a country. In Costa Rica, for example, the overall incidence of snakebites is 13 per 100 000 population per year, but there are rural regions in the country with incidences higher than 100 per 100 000 population per year.[21] A similar trend of higher incidence in rural versus urban settings has been described in Nigeria.[8] In Brazil, there is much higher incidence in the Amazonian region as compared with central and southern regions of the country.[22] These variations in incidence within countries must be considered for the design of public health policies and priorities at national and regional levels.

ECONOMIC BURDEN

Costs to low-income country governments, and the families of the victims, can be crippling, as described in studies carried out in Sri Lanka,[23] Tamil Nadu (India)[24] and Bangladesh.[25] These include the direct costs of medical treatment, including antivenom and ancillary treatments and also the management of long-term consequences of envenomings.[26] Depending on the country, these costs may have to be covered by patients or their relatives, causing an economic crisis for families, fuelling a vicious cycle of poverty. As an example, the study in Sri Lanka showed that, despite this being a country where treatment for children is free, the estimated cost to the childrens' families was US$42 (not including lost earnings for their carers). This is in the context of average daily earnings of US$4 for an agricultural worker in Sri Lanka. Snakebite envenomings also occur in domestic animals, an issue that contributes to the economic impact in rural impoverished settings.[27]

PREVENTION

Unless they feel threatened, snakes do not generally bite humans, although exceptionally there are species which regularly enter buildings searching for food, water and shelter which have been associated with presumably 'unprovoked' bites. Outdoors, around homes, village gardens and in bushland, children are often at additional risk in encounters with snakes because of their innate curiosity. Boys in particular have been found to be more inclined to try to catch, kill or otherwise interfere with snakes they encounter in these settings, and this is often reflected in their higher rates of snakebites.[28] Ideally, education about snakebite should be intensified in rural schools, and special care should be taken around school holidays. Children should be taught to avoid getting close to snakes and to walk on footpaths as well as not to put their hands into holes or nests where snakes may be lurking. Suitable footwear such as rubber boots should be worn when walking in high-risk areas, and a light source should be used when walking at night (see figure 3).

Avoiding the risk of nocturnal snakebites by animals that enter dwellings is very important.[29] Occupants may be bitten while sleeping or when reaching into a container inside the home. Measures to reduce access of snakes into homes are important, for example, not keeping livestock in the house[12] and keeping food in vermin-proof containers. The use of a well-tucked in or sealed mosquito bed net and sleeping on a bed or hammock raised off the floor have been associated with reduced incidence of nocturnal snakebites.[30]

It is vital to engage with and empower local communities through well-designed activities that educate them about the public health risk of snakebite envenoming. Teaching awareness of simple but life saving measures is also crucial, as well as advice on first-responder actions and pragmatic first aid. It is also important to engage with communities about health-seeking behaviours, attending medical facilities and in particular the role and relevance of traditional healers or culturally considered treatments for snakebite. The WHO Strategy for the Prevention and Control of Snakebite Envenoming emphasises the essential need for directly involving communities in the development of solutions to snakebite problems and ensuring that programmes instil an appropriate level of local ownership and empowerment in communities around the problem of snakebites through these engagement processes.[15]

Figure 3 A woman and a group of children walking barefoot in a rural setting in Papua New Guinea. Lack of footwear poses a high risk of snakebites. Photo: David J Williams.

Current challenges and priorities

The link between snakebite and poverty has historically led to a lack of interest from many pharmaceutical companies, research funding bodies and health agencies leading to a paucity of scientific evidence, epidemiological data and effective interventions.[31]

Health systems in many affected countries lack the systems and resources to gather robust statistical data on the scale of the problem. In Myanmar, a recent survey found incidence to be almost four times the quoted figures from the Health Ministry.[32] A household-based study on mortality in India revealed that the number of annual deaths due to snakebite envenoming was close to 45 000, which is more than 30-fold higher than the 1300 annual deaths estimated from official hospital returns.[6] A study conducted in Sri Lanka revealed that only a third of the deaths due to envenoming occur at government hospitals.[33]

Worldwide, many patients continue to seek traditional medicine before or instead of accessing 'biomedicine'.[8] The cost of medical care is a significant deterrent in many rural communities.[1] Other factors include traditional or cultural beliefs, confidence in traditional healers, distance to medical facilities and perceived or actual shortcomings of the formal healthcare system, among other factors.[34] Traditional methods to deal with snakebite envenomings include local incisions, herbal remedies, use of tourniquets, oral suction at the bite, recitation of mantras and electric shock. These are at best ineffective, but many can be harmful causing tissue necrosis, bleeding or infection and their use often leads to delays in accessing antivenoms. Community public health awareness programmes need to address deeply held beliefs around traditional medicine, as well as teaching about preventative measures and simple first aid measures.

Infrastructure also poses huge challenges to travelling long distances for medical care after envenoming. A recent geospatial

analysis of snakebite envenoming found that globally there are at least 750 million people 'at risk' of snakebites who live more than 1 hour from adequate medical facilities.[35]

Production, supply and distribution of antivenom globally is an issue. The quality, safety and effectiveness of some antivenoms has been questioned, and in many countries production of important starting materials, such as snake venoms or high quality hyperimmune animal plasma is deficient. Over the past 50 years, growing shortages of antivenoms from long-established manufacturers have created a market for alternative products. New antivenoms which have proven safe and effective have been developed. However, in other cases, the design of antivenoms has not been based on robust immunological and clinical evidence. Combined with weak regulation in both the countries of manufacture and the countries where the products were marketed, several unsafe, poorly efficacious, and in some cases, completely ineffective products entered the African and Asian markets creating more problems than they solved. Between 2007 and 2011, production of sub-Saharan African antivenoms rose from 227 400 to at least 377 500 vials, constituting 83 000 effective treatments for moderate envenomings.[36] However, some of these products reaching the market lacked efficacy against medically relevant snake venoms, causing a lack of confidence that contributed to a declining market in Africa in particular. The quality, safety and effectiveness of many African antivenoms remains uncertain, although WHO is currently undertaking a comprehensive risk-benefit assessment.

South and South East Asia have more in-country producers than Africa but efficacy and safety present a significant problem for some products. For example, in Sri Lanka, Indian polyvalent antivenoms are generally the only ones available, but often lack clinical efficacy and are associated with a high rates of early reactions.[37] India has relaxed its policies on potency since the 1950s and thus large and varying doses of antivenom are often required.[38]

International scientific collaboration is needed to create new and improved high quality antivenoms in adequate volumes in order to deliver these crucial, cost-effective medications to the rural populations that need them. A network of public antivenom manufacturing laboratories has been established in Latin America, with the goal of promoting technical cooperation and regional coordination in antivenom production, quality control and availability.[39] Similar regional efforts could be developed in sub-Saharan Africa and Asia.

LOOKING FORWARD

In the past few years, there has been steadily growing interest in snakebite envenoming by a variety of stakeholders: the WHO, the scientific community of toxinologists, non-governmental organisations, public health advocates and foundations as well as the media. As a result, governments in many countries are paying more attention to this neglected health problem.

The WHO *Strategy for the Prevention and Control of Snakebite Envenoming* launched in May 2019 has established four priority areas of work:

a. empower and engage communities,
b. ensure safe, effective treatments,
c. strengthen health systems and
d. increase partnerships, coordination and resources.

Under this strategy, the aim is to reduce mortality and disability caused by snakebite envenoming by 50% by 2030. It is expected that a diverse set of stakeholders, with leadership from the WHO, will be involved in this global strategy. As a positive development, the WHO has established a risk-benefit assessment programme for antivenoms used in sub-Saharan Africa, and a similar programme is being planned for Asia in 2020. This work is aimed to provide procurement agencies with confidence in the selection of WHO-recommended products and to ensure that there are safe and effective antivenoms available in the African and Asian regions to support additional activities such as regional antivenom stockpiling.

Another important aspect in the WHO strategy is raising the profile of the impact of snakebite envenoming and in particular the physical and psychological disabilities caused by some species of snakes. For many years, the whole area of postacute phase management and recovery for snakebite victims has been largely ignored. Effective action to improve access to rehabilitation, recovery and occupational retraining is essential if the burden of human suffering caused by such sequelae is to be reduced. This again is particularly relevant in the case of children, since the consequences of envenomings often lead to stigma and preclude normal development and later productive life.

WHO's strategy promotes a wide range of research efforts ranging from the characterisation of medically relevant snake venoms, the search for novel therapeutic alternatives that would complement antivenoms (ie, chemical inhibitors and recombinant antibodies) and investment in epidemiological, preclinical and clinical research. Various stakeholders have now turned their attention to combating and overcoming this neglected disease, including establishing new funding pathways and investments. More research focusing on snakebite prevention in children and clinical management and effective antivenom dosing in envenomated children is needed.

CONCLUSION

Like many NTDs, most deaths and serious sequelae related to snakebites are completely preventable if there is treatment (safe and effective antivenom) available locally. Public health systems need to be strengthened to be able to provide timely and effective attention to people suffering envenomings.

Undeniably, the burden of snakebite on child health globally is considerable. A disproportionate amount of this burden is borne by rural communities in low-income countries and thus treatment and prevention of snakebite often faces additional challenges of poor infrastructure and social inequality. When making recommendations for the management of paediatric snakebite globally, treatment strategies must address the socioeconomic reality in the countries most affected, as well as the local cultural contexts where snakebites occur.

Thankfully, with its recent reinstatement onto the WHO list of NTDs, passage of the 2018 resolution by the World Health Assembly and now release of a global strategic plan by WHO, we may finally see that after many decades of neglect, snakebite envenoming is beginning to receive the attention it deserves.

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