# Recommendation for the Adoption of an Additional Disease as a Neglected Tropical Disease

## The Case for Snakebite Envenoming

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Costa Rica

*January 2017*

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# EXECUTIVE SUMMARY

This paper provides evidence for the adoption of snakebite envenoming as a neglected tropical disease (NTD) by the World Health Organization (WHO). Snakebite envenoming primarily affects poor rural communities in tropical and sub-tropical countries. It causes substantial morbidity, disability and death, particularly in Africa, Asia, Oceania and Latin America. Snakebites can leave victims maimed, disfigured and psychologically scarred, and many suffer stigmatization and discrimination often with lifelong debt and facing destitution. Investment in health systems disease management, control and research which could drive the development of new medicines, diagnostic tools and improved control strategies has not yet matched the burden of suffering. However, with coordinated action, the disease burden caused by snakebite envenoming can be immediately brought under control.

This dossier argues that the high morbidity and mortality of snakebite among tropical and sub-tropical populations living in poverty, warrants a global response that would lead to immediate effective control. Through a suite of activities under the leadership of and integrated within the WHO NTD department's intensified disease management (IDM) approach, snakebite envenoming meets the requirements to be classified as a Category A NTD.

We submit that:

1. In spite of shortfalls in available data, there is evidence that 1.8-2.7 million people a year develop clinical illness (envenoming) after snakebite, and between 94-125,000 of them die [1, 2]. At least 46,000 of these deaths occur in India alone [3]. In Sub-Saharan Africa, where data is fragmentary, mortality ranges from 7-20,000 deaths per year [1, 2, 4], but may be under-estimated, given that in West Africa alone, annual mortality has been estimated at 3,557-5,450 [5]. Those most at risk include poor rural dwellers, agricultural workers, working children (10-14 years of age), those living in poorly constructed housing, and people with limited access to education and health care [6-9]. Snakebite envenoming pushes poor people further into poverty by virtue of high treatment costs, loss of income and enforced borrowing [10, 11].
2. Venomous snakes are widely distributed throughout the sub-tropical and tropical world, exposing a large proportion of the world's population to the risk of envenoming.
3. Snakebite envenoming is nevertheless immediately amenable to effective control through a coordinated strategy focused on improved case management. This approach, which embraces intensified efforts to promote prevention, the use of effective first aid, and the early administration of already available, effective snake antivenoms, coupled with better treatment during recovery and rehabilitation would substantially reduce morbidity, disability and mortality.
4. Investment in research to develop new therapeutic, diagnostic and control tools has been meagre for decades, and given the enormity of the potential disease burden, and the vast populations that are at risk, the poor level of investment has been singularly insufficient. Investment in appropriate research and development at a level commensurate with the magnitude of the burden of injury would directly lead to new treatments (antivenoms and ancillary treatments such as enzyme inhibitors), improved diagnosis (and disease surveillance), and the development of a suite of tools and resources that could substantially improve our ability to control the incidence, morbidity, disability and mortality that snakebite envenoming causes.

The adoption of snakebite envenoming as an additional NTD will stimulate the development of a comprehensive control strategy that can immediately reduce the suffering caused in some of the

world's poorest and most marginalized communities. Strong leadership from the WHO in collaboration with partner organizations is essential. The commonality of many key features of snakebite envenoming with other NTDs makes integration into the WHO work programme timely, logical and essential.

## SECTION 1: THE BURDEN OF SNAKEBITE ENVENOMING JUSTIFIES A GLOBAL RESPONSE

- Despite a lack of accurate and systematic global or regional analyses, available evidence clearly shows that the burden of snakebite mortality and morbidity is equal to, or in some cases greater than, many currently recognised NTDs.
- Current data fails to capture the relatively high burden faced by poor rural communities in low-resource settings who suffer from limited access to treatment and lack a political voice.
- As a consequence of poorly treated snakebite envenoming, hundreds of thousands of victims suffer long-term disability leading to mental distress, discrimination and stigmatization.
- The cost of treatment and the loss of productivity and earnings associated with snakebite create and perpetuate a cycle of poverty that hinders socioeconomic development for individuals and communities.

### The estimated burden

Snakebite is a disease of predominantly poor, rural communities in some of the most vulnerable economies in the world. As with many other diseases already prioritised under the NTD designation, clear data on the global impact of snakebite envenoming (cases in which snakebite produces pathology) are poor, due largely to inadequate surveillance leading to under-reporting. There may be 1.8-2.7 million cases of envenoming globally each year, with 94,000-125,000 deaths [1, 2]. In spite of their uncertainties, current estimates of this magnitude demand a coordinated, global response led by the WHO. Their impact relative to other NTDs is substantial; exceeding the reported annual incidence (400,000 cases) and mortality (40,000 deaths) of visceral leishmaniasis [12], and mortality due to schistosomiasis (5.7 million cases and 15,000 deaths) [13]. Snakebite and some other diseases of poverty have a substantial impact on largely poor, rural communities (Table 1; see also Global Burden of Parasitic Disease website):

| Disease | Annual incidence (000s) | Deaths | DALYS (000s) | Annual Donor $ per DALY |
|---|---|---|---|---|
| Chagas disease | 217 | 7,800 | 527 | Not Available |
| Dengue Haemorrhagic Fever | 73 | 28,755 | 1,444 | 20.4 |
| Lymphatic filariasis | 36,000 | 300 | 2,839 | 5.1 |
| Human African Trypanosomiasis | 37 | 9,100-17,971 | 1,264 | 7.9 |
| Onchocerciasis | 30,000 | 1 | 598 | 146.9 |
| Intestinal Nematode | Not Available | 3,304 | 5,266 | 3.3 |

| | | | | |
|---|---|---|---|---|
| Infections | | | | |
| Leishmaniasis | 1,691 | 48,404 | 3,373 | 3.3 |
| Schistosomiasis | 5,733 | 21,797 | 4,026 | 3.9 |
| **Snake bite envenoming**[1,2] | **1,841-2,682** | **94,000-125,000** | **6,070-8,076** | **0** |

Despite the lack of any adequate systematic assessment of the real impact of snakebite envenoming worldwide, several studies performed over the years have highlighted the substantial burden of this tropical disease suffered by impoverished rural communities. The distribution of envenoming and mortality worldwide is variable, numerically lowest in Europe and North America, and highest in sub-Saharan Africa and Asia (Figure 1). Throughout 16 West African nations alone, there are 4,494 (95% CI: 3,557-5,350) deaths per year, translating to 1.2 deaths/100,000 population per annum (95% CI: 0.9-1.4/100,000) [5]. In Bangladesh, a nationwide epidemiological survey estimated the incidence of snakebite at 623.4/100,000 population per annum (95% CI: 513.4-789.2/100,000), translating to 589,919 snakebites per year resulting in 6,041 deaths [14]. In one large hospital in West Bengal, snakebite was the most common cause of poisoning, ahead of organophosphate exposure, rodenticides, alcohol, other chemicals, and drugs [15], while in Kampala (Uganda) it ranked as the fourth most common cause of admission for treatment of poisoning [16]. At Kaltungo Hospital in Gombe State, Nigeria, 6,687 snakebites were treated in just three years, while in Burkina Faso 114,126 snakebites were reported nationally over a five-year period (2010-2014) [17, 18].

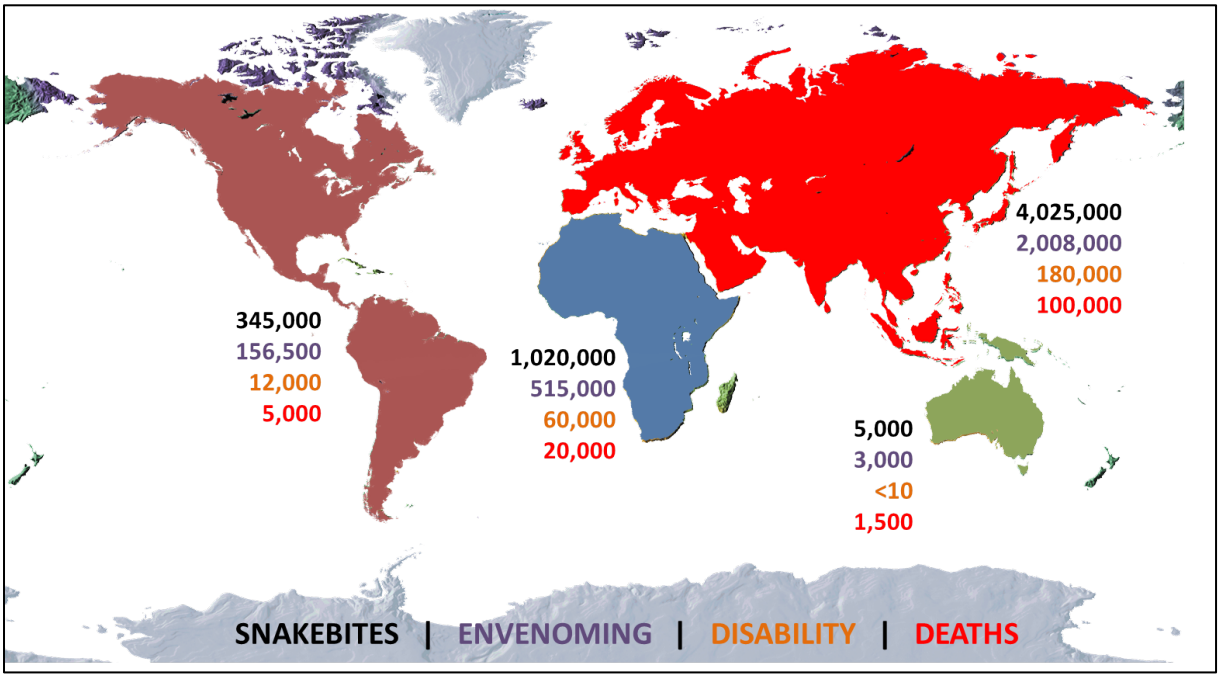



**Figure 1.** Estimations of numbers of snakebite envenomings and deaths in various regions of the world [1, 2].

Gaining a better understanding of the burden of snakebite envenoming at regional, national and district levels is the major challenge to designing and targeting an adequate response. Community-based studies conducted in some countries have revealed much higher incidences of snakebite envenoming and its consequences than hospital returns and other official ministry statistics have suggested [10, 14, 19-22]. A nationwide community-based study of snakebite mortality in India provided a direct estimate of 45,900 (99% CI: 40,900-50,900) snakebite deaths in 2005, which is more

than 20 times higher than the Government of India's official figure [3]. Similarly, when comparing the reported hospital-registered mortality in one district of Sri Lanka with data from the Registrar-General on deaths, it was found that hospital statistics missed 62.5% of deaths [23]. In the Lao People's Democratic Republic snakebite incidence ranging from 355/100,000 persons per year to 1,105/100,000 persons per year have been reported [20]. A study in Papua New Guinea observed an incidence of 215/100,000 persons per year in one province, but with localised incidence as high as 526/100,000 persons per year, and provincial mortality of 7.9/100,000 persons per year [24]. A landmark study from Nigeria in the 1970s reported an incidence of 497/100,000 persons per year with 12.2% case fatality [21]. More recently case fatality rates as high as 35-45% have been reported in the same area of Nigeria in the absence of effective antivenom, while provision of a single vial of an effective antivenom to snakebite victims, saw this figure drop to just 1.5% among a cohort of 5,367 patients [17].

## The hidden nature of a skewed disease burden

National data on the incidence of snakebite often overlook and mask the high incidence of this disease in specific rural settings usually inhabited by indigenous groups and other impoverished sections of the population. This is because the addition of urban populations to national snakebite incident rate data skews calculations by diluting the impact of snakebite in the rural areas. This phenomenon has been dubbed the 'tyranny of mean values' [25]. In Nigeria, for example, the annual incidence of urban hospital-admitted cases was 3.1/100,000, compared to rural hospital-admitted case incidence of 65.7/100,000 [4]. Similarly, in Costa Rica, the annual incidence nationally has been estimated at 13.8/100,000, but when urban data is excluded, the substantially higher incidence in districts along the rural Pacific coast (100 to 187/100,000) is revealed [26]. In Brazil, the annual incidence in the Amazonian region is much higher than the incidence in the whole country [27]. A meta-analysis of Sub-Saharan African data reported annual urban incidence and mortality rates of 5.2/100,000 [95% CI: 4.1–6.4] and 0.06/100,000 [95% CI: 0.02–0.1] respectively compared to annual incidence of 56.4/100,000 [45.2–67.7] and mortality of 1.35/100,000 [0.96–1.75] across many African nations [4]. A study of snakebite in 16 West African nations reported highly variable incidence rates of 8.87–93.3/100,000 and mortality of 0.5–5.9/100,000 [5].

In many regions of the world, large proportions of people affected by snakebite have been shown to make use of traditional medicine rather than attending conventional health facilities. In many cases this may be culturally-based, but it also occurs through necessity (when conventional health care is inaccessible) and through ignorance of the availability of conventional treatment. A study in Mali reported 49.7% of victims seeking initial treatment from traditional sources [28]. In Nepal 56% of victims resorted to traditional medicine as primary health-seeking behaviour [29] and in Kenya the figure is at least 68% [8]. The reasons for this dependence on traditional medicine are cultural, financial and logistical. In addition to affecting the clinical outcomes of snakebite envenoming, it also contributes to the invisibility of snakebite envenoming in conventional measurements of disease burden because traditionally treated patients are unreported.

## The broad scope of suffering

Snakebite envenoming may lead to death, but for many more victims it causes deep and long-lasting physical and psychological outcomes. Snakebite incurs large numbers of disability-adjusted life years (DALYs) in Africa, influenced by factors such as the size and density of human and snake populations, environment and effectiveness of health systems (e.g., annual DALYs in Guinea Bissau

and Nigeria were 1,550 and 124,484, respectively). Overall, 319,874 DALYs annually are lost from snakebite in West-Africa [5].

It is estimated that snakebite contributes to 400,000 permanent disabilities globally each year, including amputations of which there are an estimated 6,000-14,000 in sub-Saharan Africa alone [4]. Examples of other types of sequelae secondary to snakebite envenoming include limb contracture, neurological complications [30], chronic ulceration, sometimes evolving to carcinoma [31], chronic renal failure [32, 33] and long term musculoskeletal disorders including limb swelling, muscle wasting, altered gait, strictures and impaired balance [30]. A permanently disabled family member becomes a long-term drain on resources, generating an expanded wave of 'social suffering' that affects the victim as well as their relatives and the community as a whole [34, 35].

The psychological effects of snakebite are under-recognised. A Sri Lankan study suggested that snakebite could precipitate long-term psychological sequelae; the occurrence of post-traumatic stress syndrome was similar to that observed after the 2004 Asian tsunami or road traffic accidents [35]. Acute stress disorder, post-traumatic stress disorder (PTSD), chronic PTSD and social-anxiety are common in snakebite patients, particularly in women and young people [36, 37]. Non-physical symptoms including frequent psychological re-experiencing of the event, persistent avoidance of thoughts and situations associated with the attack, emotional unresponsiveness, increased irritability, disturbed sleep and being easily startled, were reported. The combination of physical and psychological sequelae can result in stigmatization of snakebite victims, greatly affecting their contribution to, and participation in community life [35].

Despite the fact that most people bitten by snakes are young men or boys [3, 38-42], women and girls are also vulnerable to snakebites associated with agricultural activities or snake infestation of their home environment [43]. There is a high risk of maternal mortality and foetal loss [44-46] that adds to the other physical and psychological sequelae of snakebite envenoming in diminishing the quality of life and socioeconomic prospects for young women and girls [45].

## The high burden of snakebite in impoverished rural communities

The occurrence of high rates of snakebite morbidity and mortality coincides with the poverty in regions of a developing economy [8], and has been well demonstrated in Costa Rica [7, 26]. This is in part explained by the presence of some of the medically most important snake species in impoverished rural, agricultural regions of Africa, Asia and Latin America, and also by the dearth of effective preventive measures in these populations, such as lack of footwear, bed nets and well-constructed houses [47, 48]. The link between poverty and inadequate health services becomes clear in studies focusing on the association between delay in medical attention and case fatality rate and incidence of sequelae [49].

There are striking variations in the mortality rate and case fatality rate between regions where antivenom and other medical treatments are available, and impoverished rural regions where access to antivenom and medical attention is rudimentary. Case fatality rates higher than 10% have been recorded in some regions of Nigeria and are associated with very low rates of attendance at medical facilities [21, 49]. Communities living in poverty have poor access to health services, and when people decide to seek medical treatment, treatment may be delayed by many hours [49, 50]. For all patients, mortality and morbidity is exacerbated by delayed treatment, which is a feature of snakebite in rural and regional communities [19, 49, 51-53]. Delayed presentation is often due to distance, lack of transport, fear or ignorance of antivenom, mistrust of healthcare workers, and favouring inappropriate

traditional therapies [19]. In some parts of Africa, more than 75% of people visited traditional practitioners before seeking conventional medical care [4].

### The economic burden of snakebite

The cost of treatment for snakebite envenoming is a major barrier to effective health care. For antivenom alone, depending on the product used, the cost has been reported to range from US$55-640 per effective treatment, with an average of US$124 [54]. Taking into account the cost of an effective dose of antivenom, diagnostic tests, transport to hospital, sustenance and supportive care during hospitalisation, as well as treatment of any adverse antivenom reaction, the average treatment cost in a Nigerian study was US$216.25 [53]. In India, it has been reported that, compared to a mean annual income of US$147-221, the initial cost of treatment in some communities is as high as US$5,150, with an additional US$5,890 for long-term costs [10]. This amounts to approximately 12 years' worth of income for the average farmer or herdsmen. In addition, delays in seeking treatment are associated with higher costs of care [10]. In neighbouring Bangladesh, the mean cost to a household of snakebite envenoming was US$231 but ranged as high as US$2,294, whilst median household income was only US$50 per month [11]. A study conducted in Zimbabwe found that the average cost of keeping an envenomed patient in hospital (excluding cost of treatment itself) was US$225 per day [55].

For rural people who already live in poverty, snakebite envenoming drags them deeper into a vicious cycle of poverty, owing to (i) unemployment as a consequence of the bite, and (ii) the high cost of treatment in many settings, which forces and their families to sell crops, cattle, belongings, land, or to take out loans [10, 11]. While data on the contribution to poverty are lacking, research in India demonstrates that 18% of victims or their families had to sell crops worth 9 months of average salary, another 14% sold valuable items worth 3.6 years of income, 9.3% sold livestock worth 1 year of income, 5.4% sold bicycles or vehicles costing up to 9 months income, and 3.9% sold land that accounted for a staggering 14 years of personal income [10]. In Bangladesh 73.5% of victims in one study resorted to spending savings and 61.4% took out loans to meet treatment costs [11]. Denied the ability to work and generate income, the prospects for further socioeconomic advancement of snakebite victims are dismal. Snakebite fatalities, as well as cases where there is severe incapacitation or disability, increase the economic damage to families, and the resulting loss of productivity affects the whole community. In some instances, families are forced to remove children from education due to the lack of resources to meet school fees after a family member falls victim to snakebite [10]. In other cases, children must forego education in order to assist with income generation, or to care for a disabled snakebite victim.

## SECTION 2: POPULATIONS AT RISK FROM SNAKEBITE ENVENOMING

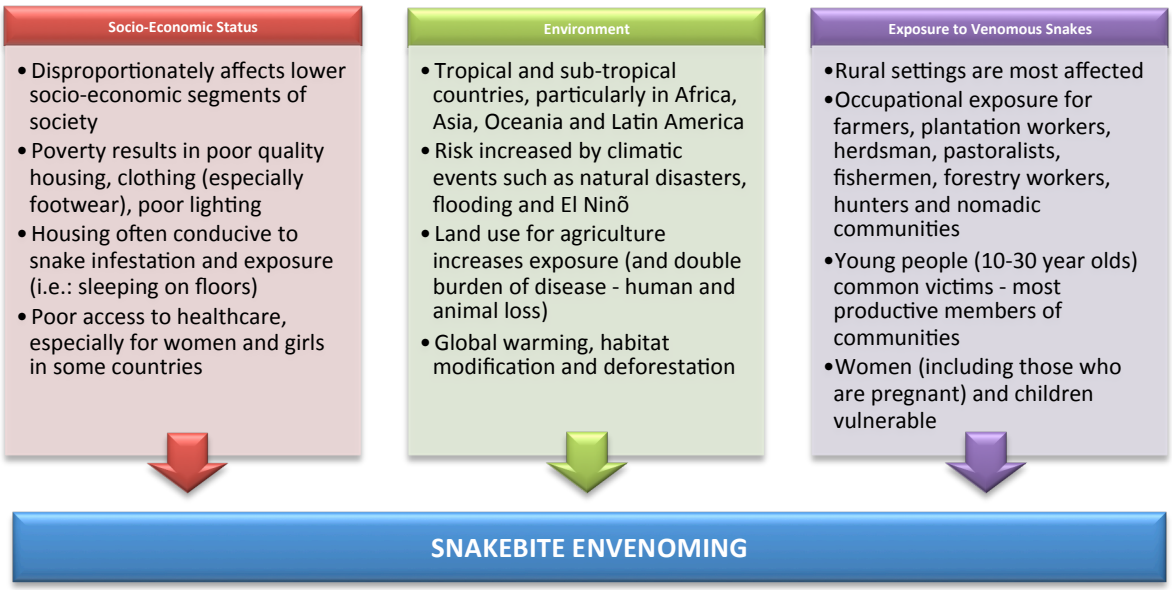
- The populations at most risk from snakebite are those living in rural parts of the tropics and subtropical areas; predominantly Africa, Latin America and Asia.
- Communities living in rural areas and indigenous peoples have the highest risk of exposure to and contact with snakes.
- Occupational exposure subjects agricultural workers, plantation workers, fishermen and hunters to a high risk of snakebite.
- Snakebite particularly affects the lower socioeconomic segments of society.
- Incidence of snakebite is highest for those in the age range 10-30 years old.

- Women and children are especially vulnerable.

## Risk factors

The distribution of snakebite envenoming around the world is subject to three main drivers; socio-economic factors (often related to poverty), environmental factors and heightened exposure to venomous snakes—usually through occupation or habitation (Figure 2).

**Figure 2:** The main drivers for snakebite envenoming.




## Distribution driver: Socio-economic status

Snakebite particularly affects the lower socio-economic segments of society. Countries with lower gross domestic product (GDP), human development index (HDI) and low healthcare expenditure are the most affected by snakebite [8, 54]. Multiple studies of snakebite from around the world all point to low socio-economic status or poverty as a key demographic feature of populations in which snakebite incidence and mortality are high [3, 6, 8-11, 14, 18, 26, 56-67]. Many of the populations at greatest risk are rural agricultural communities [4, 20, 29, 57, 68-82]. In Belo Horizonte in south-east Brazil, a case-control study found that the odds ratio among rural people for snakebite envenoming was 14.7 [68]. In Lao People's Democratic Republic poverty was identified as a key factor in the higher incidence of snakebite reported in Phin district, Savannakhet Province [20]. Almost half of all snakebites reported in the Niakhar area of Senegal occurred in poor agricultural workers [74]. A meta-analysis of snakebite envenoming in Sub-Saharan Africa found that 95% of an estimated 314,078 (95% CI: 251,513-377,462) envenomings each year occurred in rural populations, and that young men and boys involved in agricultural work were most at risk [4]. While that study estimated mortality at 7,331 (95% CI: 5,148-9,568) based on attendance at health facilities, it also reported that household surveys indicate that both incidence and mortality are likely 3-5 times higher than these estimates. A study in Tanzania found that snakes were frequently encountered in areas where livestock were grazed, and as a result the incidence of snakebite was higher there than among other agricultural activities [69]. The association of snakebite with livestock farming undoubtedly results in a double burden of disease (human and animal loss) and highlights the importance of approaches which manage the risk of envenoming at the human-animal ecosystem interface. In Costa Rica, cattle are often victims of

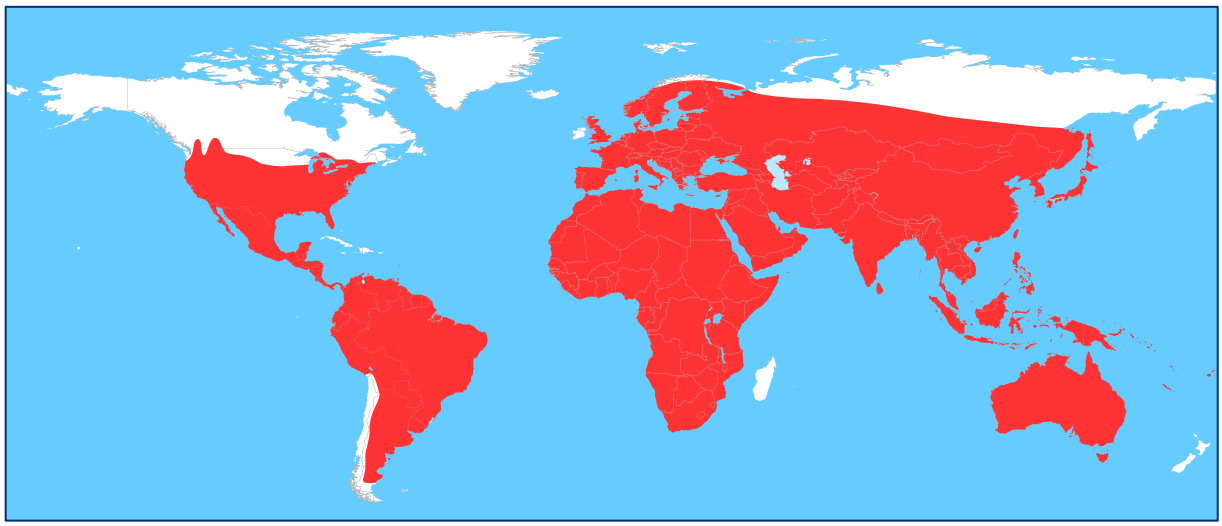
snakebite envenoming, and approaches to treating envenoming with antivenoms have been examined as a means of reducing economic losses to farmers [83].

Poverty limits access to secure dwellings, clothing (especially footwear, which may even be non-existent) and other amenities, such as indoor sanitation, lighting, and services such as transport and health care. Poor socio-economic status means that people living in poorly secured dwellings often sleep on the ground, which results in a significantly increased risk for snakebite. In northern India, Sri Lanka, Nepal and some other parts of Asia, bites by neurotoxic kraits are common under these circumstances [29, 38, 75, 84-88]. In Sub-Saharan Africa some species of cobra will enter homes at night in search of food (rodents), leading to bites to sleeping victims [89, 90]. Many victims are bitten while they are walking outdoors (during the day and in the night) in situations where footwear would prevent a large proportion of bites [22, 56, 59, 70, 72, 91-99]. Footwear is associated with lower odds ratios of infection for several NTDs, such as buruli ulcer, hookworm and soil-transmitted helminth infections, but its effectiveness in preventing snakebite, while logical, is yet to be formally evaluated [100]. Access to footwear is a financial challenge to many people of low socio-economic status in snakebite prone regions of the world [101, 102]. A further consequence of poverty is poor access to sanitation [103], and many victims of snakebite are bitten, particularly at night, because of their lack of access to a toilet, which forces them to walk away from their dwelling to urinate or defecate.

## Distribution driver: Environment

Venomous terrestrial and marine snakes are distributed throughout sub-tropical and tropical regions of the world (Figure 3). Snakes are ectothermic poikilotherms that rely on external sources of heat, and as a consequence they are far more abundant in warmer climates. This restricts the hyper-endemic regions for snakebite to tropical countries of Africa, South Asia, New Guinea and Latin America. In those countries, snake-human contact is relatively common although incidence may be seasonal (often during the rainy season) or may peak during periods of heightened agricultural activity, particularly if they coincide with the reproductive cycle of venomous snakes, or due to climatic or seasonal factors [3, 43, 105-107]. A study in Costa Rica showed that incidence of snakebites had increased in association with El Niño Southern Oscillation (ENSO), affecting primarily impoverished populations [7]. The emergence of powerful Geographical Information System (GIS) applications has the potential to rapidly inform control measures for snakebite envenoming by enabling environmental, seasonal and climatic factors to be evaluated and modelled [26, 60, 105, 107-109]. Evidence from China suggests that some snake distributions will shift towards temperate regions of the world as global warming continues, although expansion or contraction in other directions is also predicted based on observed changes over the last half century [110]. Living in poorly constructed homes, in conflict zones, or in places subject to natural disasters predisposes poor people to snakebites [111]. In Asia, snakebite envenoming has become a leading cause of mortality following floods brought on by monsoons [47, 111] and predictable seasonal storm surges and tidal bores in Bangladesh [112]. In Nepal up to 80% of snakebites have been reported to occur during the monsoon season [19] and this pattern has been observed in other countries, including India, Cameroon, Papua New Guinea, Republic of Congo, and Nigeria [3, 24, 43, 72, 77]. Seasonal variations in snakebite envenoming are often most pronounced in temperate regions where the summer/winter temperature differential is the greatest. In South Africa, it was reported that 84% of snakebites occurred during the warmer months of the year [113]. Similar season patterns have been observed in Brazil [68] and Papua New Guinea [24] and the result of seasonal weather changes, whereas in some tropical countries such as Burkina Faso the seasonal variation has been linked to agricultural activities [114].

**Figure 3**: Global distribution of terrestrial and marine venomous snakes showing regions where people are at risk of snakebite envenoming (Source: WHO Snake Antivenoms Database).



## Distribution driver: Exposure to snakes (high risk groups)

Snakebite predominantly affects people living in rural areas, mostly farmers, plantation workers, herdsmen, pastoralists, fish farmers, fishermen and hunters [104]. It causes mortality and morbidity among tea pickers in southern India and Sri Lanka [112, 115], coffee plantation workers in Western Vietnam and Brazil [116], rubber tappers in Liberia [117], Thailand [118], Malaysia [119], other South-East Asian countries, and Brazil (seringueiros) [22], and sugar cane workers in South Africa, Saint Lucia and Martinique [120]. In Myanmar, snakebite has been the fifth single leading cause of death, affecting particularly the rice paddy farmers [121]. It is also a risk for fishermen using hand nets and lines in warmer tropical seas [122]. Furthermore, snakebite is a hazard for indigenous nomadic peoples, hunter-gatherers, tribals, firewood collectors, gypsies, itinerants, and indigents. This has been documented in South America [22, 123, 124], Africa (e.g., Hadza hunter-gatherers of Tanzania, the African Bushmen of the Kalahari/Southern Africa, the nomadic Fulani and Turkana pastoralists of savanna West Africa and Kenya) [53, 125], India and Sri Lanka [57]. It has been an important cause of deaths among the Aborigines of Australia, the Malaysian Orang Asli, New Guinean Fore highlanders, and Yanomami and Waorani tribes in the Amazon [124, 126, 127].

Morbidity and mortality occurs most frequently in people aged from 10-30 years old [9, 82, 91, 128, 129], often the most economically productive members of their communities. In some places, children are regular victims of envenoming [130, 131] and young children (less than 5-years-old) have been shown to suffer higher case fatality [132]. In India, the proportion of all deaths from snakebites was highest at ages 5–14 years, especially in regions where child agricultural labour is prevalent [3, 133]. Children are exposed while playing [134] or when walking in long grass, fields or forests. In Papua New Guinea, the case fatality rate following snakebite was higher in children (14.6%) than in adults (8.2%) [135]. Women may face particular disadvantage in accessing medical care in some cultures, while pregnant women are extremely vulnerable to risks of ante-partum haemorrhage, abortion and foetal death [44, 53]. Snakebite has been recognised in Nigeria and Sri-Lanka as an important cause of maternal and foetal loss as well as abortion [4, 53, 129].

## SECTION 3: STRATEGIES FOR CONTROL

- A coordinated programme managed by WHO and based on intensified disease management could result in immediate, effective control of snakebite morbidity, disability and mortality.
- The use of antivenom is one of the main control measures for snakebite envenoming, and while the effectiveness of this antidote has been hindered in the past by a range of issues, the adoption of an IDM approach can efficiently overcome these problems.
- Reliance on antivenom availability alone ignores the potential to implement a much broader innovative, intensified campaign to tackle snakebite envenoming at a disease management level that emphasises the role of community education and prevention.
- Snakebite envenoming shares all of the characteristics of other NTDs which are managed through intensified disease management.
- A comprehensive strategy for controlling the burden of injury due to snakebite should be established in consultation with all stakeholders, and must include a timetable for all the activities.

### Current approach to control

The mainstay of efforts to control the consequences of snakebite envenoming for over 120 years has been immunotherapy with animal-derived antivenom preparations. Antivenom is the most effective treatment for most kinds of snakebite envenoming [136]. This post-bite therapy case management approach is essential, given the inappropriateness and inefficacy of preventive strategies such as pre-bite immunisation [136-139]. However, in addition to poor availability and accessibility of antivenoms in some regions of the world, a major barrier to the successful control of snakebite envenoming using this approach has, until recently, been the lack of appropriate control and regulation of snake antivenom preparations themselves [140]. No minimum specifications for antivenom potency, dosage, effectiveness or safety exist and some manufacturers even lack the resources to carry out currently accepted mouse potency assays. Poor health systems and weak regulatory frameworks to ensure the suitability, safety and efficacy of products have given rise to a situation in which some marketed antivenoms are both unsafe and ineffective [141, 142]. In addition, the absence of formal programmes to control and treat snakebite envenoming has affected the market so that antivenom manufacturers have struggled to establish and maintain sales, leading some, such as Berhingwerke (Marburg, Germany), Syntex (Brazil) and, most recently, Sanofi Pasteur (Lyon, France), to abandon production [143]. Antivenom treatment often needs to be supplemented by other medical interventions, ranging from cardio-respiratory resuscitation and mechanical ventilation [135, 144, 145], to haemodialysis [145-147], wound debridement and reconstructive surgery [5, 111, 148], and, of course, rehabilitation services [149]. Reliance on antivenom availability alone ignores the potential to implement an innovative, intensified campaign to tackle snakebite envenoming at a disease management level, whereby prevention, improved primary first aid and transport to medical care, treatment, rehabilitation and training of medical staff are all addressed in an integrated manner to reduce morbidity, mortality and disability.

### Proposal for immediate control through Intensified Disease Management (IDM)

Snakebite envenoming shares all of the characteristics of other NTDs (Buruli ulcer, Chagas disease, Trypanosomiasis, Leishmaniasis and Yaws) which are managed through intensified disease management (IDM):

1. It can be potentially costly and difficult to diagnose, treat and followup patients (crucial for those who have residual disability);

2. The burden of injury is poorly understood because reporting and surveillance systems require urgent improvement;
3. Specific control tools are lacking, but investment in research and design of programmes promise opportunities to improve prevention, first aid, diagnosis, treatment and rehabilition;
4. Investment in research and development has been disproportionately low, considering the scale of the problem;
5. The vast majority of victims are are disadvantaged by their poverty and rural abodes, often in remote areas, that have limited access to diagnosis and treatment.

It would prove impossible and ecologically unsound to eradicate venomous snakes and, in doing so, eliminate all instances snakebite envenoming around the world. However, as with many other neglected tropical diseases, there are enormous opportunities for effective control through coordinated programmes of prevention and case management, coupled with effective regulation and control of antivenoms, improved access to affordable, safe, clinically effective and WHO prequalified antivenoms. The impossibility of eliminating snakebite envenoming may set it apart from some other NTD programmes that have eradication as a feasible target, but should certainly not exclude snakebite from recognition as an NTD. Like other environmental NTDs, such as buruli ulcer and leishmaniasis that are susceptible only to control programmes, due to their complex epidemiology, lack of diagnostic tools and effective therapies, snakebite is immediately amenable to control by applying some of the same strategies and methodologies that are employed in these diseases. Realistic control targets can be set once reliable baseline data have accrued. Targets for reduced DALYs, quality-adjusted life years (QALYs), costs of treatment, national GDP losses, numerical mortality, morbidity and disability should be established and adopted to measure progress towards achieving effective control. This is similar to the setting of case and mortality reduction targets for the dengue virus, or the adoption of percentage targets for cases of leishmaniasis or Buruli ulcer, treated with effective medicines.

The effective control of snakebite envenoming through intensified case management will incorporate a range of strategies, including:

**1.** Active prevention of contact (e.g., footwear, snake-proofing dwellings, use of protective [mosquito] bed-nets, raised sleeping platforms and improved lighting at night), together with educational programmes which detail safer methods for carrying out chores (such as collecting firewood, picking up piles of raked leaves, etc.) and work tasks (such as harvesting crops, hunting, etc.). The use of footwear to prevent envenoming also potentially affords protection against hookworms and other soil-transmitted helminths, *Burkholderia pseudomallei*, schistosomiasis, buruli ulcer, tropical ulcers and podoconiosis. Bed-nets are well established control strategies for preventing arthropod-borne diseases, protecting against ectoparasite infestation and nocturnal krait bites [87]. Prioritizing, developing and implementing prevention strategies, and ensuring adequate and effective communication of key messages is fundamental.

**2.** Establishment of effective, safe and affordable first aid strategies that delay the evolution of clinical illness, allowing victims of envenoming to reach health care facilities for diagnosis and treatment. Current methods need to be validated and a consensus reached on what is appropriate and practicable. WHO promotion of a validated first aid approach to snakebite envenoming could substantially improve survival, and be integrated with community programmes to encourage appropriate health-seeking behaviours.

**3.** Training of health professionals to implement standard treatment protocols and algorithms, and provision of diagnostic tools (such as rapid immunoassay for research purposes), will strengthen health systems and so improve medical management of snakebite victims.

4. Development of a robust system for hospital and community-level surveillance of snakebite envenoming, including mandatory reporting of cases seeking treatment, notification of deaths, and active detection of cases through community surveys and outreach programmes. The use of integrated mapping technologies can greatly aid this process. A system similar to the human African trypanosomiasis (HAT) Atlas project, applied to snakebite and integrating biological data (venomous snake distributions) with complex clinical and epidemiological geospatial data could be combined with health infrastructure, transportation, drug distribution and other information to develop a dynamic and responsive resource planning tool. This could be used to ensure that the right antivenoms are available, in sufficient quantities, in the right places at the right times.

5. Establishment of standard definitions and measurements to facilitate the accurate collection of data and comparability. An important issue is the definition of treatment effectiveness by identifying more objective end-points. Current measures of antivenom efficacy focus on the ability of antivenom to prevent lethality (in animal models of variable validity), yet the reality of snakebite envenoming is that lethality is just one outcome measure, albeit the most important. Reliable indicators of morbidity and disability need to be established, as has been done for trachoma and is in progress for lymphatic filariasis. Effectiveness of antivenoms must be measured against specific clinical types of envenoming (e.g., local necrosis, haemorrhage, coagulopathy).

6. Improved access to medicines, especially safe, effective and affordable antivenoms through programmes that reduce prices through collective bulk purchasing by consortia (governments, NGOs, aid donors) and improved distribution. These biologicals should be financed through strategies ensuring that no end-user has to pay more than an equitably nominal cost for treatment. Whether this is achieved through donations from WHO partners or through financing that exemplifies *Access to Medicines* principles, removal of high costs from end users and their families is essential if effective control is to be promoted and achieved. Access to low-cost or cost-free antivenom is usually required only once in a person's lifetime (after their snakebite), while successful treatment will restore that person to productive life without the need for the redosing that is essential to control or eliminate some other NTDs. Building capacity that can ensure that antivenoms are delivered to where they need to go, and that their usage is monitored and reported as part of an ongoing forward-needs assessment process will underwrite the long-term sustainability of the programme.

7. Like drugs for diseases such as leishmaniasis, antivenom production is sometimes impaired by factors such as poor quality control, low production and failure to anticipate production levels that can provide an adequate, sustained supply. Collaboration with the WHO Essential Medicines and Health Products (EMP) department to improve manufacturing and quality control (QC) systems and to prequalify antivenoms will address and correct problems with both production quality and quantity. Improvements to regulatory systems, the establishment of regulatory networks and strengthened procurement and distribution systems will ensure that high quality products are licensed, purchased and their need accurately forecast.

8. Strengthening of health systems to improve the treatment of snakebite envenoming in health facilities from admission through to discharge, and follow-up (especially important where local tissue injury and disability are involved). As with other NTDs for which preventive chemotherapy is unavailable, and where intensified case management is the focus, the priority should be accurate early diagnosis, effective treatment and management of complications.

9. Investment in the improvement of existing antivenom treatments, and in the development of innovative future treatments. Current antivenoms require improved safety, efficacy, coverage and

standardization. No minimum specifications for the neutralising potency or efficacy of antivenoms, nor the ability to measure this, currently exist in most countries. Even where specifications have been established, they may be irrelevant to the clinical realities of human envenoming. Investment in research can help to ensure that antivenoms are able to effectively neutralise the important clinical effects of snake venoms. There must be investment in improving reporting and surveillance; prevention; first aid; ancillary treatments; rehabilitation; and research on economic impacts, clinical and other benefits. These aspects should be emphasised within any global programme.

In addition to an intensified disease management approach to the control of snakebite envenoming, the application of strategies currently being used to address neglected zoonotic diseases, that focus on assessment of burden, the health economics of interventions, Member State capacity building, advocacy, and the building of strong collaborative partnerships and multi-disciplinary and cross-sectoral partnerships, can also contribute to effective, immediate control. Developing a more dynamic understanding of the natural ecology of venomous snakes and the factors which contribute to increased risk of human envenoming would greatly enhance efforts at control. Snake species are diverse, occupying a multitude of environmental niches, and even among similar species the factors which create human-snake conflict and lead to envenoming may vary markedly. Just as the control of zoonotic diseases such as rabies, HAT or schistosomiasis requires an understanding of the ecology of animals involved in harbouring and transmitting disease, controlling snakebite effectively necessitates an in-depth understanding of the ecology and biology of venomous snakes, and the environmental parameters that bring snakes into contact with humans.

Evidence suggests that human influence on the environment can lead to greater incidence of snakebite [150]. Some agricultural practices (e.g., plantation farming, land-clearing for livestock, soil tilling) can result in large rises in the number of snakebites. Understanding the complex ecological factors that drive this increased incidence would be very useful in designing programmes to mitigate risk and avoid snakebites. In much the same way as the control of rabies depends on either pre-exposure or post-exposure prophylaxis with vaccines, the treatment of snakebite is dependent on post-exposure treatment with antivenom (an animal immunoglobulin preparation). Controlling snakebite through improved access to effective antivenoms offers the best option for immediate reductions in morbidity and mortality. Thanks to work that has been undertaken by the WHO over the past 12-18 months, Sub-Saharan Africa will soon have a list of antivenom products deemed to be safe and effective against the venoms of snakes from across the continent. A more formal prequalification for antivenoms will also be developed by the WHO between now and 2018. In much the same way the NTD department's approach to rabies calls for investment in vaccines, parallel investment in stockpiles of WHO recommended snake antivenoms, and targeted partnership at country, province, district and local government level with health ministries, could lead to substantial improvements in the treatment of envenoming, reducing the impact of injury significantly and sustainably.

Other approaches used by the WHO NTD department in the fight to control, eliminate or eradicate NTDs can also help in the control of snakebite envenoming. Improved sanitation and the promotion of healthy environments (part of the WASH strategy) can directly contribute to reductions in vermin populations (e.g., rodents) upon which some venomous snakes feed, and the presence of which increases the risk of snakebite envenoming. Likewise improving access to toilets and latrines can alter behaviours which expose people to increased risk of snakebites. Communities with safe water supplies make women and girls in particular, less vulnerable to snakebite by reducing the distance travelled to fetch water, wash clothes or bathe. While these are indirect measures, they should nevertheless be

assessed for impact as part of a common global strategy designed to reduce the risk of exposure to snakebite envenoming.

### Implementation

The first step towards implementation should be the development of a comprehensive roadmap for controlling the burden of injury due to snakebite. This must be established in consultation with all stakeholders, and must include a timetable for all of the activities. Partners who can assist the WHO with advocacy, coordination and the identification and mobilization of resources should be identified and a working group established to implement the roadmap. In tandem, the WHO should engage in projects within its current capacity to (i) raise the issue through effective communications, (ii) improve access to safe, effective and affordable antivenoms, (iii) improve medical management of snakebite envenoming by health professionals, and (iv) develop tools, resources and activities essential to facilitating rapid deployment of a full programme of action once personnel and funding are in place.

## SECTION 4: ADDRESSING RESOURCE ALLOCATION AND COMMITMENT

- Globally, very few resources (research, financial, time, management and human) are allocated to the development of diagnostic tools, medicines and control measures to address this increasingly recognised public health hazard.
- Commitment at national, regional and global levels is severely lacking to foster appropriate resource allocation.

### Antivenom development

The lack of recognition given to snakebite envenoming has contributed to poor investment in research and development aimed at reducing or controlling the burden and its clinical consequences. Antivenoms have been used to treat snakebite envenoming for more than 120 years and are recognised by the WHO on the Model Essential Medicines list. In spite of this, the design, production and formulation of antivenom products remain largely unchanged due to negligible investment in research. The results of this neglect have been acknowledged by the World Health Organisation [151].

Antivenom development is expensive, in part because products must be designed to neutralise an array of toxins from several different snake species in most regions where the antivenom will be used. There is therefore no universal formulation that can be used globally. Lack of investment makes producers reluctant to innovate, preferring to avoid regulatory bureaucracies by manufacturing their products using traditional, available technologies. This is despite the fact that focal investment in production innovation could ultimately reduce costs, improve production efficiencies, increase quality and deliver greater safety and effectiveness. Support for research and development to produce improved products or new and innovative therapeutic interventions at a level that is commensurate to the burden of injury and human suffering is urgently needed, and would help greatly in efforts to effectively control the worst consequences of snakebite [152]. Major drug companies around the world have neglected production of antivenom because it is not profitable. The production of Fav-Afrique by Sanofi Aventis is permanently discontinued; the last batch was released in January 2014, with an expiry date of June 2016 [143]. In Africa, the production of antivenom constitutes less than 25% of the amount needed to treat moderate snakebite envenoming [54, 153].

A lack of investment in research and innovation within the antivenom field has hindered the development of new products, and resulted in the persistence of outdated production methodologies

and a lack of fundamental clinical research necessary to define realistic measures of effectiveness and to push antivenom research and development (R&D) towards new technologies and improved minimum standards of safety and effectiveness. The proliferation of poorly manufactured, ineffective, expensive and sometimes dangerous antivenoms is the consequence of poor regulation, and limited investment in antivenom innovation. Unscrupulous marketing of unsuitable and mislabelled antivenoms is not uncommon in some countries [142]. Not surprisingly, these factors undermine confidence in antivenoms, leading to mistrust, further neglect and a futile cycle of declining availability. It has been estimated that less than 10% of the predicted antivenom needed for sub-Saharan Africa has been properly assessed for safety and efficacy [54, 153].

## Diagnostics

Where good quality polyspecific antivenoms are available that provide protection against the toxic effects of all medically important venomous snakes in a given region, the need for specific diagnosis to enable antivenom selection is reduced. In some countries and regions, lack of such products means that clinicians may need to make informed diagnostic decisions in order to select the correct antivenom product, and decide upon the right dose. In such cases, observation of clinical signs and symptomatology is often a poor guide to the severity of an envenoming, or is unable to predict the likelihood of late sequelae forming. Current clinical methods for determining severity of snakebite, and efficacy of treatment, are largely observational and lack the accuracy and specificity of modern laboratory testing [154, 155]. Where decisions about antivenom choice need to be made, knowing the species of snake involved in the bite is important in determining treatment and dose, and can affect prognosis. Diagnostic tools that can improve the quality of clinical and epidemiological studies, and lead to better informed resource allocation, design of improved antivenoms, or enhanced community education are needed. Immunodiagnosis of circulating snake venom antigen has been shown to be a reliable way of identifying the biting species [155-158], but commercial point-of-care venom detection kits have so far been marketed only in Australia [159, 160]. One of the potential benefits of increased investment in diagnostics would be improved disease surveillance and causal attribution, which in turn would guide the future development of therapeutics, including antivenoms and inhibitors of specific toxic activities by other agents. In some settings this improved data would make it possible to reduce, modify or enhance the formulation of antivenom products to better neutralise the venoms of the species which cause the greatest burden of injury.

## Human resources

Many of the places in which snakebite is endemic are resource poor, and access to health professionals and to health facilities is often very limited. This contributes to poor health-seeking behaviours, delayed presentation to health facilities, and poor outcomes. Many remote health facilities lack the resources to adequately manage snakebite patients. In India, once a patient decides to seek conventional medical care, primary health centres are typically their first contact point, but many of these are without permanent staff and do not stock antivenoms. This contributes greatly to the current situation in which more than 90% of snakebite deaths occur before victims reach a secondary or tertiary-level hospital [161].

During medical and nursing school, many doctors and nurses may never come across the management of snakebite. Moreover, the literature available to health professionals presents a perspective that often fails to reflect the local context and makes assumptions not relevant to the rural contexts and resource settings that the snakebites are occurring in. A comprehensive snakebite management program tailored to local needs is essential to manage snakebite effectively [136, 138, 162-164]. This should

include both curriculum based teaching at medical schools as part the training of doctors and nurses, and the establishment of standalone snakebite management education programmes that target health professionals at all levels and especially those working in rural settings with a high incidence of snakebites.

## Financial and political commitment

A survey of National Health Authorities from 23 high-burden countries proved that snakebite ranks low on the international health agenda, with national health agencies (NHAs) ranking it as their lowest priority. As a result, NHAs have committed very little towards potential solutions, such as training healthcare workers, conducting epidemiological studies and developing comprehensive strategies for dealing with snakebite [165]. Indeed, the lack of reliable data on basic epidemiology of snakebite is cited by virtually every author to have published on this topic in the last 10 years. Whilst antivenom has been placed on the WHO Essential Medicines list, it has received no financial support from non-government donors to facilitate its procurement or distribution. In a list of 10 neglected health conditions in 16 countries in West Africa, snakebite ranked fourth in the number of DALYs lost, yet no funding was received from donor organisations for the procurement of antivenom, even though it remains the only specific antidote against snake envenoming [5].

The resources allocated are not commensurate with the burden of injury and death. In a study that evaluated funding for developing world health interventions from 42 major donors (comprising industrialized countries 23, international financial institutions 5, multinational pharmaceutical companies 6 and philanthropic foundations 8), annual donor dollar direct funding for 8 of 10 NTDs ranged from $3.30 per DALY for Intestinal Nematode Infections to $146.96 per DALY for Onchocerciasis [166]. There is no evidence that any amount was provided for snakebite envenoming by these donors during the period of the survey [167].

It is also possible that, by not ensuring availability of safe and effective antivenoms, governments are breaching obligations to ensure a right to health, under the United Nation's (UN) International Covenant on Economic, Social and Cultural Rights (ICESCR). Signatories to this convention must meet certain minimum expectations, regardless of their economic status, including the provision of safe and effective essential drugs, as defined by the WHO Action Programme on Essential Drugs. Since 2005 this has included some antivenoms [168]. This does not enshrine an individual's "right" to be healthy, but upholds governments' obligations to protect the healthof their citizens and provide access to life-saving treatments. In areas where snakebite is endemic, this would include ensuring adequate supplies of those antivenoms that have been proven to be safe and effective [168]. Ultimately, interventions must support health systems and strengthen government intentions and policies to provide universal health coverage.

Mr Kofi Annan recently called a meeting of stakeholders, including the WHO NTD department, and Essential Medicines Department, during which Mr Annan pledged his support, convening power and leverage on Heads of State to drive the campaign at a global level, and in particular in sub-Saharan Africa. Government commitment has also been strong with a Member State side event at the 69$^{th}$ World Health Assembly (WHA) sponsored by 19 member states, and more recently, strong commitments to support a resolution on snakebite at the WHA (2018) has been pledged at a meeting among ambassadors and UN permanent delegations from the following countries:

| | | | |
|---|---|---|---|
| Angola | Chad | Mexico | Peru |
| Benin | Colombia | Namibia | Uganda |
| Brazil | Costa Rica | Pakistan | |
| Cameroon | Ecuador | Panama | |
| Honduras | Guatemala | Philippines | |

## Conclusion

This dossier has presented the evidence for the addition of snakebite envenoming to the WHO category A list of Neglected Tropical Diseases. It makes a compelling argument in terms of core criteria that snakebite envenoming;

1. disproportionately affects populations living in poverty; and causes important morbidity and mortality—including stigma and discrimination—in such populations, justifying a global response;
2. primarily affects populations living in tropical and sub-tropical areas;
3. is immediately amenable to broad control, elimination or eradication by applying one or more of the five public health strategies adopted by the Department for the Control of NTDs; and/or
4. is relatively neglected by research (i.e., resource allocation is not commensurate with the magnitude of the problem) when it comes to developing new diagnostics, medicines and other control tools.

The creation of a universal roadmap for intervention, led by WHO and in collaboration with multi-sectorial expertise, will be the first step in a comprehensive action plan to control and eradicate the global burden of snakebite envenoming. The roadmap production process will identify the core areas for intervention, and as a first step consider the priorities outlined on page 13:

- awareness raising of the issue through effective communications;
- aim to improve access to safe, effective and affordable antivenoms;
- improve medical management of snakebite envenoming by health professionals, and;
- develop tools, resources and activities essential to facilitating rapid deployment of a full programme of action once personnel and funding are in place.

Member States and the global snakebite community, including public, private and civil society stakeholders are ready now to support WHO in every way possible to ensure adequate funding is made available, appropriate expertise is brought to the table and interventions are evidence-based and supported by the very best data available. The time is now to end the scourge of snakebite, and we commend this document to the Strategic and Technical Advisory Group for Neglected Tropical Diseases.

# Appendix A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