Toxicon:X 9–10 (2021) 100066

Contents lists available at ScienceDirect

Toxicon: X

journal homepage: www.journals.elsevier.com/toxicon-x

Snakebite envenoming in different national contexts: Costa Rica, Sri Lanka, and Nigeria

José María Gutiérrez [a,*], Kalana Maduwage [b], Garba Iliyasu [c], Abdulrazaq Habib [c]

[a] *Instituto Clodomiro Picado, Facultad de Microbiología, Universidad de Costa Rica, San José, 11501, Costa Rica*
[b] *Department of Biochemistry, Faculty of Medicine, University of Peradeniya, 20400, Sri Lanka*
[c] *Infectious and Tropical Diseases Unit, Department of Medicine, College of Health Sciences, Bayero University, Kano, Nigeria*

ARTICLE INFO

Handling Editor: Raymond Norton

Keywords:
Snakebite envenoming
Costa Rica
Sri Lanka
Nigeria
Antivenoms
Public health systems

ABSTRACT

Snakebite envenoming is a neglected tropical disease that predominantly affects impoverished rural communities in sub-Saharan Africa, Asia, and Latin America. The global efforts to reduce the impact of this disease must consider the local national contexts and, therefore, comparative studies on envenomings in different countries are necessary to identify strengths, weaknesses and needs. This work presents a comparative analysis of snakebite envenomings in Costa Rica, Sri Lanka, and Nigeria. The comparison included the following aspects: (a) burden of envenomings, (b) historical background of national efforts to confront envenomings, (c) national health systems, (d) antivenom availability and accessibility including local production, (e) training of physicians and nurses in the diagnosis and management of envenomings, (f) prevention campaigns and community-based work, (g) scientific and technological platforms in these topics, and (h) international cooperation programs. Strengths and weaknesses were identified in the three contexts and several urgent tasks to improve the management of this disease in these countries are highlighted. This comparative analysis could be of benefit for similar studies in other national and regional contexts.

1. Introduction

Snakebite envenoming (SBE) is a neglected tropical disease that exerts a heavy toll in terms of mortality and disability on a global basis, especially in sub-Saharan Africa, Asia, and Latin America (Chippaux, 1998; Gutierrez et al., 2017; Kasturiratne et al., 2008). Owing to the great diversity of venomous snakes and to the complexity of national and regional contexts where snakebites occur, it is of relevance to assess the characteristics of this disease in different continents and countries, to grasp common and variable features which may contribute to the design of effective intervention strategies. These should consider the common characteristics of SBE, while at the same time taking into consideration the different political, cultural, socio-economic, ecological, and health systems contexts of different countries. Such balance will provide better tools for effectively address this neglected tropical disease at various levels.

This work presents a comparison of several parameters associated with SBE in three countries of three continents, i.e., Costa Rica, Sri Lanka, and Nigeria, and illustrates the complexity of snakebites and their management in different settings. Table 1 and Fig. 1 depict some basic parameters which highlight the contrasts between these countries, as well as the burden of envenomings. The need to search for common interventions which, at the same time, consider the local contexts, becomes clear from the comparative analysis presented in this work.

2. The burden of snakebite envenoming

2.1. Costa Rica

Several studies have been carried out to assess the burden of SBE in Costa Rica. Based on records from the national social security system (*Caja Costarricense del Seguro Social*-CCSS), the average number of cases per year for the period 1990–2000 was 504, with an incidence ranging between 14 and 19 cases per 100,000 population per year (Sasa and Vazquez, 2003). The average incidence in the country for the period 1990–2007 was estimated in 13.8 cases per 100,000 population per year (Hansson et al., 2013). A more recent study described, for the period 2012–2014, an average of 473 cases per year, with incidences of 9.44 and 10.76 cases per 100,000 population per year (Sasa and Segura-Cano, 2020). Thus, the total number of snakebites occurring in this country per

* Corresponding author. Instituto Clodomiro Picado, Facultad de Microbiología, Universidad de Costa Rica, San José, Costa Rica.
E-mail address: jose.gutierrez@ucr.ac.cr (J.M. Gutiérrez).

https://doi.org/10.1016/j.toxcx.2021.100066
Received 9 March 2021; Received in revised form 18 May 2021; Accepted 19 May 2021
Available online 25 May 2021
2590-1710/

Table 1
Comparison of some indicators of Costa Rica, Sri Lanka, and Nigeria[a].

Indicator	Costa Rica	Sri Lanka	Nigeria
Population	5.0 million	21.8 million	200.9 million
Area	51,100 km^2	65,610 km^2	923,770 km^2
GNI[b] (US $)	59.05 billion	87.69 billion	407.59 billion
GNI per capita (US $)	11,700	4020	2030
Life expectancy at birth (years)	80	77	54
Mortality rate (under 5 years, per 1000 live births)	8.6	7.1	117
Immunization measles (% of children between 12 and 23 months)	95%	99%	54%

[a] Source: World Bank (data.worldbank.org); data of 2019.
[b] GNI: Gross National Income.

year has remained relatively stable over the last decades, although the incidence has decreased owing to the increase in human population (the population of Costa Rica in the years 2000 and 2014 grew from 3,925, 331 to 4,773,119, respectively) (Instituto Nacional de Estadística y Censos, 2015; 2003).

Snakebites in Costa Rica occur predominantly in lowland humid landscapes, with highest incidences in the central and south Pacific, Caribbean, and northern regions of the country (Arroyo et al., 1999; Hansson et al., 2013; Sasa and Vazquez, 2003). Snakebites vary greatly between regions, with some districts having incidences higher than 100 per 100,000 population per year (Hansson et al., 2013). In contrast, in the western Pacific region and in the central plateau incidences are generally lower than 10 per 100,000 per year (Hansson et al., 2013). Most cases occur in two periods of the year, i.e., May–July and October–December, which are probably related to rainfall patterns and agricultural activities, and also to the reproductive cycles of the snakes (Sasa and Segura-Cano, 2020; Sasa and Vazquez, 2003). Although snakebites often occur in agricultural areas, the number of bites in domiciliary and peri-domiciliary settings is high. (Sasa et al., 2009; Sasa and Segura, 2020). In 2012 and 2013 it was reported that 55% of snakebites occurred in domiciliary or peri-domiciliary areas (Sasa and Segura-Cano, 2020). Males are affected more than females (male:female ratio of 2.3) (Sasa and Segura-Cano, 2020) and cases are predominant in age groups ranging from 10 to 30 years old (Sasa and Segura-Cano, 2020; Sasa and Vazquez, 2003).

There has been a steady drop in mortality from snakebites in Costa Rica since the decade 1950–1959, and particularly after the decade of the 1970s (Rojas et al., 1997). In the period 1993–2006, annual mortality rates ranged between 0.02 and 0.19 per 100,000 population, with case fatality rates ranging between 0.18% and 1.15% (Fernández and Gutiérrez, 1993-2006). A recent study, which covered 50% of the total number of snakebites in the country in 2012–2014, reported only one death (Sasa and Segura-Cano, 2020). There is limited information on the sequelae resulting from snakebites, but a qualitative study underscored the impact of the physical, economic, social and psychological consequences of envenomings in the southern Pacific region of Costa Rica (Arias-Rodríguez and Gutiérrez, 2020).

Costa Rica harbors a rich snake herpetofauna comprising 141 species, of which 23 belong to the families Elapidae (6 species, genera *Hydrophis* and *Micrurus*) and Viperidae (17 species, genera *Agkistrodon*, *Atropoides*, *Bothriechis*, *Bothrops*, *Cerrophidion*, *Crotalus*, *Lachesis*, and *Porthidium*) (Solórzano, 2004). Most bites (>70%) are caused by the viperid species *Bothrops asper*, locally known as *terciopelo* (Bolaños, 1984; Sasa and Segura-Cano, 2020). These are usually the most severe cases owing to the capacity of this species to inject a large volume of venom (Bolaños, 1984). Other species causing a significant number of bites are the arboreal viperids *Bothriechis lateralis* and *B. schlegelii* (Bolaños, 1984; Sasa and Segura-Cano, 2020). Coral snakes (genus *Micrurus*, family Elapidae) only cause 1–2% of cases (Bolaños, 1984).

2.2. Sri Lanka

As an agricultural country, Sri Lanka has a high snakebite disease

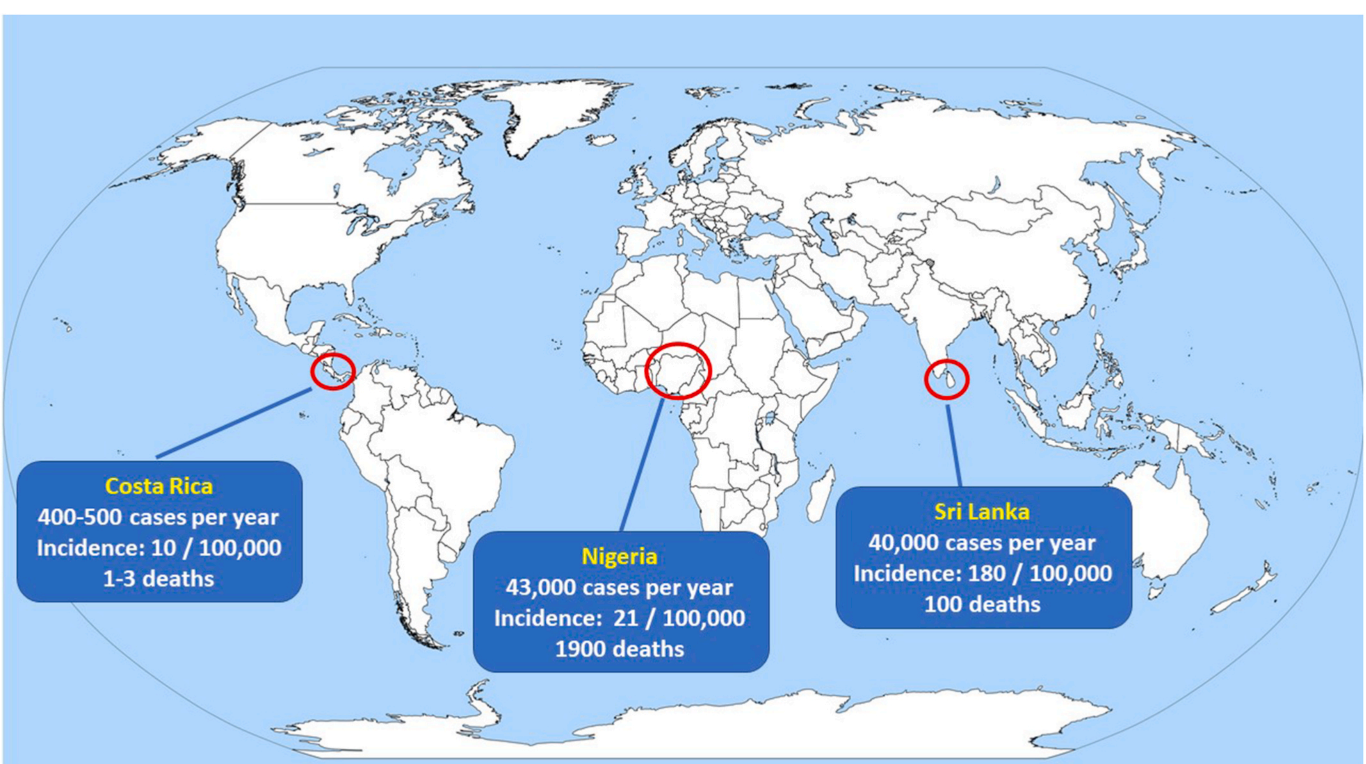

Fig. 1. Annual number of snakebites, incidence and annual number of deaths caused by snakebite envenoming in Costa Rica, Nigeria, and Sri Lanka.

burden. A recently conducted community-based study estimates the crude overall community incidence of snakebites, envenoming, and mortality in 398 (95% CI: 356–441), 151 (130–173), and 2.3 (0.2–4.4) per 100,000 population per year, respectively (Ediriweera et al., 2016). It has, by far, the highest incidence among the three countries included in this analysis, and one of the highest in the world. According to the annual health bulletin, the average number of annual hospital admissions due to snakebites is around 40,000, corresponding to an incidence of 180 per 100,000 population, with approximately 100 deaths (Annual Health Bulletin, 2017). The huge discrepancy between the community-based statistics and the hospital data reveals the underestimation of the burden of SBE in Sri Lanka and lack of hospital admissions among many victims (Fox et al., 2006). SBEs cause an estimated number of 11,101 to 15,076 disability-adjusted life years (DALYs) per year and is associated with various types of physical and psychological sequelae, such as musculoskeletal disorders, amputations, chronic kidney disease, nonhealing chronic ulcers, depression and post-traumatic stress disorders, among others (Jayawardana et al., 2018; Waiddyanatha et al., 2019; Kasturiratne et al., 2017; Williams et al., 2011).

The majority of the venomous snakebites happen in the dry zone of the country due to the distribution and abundance of deadly venomous land snakes in Sri Lanka (Kasturiratne et al., 2005). Contacts of humans and snakes are common in the rural dry zone during the frequent agricultural related activities. The majority of snakebite victims are males (64%) at the median age of 40 years (IQR 27–51) (Silva et al., 2020). There are two seasons (from February to April and October to December) where snakebites peak in the dry zone during the two harvesting seasons of paddy cultivation.

There are 107 species of snakes described from Sri Lanka which include 17 species of sea snakes (subfamily Hydrophiinae, family Elapidae). Sea snake envenomation is rare in Sri Lanka and few fatal cases have been reported following hooked-nosed sea snake (*Enhydrina schistosa*) bites (Kularatne et al., 2014). Among land snakes, eight species of the families Elapidae and Viperidae are considered as highly venomous. They include the elapids Indian/common krait (*Bungarus caeruleus*), Indian/common cobra (*Naja naja*) and Ceylon/Sri Lankan krait (*Bungarus ceylonicus*). Representatives of the family Viperidae include Russell's viper (*Daboia russelii*), saw-scaled viper (*Echis carinatus*) and three species of hump-nosed vipers (*Hypnale hypnale, H. nepa* and *H. zara*). Hump-nosed pit vipers lead to the highest number of cases, corresponding to 35–45% of total snakebites (Kasturiratne et al., 2005). However, severe envenomings and deaths due to hump-nosed pit vipers are uncommon, since the majority of the bites lead to local effects without systemic complications (Ariaratnam et al., 2008; Maduwage et al., 2013). Most fatalities due to SBE are due to *D. russelii*, with lower numbers of deaths caused by other species (Ariaratnam et al., 2008; Kularatne, 2002; Kularatne et al., 2009; Silva et al., 2020).

2.3. Nigeria

SBE is a major public health problem among communities of the savanna region of West Africa (Chippaux et al., 2007; Warrell and Arnett, 1976; WHO, 2007). It is estimated that Nigeria has the highest burden of snakebite morbidity and mortality in sub-Saharan Africa. An early survey in the 1980s put the incidence in endemic areas of the northern savanna regions at 48 per 100,000 population to 497 per 100,000 population with mortality of 5.1%–12.2% (Pugh and Theakston, 1980). In 2007, 1803 victims of snakebite with 26 deaths were seen at Kaltungo General Hospital, in Gombe state, northeastern Nigeria, with over 90% of the bites due to *Echis ocellatus* (Habib et al., 2008). Between 1999 and 2018, The Federal Ministry of Health reported 76,310 cases of snakebite with 910 cases of death in two major treatment centers in the northern savanna region (Annual Medical Records, 2008).

Using a meta-analytic approach that estimated the burden of mortality and amputation, SBE is reported to be associated with 319,874 DALYs annually in 16 West African countries. Of these, Nigeria has the highest burden with an estimated 137,105 DALYs or 43% of the total burden in the sub-region (Habib et al., 2015). Similarly, in a more recent analysis, an estimated number of 43,049 snakebite cases occur per year in Nigeria, resulting in 1927 deaths and 2368 amputations (Halilu et al., 2019).

The most vulnerable populations are mostly farmers, herdsmen and their rural-dwelling families with no effective political representation to voice their needs. These high-risk groups are also economically a productive segment of the population and their incapacitation results in reduced agricultural production and low economic performance (Harrison et al., 2009). In Nigeria, snakebite has two peak seasons coinciding with the planting and harvesting seasons which result in increases in human-snake contact. Victims are predominantly males bitten in the lower limbs in about 81% of cases, and this occurred while walking or farming (53%) and herding (8%) (Warrell and Arnett, 1976). In the Niger Delta region of the south-south zone of Nigeria, though snake activity peaked in the farming season between April and August, paradoxically women and children were found to have higher potential risks of encounter with snakes (Akani et al., 2013).

Distribution of snakes in Nigeria largely follows the vegetation and topography, with carpet viper (*Echis ocellatus*, family Viperidae) dominating in the rocky savanna region of the middle belt and the far north. It also occurs as far south as Oyo state and in Enugu and Udi hills along the Benue valley in the south east zone of the country (Warrell et al., 1977; Warrell and Arnett, 1976). Romane's carpet viper (*Echis leucogaster*) lives in the sahel savanna belt though probably it is under recognized as a cause of human bites (Warrell and Arnett, 1976; WHO, 2010). The puff adder (*Bitis arietans*, family Viperidae) is also found in these regions but less commonly than *E. ocellatus*. The spitting cobra (*Naja nigricollis*) is the commonest and most widely distributed African cobra in the savannah terrain. The forest cobra (*Naja melanoleuca*) and green mambas (*Dendroaspis* spp) largely inhabit the southern forests of Nigeria (WHO, 2010). *Bitis* spp. and *Dendroaspis* spp. populations have been declining, likely because of global climate change, habitat deterioration, and reduction in prey availability (Akani et al., 2013; Reading et al., 2010). Fig. 2 depicts the medically most important species of snakes, i.e., those classified in Category 1 by the World Health Organization (WHO), of Costa Rica, Nigeria, and Sri Lanka (WHO, 2017).

3. Historical background of national efforts to confront snakebite envenomings

3.1. Costa Rica

The first systematic approaches to study snakes and their venoms and to search for scientifically based solutions to SBE were developed by Clodomiro Picado Twight (1887–1944) (Gutiérrez, 2016, 2019; Picado, 1931). He established a collaboration with Instituto Butantan (São Paulo, Brazil) through which Costa Rica received the bothropic antivenom manufactured in Brazil (Picado, 1931). Moreover, Picado promoted a visionary legislation which enforced local authorities and farmers to provide antivenom to people suffering envenomings (Gutiérrez, 2019; Picado, 1931).

In the decade of 1960, the Ministry of Health of Costa Rica promoted an inter-institutional and international cooperative project, initially named *Programa de Sueros Antiofídicos* (Program of Antivenoms), with the participation of the Ministry of Health, the University of Costa Rica, and the Embassy of the United States of America (USA) in Costa Rica (Gutiérrez, 2010a, 2016, 2019). This resulted in the local production of polyvalent and anti-coral antivenoms, in 1967, for the treatment of viperid and elapid snakebite envenomings, respectively. The program, which was initially linked to the Ministry of Health, led to the foundation of Instituto Clodomiro Picado (ICP) in 1970, with the goal of producing the antivenoms required by the country. ICP then became a unit of the University of Costa Rica in 1972. ICP has become the centerpiece for confronting the problem of SBE in this country, in close coordination

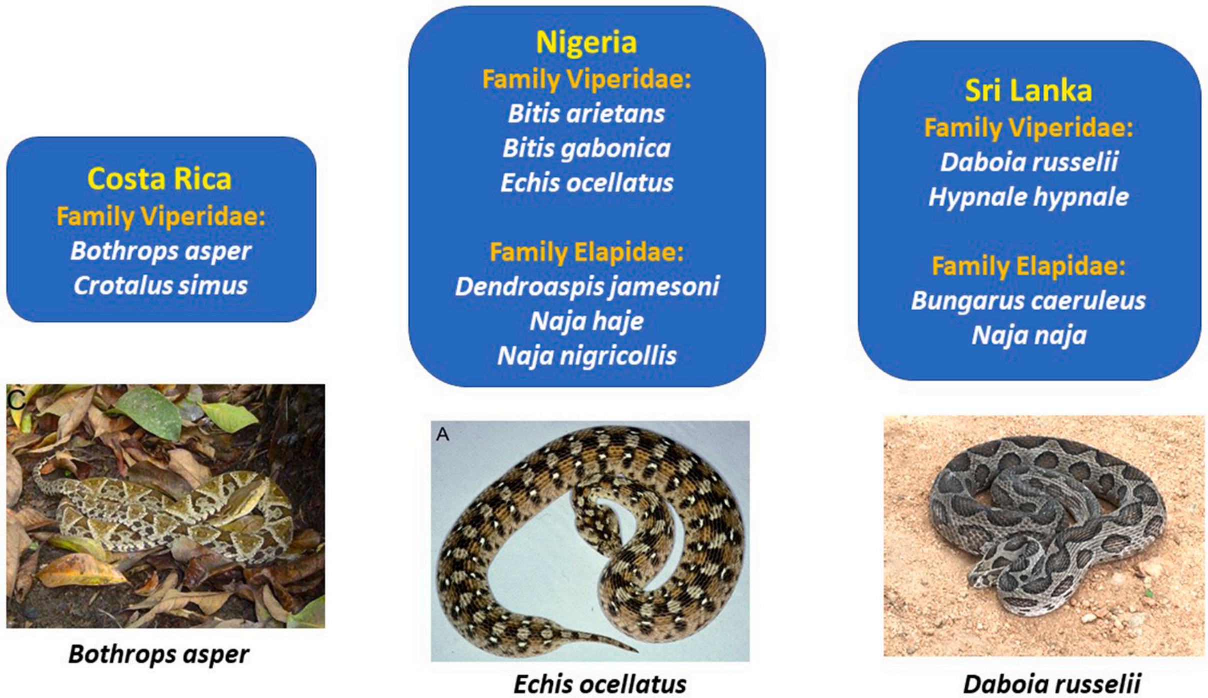

Fig. 2. Venomous snake species classified in Category 1 by the World Health Organization in Costa Rica, Nigeria, and Sri Lanka. This category corresponds to species of highest medical importance, i.e., highly venomous snakes which are common or widespread and cause numerous snakebites, resulting in high levels of morbidity, disability, or mortality (WHO, 2017). The species of highest medical impact in each country are depicted. Photo of *B. asper* by Mahmood Sasa; photo of *E. ocellatus* by David A. Warrell; photo of *D. russelii* by Kalana Maduwage. The photos of *B. asper* and *E. ocellatus* were published in Gutiérrez et al. (2006) PLoS Medicine 3: e150.

with CCSS and the Ministry of Health (Gutiérrez et al., 2020; Gutiérrez, 2016). Since 1970 Costa Rica has been self-sufficient in the provision of antivenoms to its public health system and has also distributed antivenoms to other countries in Latin America and sub-Saharan Africa (Gutiérrez, 2016, 2019).

3.2. Sri Lanka

Indian snake species-specific antivenom was first developed by the Haffkine Institute in India in 1899 as the Plague Research Laboratory. This was also the first snake antivenom used in Sri Lanka, but there are no records on when it was first introduced. A case report published in 1965 describes the management of an adverse reaction developed in a patient who received Haffikine antivenom (Munasinghe and Kulasinghe, 1965). It is highly likely that Sri Lanka has been importing Indian polyvalent antivenom for the treatment of native SBE since the early 20th century. Indian antivenom is prepared using the venom of four highly venomous snakes commonly distributed in South Asia, i.e., *Naja naja*, *Bungarus caeruleus*, *Daboia russelii* and *Echis carinatus*. However, this antivenom does not contain antibodies for Sri Lankan hump-nosed pit viper (genus *Hypnale*), which is the commonest venomous snakebite in Sri Lanka and may cause life-threatening complications.

There have been few attempts to develop antivenoms for Sri Lankan snake species. Through an international collaboration involving groups in Sri Lanka and the United Kingdom, a Fab monovalent antivenom (named PolongaTab®) against Sri Lankan *D. russelii* venom was developed and tested in a clinical trial (Ariaratnam et al., 1999). The antivenom showed good safety and efficacy profiles in envenomings by *D. russelii*. However, this did not evolve into regular production and clinical use of this antivenom. More recently, an international cooperation has opened the possibility of a technology transfer program to introduce antivenom manufacture in Sri Lanka (see below).

3.3. Nigeria

Over the years, there have been concerns over the shortage of antivenom in the country, with periods when virtually no antivenom was available, since suppliers such as South African Vaccine Producers (SAIMR) and Sanofi Pasteur were unable to meet orders from other countries, including Nigeria. This led the Federal Ministry of Health to establish the National Snakebite Control Programme (NSCP) in early 1990s, with the mandate to conduct research to characterize the problem, improve antivenom supply and develop antivenoms specific to the treatment of snakebite victims in Nigeria, and to also facilitate the establishment of local production of antivenom. The NSCP gave birth to the EchiTab Study Group Nigeria/UK to fast track antivenom development. This partnership group achieved appreciable success leading to the availability of two brands of antivenom against the three major snake species of medical importance in Nigeria (monospecific EchiTab G and polyspecific EchiTAb-plus-ICP), produced by the private company Micropharm (United Kingdom) and Instituto Clodomiro Picado (ICP), University of Costa Rica, respectively. However, despite this feat, local production is yet to commence.

In addition, the Nigerian Federal Government also commissioned a Research and Training Centre, Kaltungo, Gombe State, in 2011, to serve for the training of health-care workers. This was meant to be a subregional centre with the potential of serving Nigeria and surrounding countries in the West African sub-region. Recently, the Gombe state government constructed a dedicated a 150-bed capacity facility, the Kaltungo Snakebite Hospital and Research Centre. These two centers are adjoining the old Kaltungo General Hospital, erected in the 1960s. Furthermore, the Federal Ministry of Health has developed a protocol to serve as a standard guideline in the identification and management of SBE in Nigeria.

Over the years the Nigerian government and some state governors of the most affected states have been providing free antivenom to selected centers which then serve as hubs for the treatment of SBE. These efforts have been grossly affected by the adverse economic climate, dwindling budgetary allocation and the current Covid-19 pandemics.

4. Overview of the national health systems

4.1. Costa Rica

Costa Rica has a long tradition in public health and welfare policies since the last decades of the XIX century (Botey-Sobrado, 2019; Palmer, 2003). The Ministry of Health was created in 1927, and the *Caja Costarricense del Seguro Social* (CCSS) in 1941, becoming the institution that has the monopoly of public social security in the country (Martínez-Franzoni and Sánchez-Ancochea, 2019; Sáenz et al., 2010). Over the next decades, CCSS increased its coverage, reaching 95% of the population in 2016 (OPS, 2019). CCSS owns all public hospitals and clinics and is financed by contributions from workers, employers, and the State. This universalized public health system has allowed the country to reach high standards in terms of life expectancy, infant mortality, and other parameters (Martínez-Franzoni and Sánchez-Ancochea, 2019; Sáenz et al., 2010) (Table 1). However, there are regions and sectors of the population not yet covered by CCSS or underserved in terms of access to these services, such as a portion of the migrant population and some temporal workers (Rosero-Bixby, 2004; Sáenz et al., 2010; Voorend, 2016). CCSS provides services at primary, secondary and tertiary levels.

A significant health reform took place in the 1990s through which the primary level was strengthened by the creation of *Equipos Básicos de Atención Integrada en Salud* (EBAIS) (Basic Provision Units of Integrated Healthcare), which are distributed all over the country and have greatly improved the access to health services (Rosero-Bixby, 2004; Sáenz et al., 2010). The treatment of people suffering from SBE, including administration of antivenoms, is provided free of charge at the primary, secondary, and tertiary levels of CCSS. SBE is a disease of mandatory notification in Costa Rica. Traditional medicine is rarely used in the management of envenomings despite tradition of popular medicine in Costa Rica (Arroyo et al., 1999; Sasa and Segura-Cano, 2020).

4.2. Sri Lanka

Sri Lankan healthcare is based on allopathic public health system according to the government constitution. Delivery of healthcare is managed by the central Ministry of Health and ministries of the nine provinces. The administrative structure of health services is headed by the Cabinet Minister of Health. The national policy development, recruitment, training of healthcare staff, and provision of facilities are primary responsibilities of the central ministry. Tertiary care hospitals are managed by the central ministry, and secondary and primary care hospitals are under the management of provincial health authorities. Supply of medicinal products and equipment are procured through a central mechanism and the central ministry purchases and distributes the items even for the provincial health authorities. The government provides a free health care system to the population, including the provision of antivenoms and other drugs to manage SBE.

Before introducing the allopathic medicinal system to Sri Lanka, traditional *ayurvedic* medical practice was established over thousands of years of history. This traditional healing practice is centred on various formulations based on indigenous plants and other products. Treatment for SBE was a great concern in traditional medical practices and multiple native treatment options are well documented in the traditional medical manuscripts. Currently, many traditional medical practitioners provide these services, including for SBE. However, efficacy, safety, and effectiveness of traditional formulations for these envenomings have not been proved by scientific methodologies. The marked discrepancy of the incidence of snakebites between the ministry of health statistics and community survey studies reveal that still many snakebite victims seek traditional healing approaches (Fox et al., 2006).

4.3. Nigeria

In Nigeria, health services are delivered through primary, secondary, and tertiary healthcare systems. This structure also reflects the three tiers of government, namely local, state, and federal government. The federal government's role is mostly limited to coordinating the affairs of the University Teaching Hospitals and Federal Medical Centers (tertiary healthcare), while the state government manages the various general hospitals and comprehensive health centers (secondary healthcare). The local governments focus on dispensaries (primary healthcare) (Federal Ministry of Health, 2016). The general direction of primary healthcare is regulated by the federal government through the National Primary Health Care Development Agency (NPHCDA). The bulk of health care financing is through out-of-pocket expenses (Uzochukwu et al., 2015). However, the federal government established the National Health Insurance Scheme (NHIS) in 1995. At the initial phase, the scheme encompasses government employees and the organized private sector, with plans for expansion to include the informal sector. Since its inception, the number of Nigerians covered by the NHIS is less than 5% (Onoka et al., 2015).

Many health facilities are situated far away from the people, especially in rural and hard-to-reach populations, e.g., the nomadic Fulani. The most common barriers to accessing health services by the population are the cost of services and the distance to the health facility (Federal Ministry of Health, 2016). Prolonged delays in accessing health services are associated with poor outcomes in terms of mortality and sequelae following SBE (I. Abubakar et al., 2010; Habib and Abubakar, 2011; Halilu et al., 2019; Iliyasu et al., 2015).

5. Antivenom availability and accessibility

5.1. Costa Rica

Two types of antivenoms for human use are produced in Costa Rica: (a) Polyvalent antivenom (PoliVal-ICP®) for the treatment of envenomings by snakes of the family Viperidae, and (b) Anti-coral antivenom (CoRal-ICP®) for envenomings by coral snakes (genus *Micrurus*, family Elapidae) (Bolaños and Cerdas, 1980). The total number of 10 mL antivenom vials required per year by CCSS is around 15,000, at a rough estimated total cost for CCSS of US $350,000; this does not include other hospital-related costs for treating SBE. In addition, ICP manufactures a polyvalent antivenom (PoliVet-ICP®) for veterinary use. Antivenoms produced in Costa Rica have a good record of safety and efficacy in the treatment of envenomings (Arroyo et al., 1999; Brenes-Chacón et al., 2019; Otero-Patiño et al., 2012; Sasa and Segura-Cano, 2020). CCSS carries out the quality control of the antivenoms provided by ICP, and the regulatory agency at the Ministry of Health regularly inspects the manufacturing laboratory and extends the corresponding authorizations.

Antivenoms are directly provided to CCSS based on the needs of this institution. CCSS then distributes antivenoms to its health centers all over the country at the three levels of attention, including national and regional hospitals, clinics and, in some regions, primary health posts (EBAIS). At CCSS antivenoms are provided free of charge to patients. In the last decades there have not been problems of availability of antivenoms in the country. Although ICP manufactures both liquid and freeze-dried antivenoms, CCSS only acquires liquid antivenoms, since there is a good cold chain in the public health system of Costa Rica; freeze-dried antivenoms are distributed to other countries. Despite the wide coverage of CCSS services throughout the country, there are still regions in Costa Rica where access to health facilities is delayed (Hansson et al., 2013; Rosero-Bixby, 2004). This might explain why some patients have a delay of 5 h or more to reach health facilities, although most of them arrive to health centers within 3 h of the bite (Sasa and Segura-Cano, 2020). This has been partially solved by the allocation of antivenoms in primary health posts with the presence of physicians. In contrast to the large-scale coverage of CCSS, which ensures free of charge treatment of patients, only permanent workers on a payroll are entitled to the benefits of the Law of Labor Risks of *Instituto Nacional de Seguros* (National Insurance Institute, INS), which include rehabilitation, and compensation. Thus, a portion of agricultural workers are excluded from these benefits (Arias-Rodríguez and Gutiérrez, 2020), an issue that is currently receiving attention through a project presented to the Congress.

5.2. Sri Lanka

Importation and distribution of snake antivenom are conducted by the Ministry of Health. Sri Lankan government provides a free health care system and hence antivenom treatment is free of charge for the patient. Snake antivenom is available in all national hospitals, general hospitals, base hospitals, and some district hospitals located in snakebite prevalent areas. The Ministry of Health has taken the responsibility of continuous supply of the antivenom according to the requirements of the regions. Noteworthy, in Sri Lanka the time lapse between the bite and the access to a health facility is quite short, usually within the first 2 h after the bite (Silva et al., 2016a, 2020), although a delay has been described between admission and time of administration of antivenom owing to the need to do clinical evaluation (Silva et al., 2020).

Currently, two Indian manufacturers (VINS Bio-products and BHARAT Serum and Vaccine, Ltd.) provide snake antivenoms for Sri Lanka. These two polyvalent antivenoms are manufactured against four highly venomous snake species that inhabit India (the ‘big four’), i.e., *D. russelii*, *N. naja*, *B. caeruleus,* and *E. carinatus*). The authorization of antivenom batches imported is approved by the national regulatory agency, but no quality control assessment of preclinical safety and efficacy is carried out in the country with local venoms. The estimated annual health system cost of snakebite management corresponds to US $10 million, including antivenom and other hospital-related costs. Sri Lankan government spends approximately US$ 6.3 million annually for the importation of antivenom from India (Kasturiratne et al., 2017). Combining household and health system costs estimates, the total annual economic burden of snakebite was estimated in US $ 14 million (Kasturiratne et al., 2017).

A high incidence of early adverse reactions is a well-known problem of Indian antivenoms. The reported rate of adverse reactions to these antivenoms used in Sri Lanka varies from 43% to 81% (Kularatne, 2000; Premawardhena et al., 1999; Seneviratne et al., 2000; Theakston et al., 1990), 5%–10% of reactions corresponding to severe reactions (Kularatne, 2000; Premawardhena et al., 1999; Seneviratne et al., 2000). The country is heading towards the development of country-specific polyvalent antivenom which could be used for treating envenoming by hump-nosed vipers as well (Villalta et al., 2016).

5.3. Nigeria

The National Food Drug Administration and Control (NAFDAC), an agency under the Federal Ministry of Health, serves as the regulatory control agency licensing all antivenoms for importation, marketing, and distribution. Antivenom is provided in a decentralized manner by all the levels of government operational in the country, i.e., the federal, states and local governments. It is also provided in private sector and in retail pharmacies throughout the country. Although antivenom is administered to patients at no cost when available in government hospitals, supplies are generally neither sufficient in total volume nor available throughout the year. Furthermore, only few facilities stock antivenom, mostly in tertiary hospitals and designated district or general hospitals in known snakebite endemic locations within the country. Antivenom is not usually provided within primary health centers. The ministries of health at the federal and state level procure it independently; occasionally the former also provides the latter or facilities in the latter. The former distributes throughout the country particularly to designated snakebite treatment facilities within endemic areas while the latter distributes it only within hospitals in the state. The costs incurred by the Federal Government related to antivenom acquisition in the year 2017 were estimated at US $192,000, but this does not include purchases by state/local governments or out-of-pocket expenses.

Occasionally local government areas within states may procure antivenom for use in facilities in their areas. A snakebite endemic state in the northeast also used pool counter-part funding from LGAs within the state to procure antivenoms. The amount of funds allocated for snakebite treatment and antivenom procurement from all the sources combined is still very meager and inadequate. The Federal Ministry of Health provided less than 10,000 vials for the three-year period from 2017 to 2019, i.e., less than an annual average of 3333 vials. In contrast, two hospitals in Gombe and Plateau states in north eastern and north central zones of the country, respectively, recorded an annual average of at least 5000 patients who required much more than the antivenom provided by the federal government. Thus, affected states and local governments where snakebite is endemic need to procure an unknown variable quantity to supplement the government’s supplies. The authorization of antivenom batches imported is approved by the national regulatory agency, but no quality control assessment of preclinical safety and efficacy is carried out in the country with local venoms.

Partly due to competing priorities from other high burden diseases, Nigeria is unable to provide adequate resources for snakebite and antivenom acquisition. For instance, with regards to the burden of communicable and tropical diseases, Nigeria has the world’s highest burden of malaria, the third highest burden of HIV/AIDS and the fourth highest burden of tuberculosis, all of which require massive resources in such a large country. However, even when compared to other neglected tropical diseases it has been shown that funding for snakebite and antivenom has been grossly inadequate and not commensurate to their public health burden in West Africa (Habib et al., 2015). Thus, most antivenom used in the country is procured through private financing by affected patients and their families using out-of-pocket meager resources. Most patients are impoverished farmers in remote areas who could ill-afford the cost of antivenom and other hidden costs such as transportation to access care. Often, people must sell off personal items and livelihoods to obtain transportation to a major facility to access snakebite care and antivenom therapy. Overall, the antivenom supply from all sources is grossly insufficient, generally not available in rural areas where it is mostly needed.

6. Training of medical and nursing staff in the diagnosis and treatment of snakebite envenoming

6.1. Costa Rica

CCSS has a national protocol for the diagnosis and treatment of SBE. Permanent training programs and seminars, coordinated by ICP and CCSS, are regularly organized in the country. These include teaching activities in university courses in medical and nursing schools, as well as regular seminars offered to hospitals and clinics of CCSS, especially in regions of high incidence of snakebites. Teaching material has been prepared and is widely distributed to health professionals and students, including a poster with the algorithm for the diagnosis of envenoming and the correct use of antivenom (Gutiérrez, 2010b). These activities are also developed in other Central American countries in close coordination with ministries of health, universities, and medical associations. The topic of SBE is taught in the medical school of the public university, but only in some private universities.

6.2. Sri Lanka

Knowledge and skills required for the diagnosis and treatment of SBE among clinical staff are generally satisfactory. All medical schools in Sri Lanka conduct a series of lectures, as well as practical and clinical sessions on the diagnosis and management of SBE at undergraduate and graduate training. Clinicians who work in hospitals receiving a high number of envenomed patients develop additional experience in managing this disease. The Sri Lankan Medical Association (SLMA), the professional body of medical professionals in Sri Lanka, published the *Guidelines for the Management of Snakebite in Hospital,* which are the national reference (National Snakebite Guidelines, 2019). The Snakebite Expert Committee, a sub-committee of SLMA, frequently updates these guidelines according to recently published evidence. The expert committee is composed of experienced clinicians, and of clinical and basic science researchers who are active in the field of SBE. This guideline and other relevant information are published on the SLMA website (https://slma.lk/sbc/sbc_guidelines/). Also, a web-based snake identification service (https://snakesidentification.org/) provides rapid snake identification tool for the healthcare staff and the public.

6.3. Nigeria

The National Universities Commission, an agency of the Federal Ministry of Education, and the corresponding professional regulatory boards/councils, e.g., Nursing Council, Medical & Dental Council, and Pharmaceutical Council of Nigeria, which are supervised by the Federal Ministry of Health, regulate medical and healthcare worker training. They accredit the respective professional programs for developing the curriculum, verifying adherence, periodically revising/updating it, and ensuring the quality of the graduates.

Healthcare workers are educated and trained on SBE during their undergraduate years. Often this formal training is contextualized within the curriculum modules on medical emergencies, poisoning and tropical or rural medicine. Occasionally it is offered as a stand-alone module. It takes the form of both didactic and practical clinical learning with practical patient encounters. During postgraduate years snakebite training is also embarked upon depending on the specialty, e.g., in internal medicine, pediatrics, emergency medicine, immunology, pharmacology, toxicology, etc. Health care workers practicing in endemic rural areas also 'learn on the job' through encounters with snake bitten patients. However, it is clear from knowledge, attitude, practice, and perception surveys that Nigerian health care workers have insufficient knowledge of snakebite management (Bala et al., 2020a, 2020b; Michael et al., 2018) and that improvements need to be introduced.

The Federal Ministry of Health has developed a snakebite curriculum, a facilitator's manual, and a participant's manual for the training. Since 2017 formal in-service training of healthcare workers has been conducted in snakebite endemic states in the country under the umbrella of the African Snakebite Research Group (ASRG) project. A training-of-trainers strategy, meant to be stepped-down or cascaded down to other cadre of staff elsewhere, has been adopted. Overall, about 300 multidisciplinary group of doctors, nurses, laboratory scientists, and pharmacists have been trained.

7. Prevention of snakebites and community-based work

7.1. Costa Rica

A permanent extension program has been developed by ICP focused on communities and groups of high risk of SBE in the country. This includes regular visits to communities and workshops, seminars, and other activities at the community level, in close coordination with organized communal, labor and student groups. These actions aim at conveying and discussing the basic elements of the prevention and early management of snakebites, including the need for a rapid transportation to health facilities in case of accidents. These efforts, together with public campaigns in the media and the involvement of other groups of the civil society and the government, have contributed to the fact that few people in Costa Rica resort to inappropriate first aid interventions and, instead, attend health facilities for medical treatment in the event of a snakebite (Arroyo et al., 1999). In the last decade, special efforts have been directed to community-based programs in local indigenous communities of the ethnic groups *cabécar*, *brunca* and *gnöbe*, with preparation of bilingual (Spanish-indigenous languages) printed material related to prevention and early management of snakebites. The local communities have been directly involved in the preparation of these materials, which have been widely used at the local level, including the school system.

7.2. Sri Lanka

Even though there are no planned community-based snakebite prevention programs in Sri Lanka, multiple prevention activities are conducted by non-governmental organizations. The snakebite expert committee at the SLMA prepared documents on prevention of snakebite in English, Sinhala, and Tamil languages available on the website and in printed form. Frequent media discussions and health promoting programs highlight the snakebite prevention strategies. Practicing of harmful first-aid approaches are still prevailing in many parts of Sri Lanka, especially in the rural dry zone. Hence, meticulously designed snakebite prevention and first-aid programs need to be strengthened in Sri Lanka.

7.3. Nigeria

In its efforts to reduce the burden of snakebite, Nigeria established a Snakebite Envenoming Program under Neglected Tropical Diseases (NTD) Division in the Department Public Health, Federal Ministry of Health. Since its inception, the unit has been coordinating the control and care of SBE in Nigeria, through community engagement and distribution of educational materials geared towards improving preventive measures, reducing harmful practices as well as improving the community's health seeking behavior. These efforts have been complemented by non-governmental organizations, independent research groups and, in some instances, community self-help groups. The Nigerian Snakebite Research and Intervention Center/VASP, which is an independent university-based research organization, designs and distributes educational materials in the form of guidelines, posters, and flyers. In collaboration with the Ministry, it also organizes a yearly educational program on a national media to commemorate world snakebite awareness day. The EchiTab Study Group was also involved in establishing a Public Health Education Program on the prevention and treatment of snakebite, especially facilitating the development of effective antivenoms against venomous snakes in the country. Despite these advances, there is still need for a concerted and more coordinated community-based intervention program in Nigeria.

8. Scientific and technological research

8.1. Costa Rica

Since the pioneer work of Clodomiro Picado Twight Costa Rica has had a long tradition in scientific and technological research in the fields of snake venoms, envenoming, and antivenoms (Gutiérrez et al., 2020; Gutiérrez, 2016). This trend was consolidated with the creation of ICP in 1970, since an ambitious research program was developed in this university center. This has involved contributions in diverse subjects such as herpetology, ecology, epidemiology, biochemistry (including proteomics), toxicology of venoms, preclinical assessment of antivenoms, clinical studies, and technological development for improving antivenom production and for developing new antivenoms, among other topics (Gutiérrez et al., 2020; Gutiérrez, 2016, 2019; Lomonte, 2014).

Such endogenous research and development agenda has had a direct impact in the understanding of snake venom composition (Lomonte et al., 2014), the mechanism of action of venoms (Gutiérrez et al, 2009a, 2009b), and the improvement of antivenom technology in Costa Rica, with the introduction of caprylic acid fractionation of hyperimmune plasma (Rojas et al., 1994), a technology used for antivenom production not only for Latin America, but also for sub-Saharan Africa (Gutiérrez et al., 2005), Papua New Guinea (Vargas et al., 2011) and Sri Lanka (Villalta et al., 2016). The research activity at ICP has also contributed to graduate and undergraduate teaching programs at the University of Costa Rica and has also supported the training of scientists and students from many countries.

8.2. Sri Lanka

Even though there is no national institute for research on SBE, several research groups in the national university system are actively involved in numerous studies on topics related to snakes and SBE. Among them, groups in medical facilities at the universities of Peradeniya, Kelaniya, Colombo and the Rajarata University of Sri Lanka frequently publish studies on basic sciences, epidemiology, and clinical and therapeutic aspects related to Sri Lankan snakes and SBE. In addition, clinicians interested in this disease publish case reports and case series to highlight clinically relevant issues. A clinical trial on the recently developed new polyspecific antivenom manufactured using venoms from Sri Lankan snakes (Villalta et al., 2016) is currently underway at the teaching hospital of the University of Peradeniya. Moreover, studies on venom-induced coagulopathy and on the development of diagnostic tools are being developed by the research group at the School of Medicine, University of Peradeniya (Maduwage et al., 2020).

Collaborative research projects on clinical and therapeutic aspects of envenomings have been carried out involving the universities of Newcastle and Sydney, Australia, the South-Asian Clinical Toxicology Research Collaboration, the University of Peradeniya, and the Rajarata University of Sri Lanka (Isbister et al., 2013; Ratnayake et al, 2017, 2019). Epidemiological studies at regional and national levels are led by the research team at School of Medicine, University of Kelaniya, in collaboration with the Liverpool School of Tropical Medicine and other international partners from Australia (Ediriweera et al., 2016; Kasturiratne et al., 2005). The research group at the School of Medicine, University of Colombo, is studying the nephrotoxic effects of SBE, and the Rajarata University of Sri Lanka develops clinical studies on neurotoxicity and the long-term effects following envenoming (Silva et al., 2016a, 2016b; Waiddyanatha et al., 2019).

8.3. Nigeria

Research on clinical and public health aspects of snakebite has been conducted since the middle of the 20th century. Initially British colonial medical officers and subsequently local medical practitioners recorded the problem of snakebite in different parts of the country from 1950s (Davenport and Budeen, 1953; Onuaguluchi, 1960). With the establishment of several universities and research centers throughout the country, research continued in these institutions initially by foreign scientists and later by Nigerian academics (Pugh et al, 1979, 1980; Pugh and Theakston, 1980; Warrell et al, 1975, 1977; Warrell and Arnett, 1976).

Subsequently, academics in Nigerian universities have continued to document different aspects of snakebites. Although Nigeria was producing vaccines in the country, it had always imported antivenoms and, therefore, research has focused mainly on translational sciences related to clinical features and the treatment of envenoming. Thus, limited research is conducted on the basic science of venoms and antivenom, although lately, given the recognition of the significance of snakebite in the country, renewed efforts in these areas of research are being developed. Collaborative international research projects are being promoted in Nigeria.

9. International cooperation programs

9.1. Costa Rica

In the development of its extensive research agenda, ICP has established cooperative links with research groups in all continents (Gutiérrez, 2021; 2019, 2016). Such wide network of partnerships has allowed ICP to access technological platforms unavailable in Costa Rica which, in turn, enabled the strengthening of the local scientific base. Likewise, this cooperative platform has fostered an active exchange of students and researchers with institutions of many countries. Costa Rica, through ICP, has played a leading role in regional collaborative efforts in close coordination to Latin American Health authorities, public antivenom manufacturers and the Pan American Health Organization (PAHO). ICP has been involved in the establishment of a regional network of public institutions in charge of manufacture and quality control of antivenoms (Gutiérrez, 2016; Gutiérrez et al., 2007) which has led to the creation of the Latin American Network of Public Antivenom Manufacturing Laboratories (RELAPA) (Fan et al., 2019). The volume of antivenom produced by ICP has increased over the years (Gutiérrez et al., 2020), allowing the distribution of these life-saving products to several countries in Latin America, the Caribbean and sub-Saharan Africa (Gutiérrez et al., 2020; Gutiérrez, 2016).

Costa Rica has also played a leading role in the global efforts to increase the awareness of the impact of SBE and to implement interventions at the WHO. A highly productive partnership has been established between ICP, and the ministries of Health and Foreign Affairs of Costa Rica, through the active involvement of the Permanent Mission of Costa Rica to the organisms of the United Nations in Geneva. An international partnership was established with more than 20 countries and with organizations such as the Global Snakebite Initiative (GSI), Health Action International (HAI), Médecins sans Frontiers (MSF) and others, which led to the incorporation of SBE into the list of neglected tropical diseases by WHO (Chippaux, 2017) and the adoption of a resolution at the World Health Assembly in 2018 (Gutiérrez, 2021; Gutiérrez and Whyte, 2019).

9.2. Sri Lanka

Currently, no internationally coordinated large scale programs on research and management of SBE in Sri Lanka is under way, except for the project for developing a new polyvalent antivenom in collaboration with ICP, Costa Rica. This initiative is progressing with the continuous scientific and technological assistance of ICP. In addition, several clinical studies are funded by foreign grants with the collaboration of overseas scientists. There is an ongoing collaboration with universities in Australia, covering several research topics (see section 8.2).

9.3. Nigeria

Historically, there have been limitations in the availability of antivenoms from foreign manufacturers in Nigeria. Given this background, the Federal Ministry of Health recognized the significance of snakebite constituted a National Snakebite Control Program. Subsequently, this evolved into a consortium which was launched with the mandate to develop an antivenom against indigenous Nigerian snakes and, ultimately, establish local production facilities. The EchiTab Study Group (Nigeria-UK), comprising academics from Nigeria, Oxford, and Liverpool (UK) and staff of the Federal Ministry of Health, was established in early 1990s with the research mandate of antivenom development.

Eventually at least three candidate products were developed and underwent basic, preclinical assessment and then clinical studies (I. Abubakar et al., 2010; S. Abubakar et al., 2010). Subsequently, international cooperation depended on individual researchers in different universities. Local collaborative groups among academics were developed such as the Venom Antivenom Research Project (VASP) at Bayero

University Kano. Recently, the Liverpool School of Tropical Medicine (UK) spearheaded a consortium of several institutions to form the African Snakebite Research Group (ASRG) project and the Scientific Research Partnership for Neglected Tropical Snakebite (SRPNTS), involving investigators from Nigeria.

Table 2 summarizes the main issues discussed in the previous sections, comparing the three countries. There are similarities and differences between them, which call for specific actions tailored to the national needs while strengthening common avenues for confronting the problem.

10. Current and future needs to improve the management of snakebite envenoming

Table 3 presents some of the most pressing needs identified in these three countries to improve the study of snakes, snake venoms, and SBE, and to develop integrated interventions at various levels aimed at reducing the impact of this disease through national programs and international cooperation strategies. In some issues, the needs of the three countries are similar while in others there are differences depending on local contexts, strengths, and weaknesses.

11. Concluding remarks

This comparative analysis of the situation of SBE and their management in these three countries highlights several common issues while also showing notable differences in various aspects on the burden of SBE and the ways these countries have confronted this disease. The geographical scales, the cultural and political contexts, and the institutional developments in education and public health, have determined similarities and differences in the issues discussed. In addition to the burden of SBE, which is much higher in Sri Lanka and Nigeria than in Costa Rica, the most notorious contrasts are related to the quality, availability, and accessibility of antivenoms, the priority given to this topic by public health authorities, the difficulties for accessing health facilities in rural settings, and the development of endogenous scientific and technological research on this topic.

The identification of strengths and weaknesses in each country should pave the way for the implementation of interventions aimed at reducing the impact of SBE. The effective confrontation of this health issue demands integrated strategies, led by public health authorities and involving diverse stakeholders, regional coordination, and international cooperation. Some of the most relevant actions to be implemented in these three countries, along the WHO strategy to control and prevent SBE (WHO, 2019), are depicted in Box 1. A central piece of these efforts is the political commitment and leadership of public health institutions, particularly the ministries of health, as well as local health authorities, together with the involvement of the scientific communities and the organizations of the civil society, and the consolidation of international cooperation schemes.

Credit author statement

Conceptualization: JMG, KM, AH. Literature review and collection of information: JMG, KM, GI, AH. Analysis of the information: JMG, KM, GI, AH. Preparation of first version of manuscript: JMG, KM, GI, AH.

Table 2
Comparison between Costa Rica, Sri Lanka and Nigeria of the various parameters related to snakebite envenoming and its management.

Parameter	Costa Rica	Sri Lanka	Nigeria
Burden of snakebite envenoming	400-500 cases per year Incidence: 10/100,000 1-3 deaths	40,000 cases per year Incidence: 180/100,000 100 deaths	43,000 cases per year Incidence: 21/100,000 1900 deaths
National health system	- Public social security system covers 95% of the population. - Antivenom provided free of charge. - Few patients procure traditional medicine	- Public health system provides wide coverage. - Antivenom provided free of charge. - High proportion of patients procure traditional medicine	- Public health system of incomplete coverage. - Antivenom frequently obtained through out-of-pocket expenses. - High proportion of patients procure traditional medicine.
Antivenom availability, accessibility, and quality	- Antivenom manufactured in the country and widely distributed through the public health system, free of charge. - Most people reach hospitals within 3 h of the bite. - Good accessibility in rural regions, with some exceptions. - Satisfactory antivenom efficacy and safety profiles. - Quality control done by the manufacturer and CCSS.	- Antivenom imported from India distributed through the public health system free of charge. - People reach hospitals within 2 h of the bite. - Good accessibility in rural regions. - Uncertain efficacy and high incidence of adverse reactions. Not all species covered. - Quality control done only by the manufacturers.	- Antivenoms of variable quality imported from various countries. - Irregular and insufficient availability. - Poor accessibility, especially in remote rural settings. - Depending on the region there are long delays to reach hospitals for some people. - Quality control done only by the manufacturers.
Training of health staff	- Teaching of the topic in some university programs, but not in others. - Permanent education programs to physicians in the public health system. - National guidelines for diagnosis and treatment of envenoming.	- Teaching of the topic in university courses. - Permanent education programs to physicians in the public health system. - National guidelines for diagnosis and treatment of envenoming.	- Teaching of the topic in university courses. - Permanent education programs in the public health system. - National guidelines for diagnosis and treatment.
Prevention campaigns and community-based work	- Prevention activities at the community level with participation of diverse stakeholders. - Preparation and distribution of materials on prevention and early management of snakebites in Spanish and several local indigenous languages.	- Prevention activities at the community level with participation of diverse stakeholders. - Preparation and distribution of materials on prevention and early management of snakebites in English, Sinhala, and Tamil.	- Prevention activities at the community level with participation of diverse stakeholders. - Preparation and distribution of materials on prevention and early management of snakebites.
Research	- Strength in basic and technological research, as well as in antivenom development. - Weakness in clinical research.	- Limited basic scientific research and technological development. - Strengths in epidemiological and clinical research.	- Limited basic scientific research and technological development. - Strengths in epidemiological and clinical research.
International cooperation	- Strong programs of cooperation in research, antivenom development and distribution. - Active international advocacy.	- Limited international cooperation. - Cooperative projects with Australia and Costa Rica on clinical research and antivenom development.	- Cooperation with the UK and Costa Rica. - Participation in the African Snakebite Research Group, involving the UK and other African countries.

Table 3
Some pressing needs in Costa Rica, Sri Lanka, and Nigeria to reduce the impact of snakebite envenoming.

Issue	Costa Rica	Sri Lanka	Nigeria
Antivenom production	- Consolidate production for local needs and for other countries in Latin America and elsewhere. - Improvements in the manufacturing facilities.	- Consolidate the local serpentarium. - Introduce local antivenom production through technology transfer programs.	- Development of local serpentarium to provide venoms. - Develop a strategy for local manufacture.
Antivenom availability and accessibility	- Expand distribution to primary health centers in areas of high incidence of snakebites.	- Design distribution strategies based on sound epidemiological data.	- Ensure acquisition of adequate volume of antivenom for the country's needs. - Design models of distribution based on sound epidemiological data, ensuring access in regions of high incidence of envenomings.
Quality control of antivenoms	- Develop *in vitro* assays that could reduce the use of mice.	- In country implementation of control of imported antivenoms using Sri Lankan venoms.	- In country implementation of control of imported antivenoms using Nigerian venoms.
Training of health workers	- Expand the teaching of this subject to all university medical schools. - Update of national guidelines for diagnosis and treatment. - Expand the use of digital tools in permanent education programs.	- Consolidate teaching in universities and in permanent education programs. - Update of national guidelines for diagnosis and treatment. - Expand the use of digital tools in permanent education programs.	- Consolidate teaching in universities and in permanent education programs. - Update of national guidelines for diagnosis and treatment. - Expand the use of digital tools in permanent education programs.
Prevention and early management	- Expand the design and implementation of prevention and early management campaigns to groups and regions of high snakebite incidence, paying attention to local cultural contexts and with strong involvement of local communities.	- Expand the design and implementation of prevention and early management campaigns to groups and regions of high snakebite incidence, paying attention to local cultural contexts and with strong involvement of local communities. - Dialogic approaches with traditional healers for improving the access of patients to health facilities.	- Expand the design and implementation of prevention and early management campaigns to groups and regions of high snakebite incidence, paying attention to local cultural contexts and with strong involvement of local communities. - Dialogic approaches with traditional healers for improving the access of patients to health facilities.
Clinical management	- Improve clinical management through training of health professionals and the introduction of evidence-based interventions for managing the complications of envenomings.	- Improve clinical management through training of health professionals and the introduction of evidence-based interventions for managing the complications of envenomings.	- Improve clinical management through training of health professionals and the introduction of evidence-based interventions for managing the complications of envenomings.
Follow up of sequelae	- Introduce legislation and programs to deal with the physical and psychological sequelae of envenomings, - Develop rehabilitation and economic compensation programs to mitigate the consequences of envenomings.	- Introduce legislation and programs to deal with the physical and psychological sequelae of envenomings, - Develop rehabilitation and economic compensation programs to mitigate the consequences of envenomings.	- Introduce legislation and programs to deal with the physical and psychological sequelae of envenomings, - Develop rehabilitation and economic compensation programs to mitigate the consequences of envenomings.
Research	- Consolidate the local strengths in basic and technological research in venoms and antivenoms. - Strengthen epidemiological and clinical research. - Promote inter-disciplinary research. - Consolidate international research cooperation activities and develop new initiatives with countries from all continents.	- Improve the national capacities to develop basic and technological research in venoms and antivenoms. - Strengthen epidemiological and clinical research. - Promote inter-disciplinary research. - Establish novel international cooperation programs.	- Improve the national capacities to develop basic and technological research in venoms and antivenoms. - Strengthen epidemiological and clinical research. - Promote inter-disciplinary research. - Consolidate international cooperation programs and develop new initiatives with countries in sub-Saharan Africa.

Box 1
Key areas of intervention aimed at improving the prevention and management of snakebite envenoming in Costa Rica, Sri Lanka, and Nigeria

- Collection of sound data on incidence, morbidity, mortality, and sequelae (social, economic, physical, psychological) of snakebite envenoming.
- Strengthening of the public health system through cross-cutting approaches, incorporating snakebite envenoming into packages that integrate interventions for several health issues.
- Strengthening of national regulatory agencies, especially in the quality control, to ensure efficacy and safety of antivenoms distributed in these countries.
- Improving antivenom availability and accessibility, including programs for antivenom acquisition, distribution and, when appropriate, local manufacture.
- Engagement of local community organizations in the development of programs for the prevention and adequate management of envenoming.
- Improving the training of physicians and nurses in the diagnosis and management of envenoming.
- Fostering of endogenous scientific and technological research in snakes, snake venoms, snake bites, and their determinants and treatments, through the consolidation of trans-disciplinary teams and international cooperation.
- Promoting partnerships between a diverse set of stakeholders at national, regional and international levels.

Revision and editing of manuscript: JMG, KM, GI, AH. All authors agree with the final content of this manuscript.

Ethical statement

In the preparation of this review article the authors followed the international ethical guidelines recommended for the preparation of manuscripts for publication in scientific journals.

Declaration of competing interest

J.M. Gutiérrez works at Instituto Clodomiro Picado (University of

Costa Rica), where some antivenoms mentioned in this work are manufactured. The other three authors have no known competing interests.

Acknowledgments

The authors thank their colleagues in Costa Rica, Sri Lanka, Nigeria and elsewhere for fruitful discussions and reflections on the topics of this review, and for stimulating collaborative research and clinical work over the years.

References

Abubakar, I., Abubakar, S., Habib, A., Nasidi, A., Durfa, N., Yusuf, P., Larnyang, S., Garnvwa, J., Sokomba, E., Salako, L., Theakston, R., Juszczak, E., Alder, N., Warrell, D., 2010. Randomised controlled double-blind non-inferiority trial of two antivenoms for saw-scaled or carpet viper (*Echis ocellatus*) envenoming in Nigeria. PLoS Neglected Trop. Dis. 4, e767. https://doi.org/10.1371/journal.pntd.0000767.

Abubakar, S., Abubakar, I., Habib, A., Nasidi, A., Durfa, N., Yusuf, P., Larnyang, S., Garnvwa, J., Sokomba, E., Salako, L., Laing, G., Theakston, R., Juszczak, E., Alder, N., Warrell, D., 2010. Pre-clinical and preliminary dose-finding and safety studies to identify candidate antivenoms for treatment of envenoming by saw-scaled or carpet vipers (*Echis ocellatus*) in northern Nigeria. Toxicon 55, 719–723. https://doi.org/10.1016/j.toxicon.2009.10.024.

Akani, G.C., Ebere, N., Franco, D., Eniang, E.A., Petrozzi, F., Politano, E., Luiselli, L., 2013. Correlation between annual activity patterns of venomous snakes and rural people in the Niger Delta, southern Nigeria. J. Venom. Anim. Toxins Incl. Trop. Dis. 19 (2) https://doi.org/10.1186/1678-9199-19-2.

Annual Health Bulletin, 2017. Ministry of health and indigenous medical services, Sri Lanka. http://www.health.gov.lk/moh_final/english/public/elfinder/files/publications/AHB/2017/AHS2017.pdf.

Annual Medical Records, 2008. Annual medical records of antivenom treatment centre. EchiTAb anti-snake study group UK/Nigeria. General hospital Kaltungo, Gombe state. Nigeria.

Ariaratnam, C.A., Meyer, W.P., Perera, G., Eddleston, M., Kuleratne, S.A.M., Attapattu, W., Sheriff, R., Richards, A.M., Theakston, R.D.G., Warrell, D.A., 1999. A new monospecific ovine Fab fragment antivenom for treatment of envenoming by the Sri Lankan Russell's viper (*Daboia russelii russelii*): a preliminary dose-finding and pharmacokinetic study. Am. J. Trop. Med. Hyg. 61, 259–265.

Ariaratnam, C.A., Thuraisingam, V., Kularatne, S.A.M., Sheriff, M.H.R., Theakston, R.D. G., de Silva, A., Warrell, D.A., 2008. Frequent and potentially fatal envenoming by hump-nosed pit vipers (*Hypnale hypnale* and *H. nepa*) in Sri Lanka: lack of effective antivenom. Trans. R. Soc. Trop. Med. Hyg. 102, 1120–1126. https://doi.org/10.1016/j.trstmh.2008.03.023.

Arias-Rodríguez, J., Gutiérrez, J.M., 2020. Circumstances and consequences of snakebite envenomings: a qualitative study in South-eastern Costa Rica. Toxins 12. https://doi.org/10.3390/toxins12010045.

Arroyo, O., Rojas, G., Gutiérrez, J.M., 1999. Envenenamiento por mordedura de serpiente en Costa Rica en 1996: epidemiología y consideraciones clínicas. Acta Med. Costarric. 41, 23–29.

Bala, A.A., Jatau, A.I., Yunusa, I., Mohammed, M., Mohammed, A.-K.H., Isa, A.M., Sadiq, W.A., Gulma, K.A., Bello, I., Malami, S., Michael, G.C., Chedi, B.A.Z., 2020a. Development and validation of antisnake venom knowledge assessment tool (AKAT) for healthcare practitioners. Toxicon:X 8. https://doi.org/10.1016/j.toxcx.2020.100064, 100064.

Bala, A.A., Jatau, A.I., Yunusa, I., Mohammed, M., Mohammed, A.-K.H., Isa, A.M., Wada, A.S., Gulma, K.A., Bello, I., Michael, G.C., Malami, S., Chedi, B.Z.A., 2020b. Knowledge assessment of snake antivenom among healthcare practitioners involving educational intervention in northern Nigeria: a study protocol. Ther. Adv. Drug Saf 11. https://doi.org/10.1177/2042098620935721, 2042098620935721.

Bolaños, R., Cerdas, L., 1980. Producción y control de sueros antiofídicos en Costa Rica. Bol. Of. Sanit. Panam 88, 189–196.

Bolaños, R., 1984. Serpientes venenos y ofidismo en Centroamérica. Editorial Universidad de Costa Rica, San José, Costa Rica.

Botey-Sobrado, A., 2019. Los Orígenes del Estado de Bienestar en Costa Rica: Salud y Protección Social. Editorial Universidad de Costa Rica, San José, Costa Rica (1850-1940).

Brenes-Chacón, H., Gutiérrez, J.M., Camacho-Badilla, K., Soriano-Fallas, A., Ulloa-Gutiérrez, R., Valverde-Muñoz, K., Ávila-Agüero, M.L., 2019. Snakebite envenoming in children: a neglected tropical disease in a Costa Rican pediatric tertiary care center. Acta Trop. 200 https://doi.org/10.1016/j.actatropica.2019.105176, 105176.

Chippaux, J.-P., 2017. Snakebite envenomation turns again into a neglected tropical disease! J. Venom. Anim. Toxins Incl. Trop. Dis. 23 (38) https://doi.org/10.1186/s40409-017-0127-6.

Chippaux, J.-P., Massougbodji, A., Stock, R.P., Alagón, A., 2007. Clinical trial of an F(ab')$_2$ polyvalent equine antivenom for African snake bites in Benin. Am. J. Trop. Med. Hyg. 77, 538–546.

Chippaux, J.P., 1998. Snake-bites: appraisal of the global situation. Bull. World Health Organ. 76, 515–524.

Davenport, R.C., Budeen, F.H., 1953. Loss of sight following snake bite. Br. J. Ophthalmol. 37, 119–121. https://doi.org/10.1136/bjo.37.2.119.

Ediriweera, D.S., Kasturiratne, A., Pathmeswaran, A., Gunawardena, N.K., Wijayawickrama, B.A., Jayamanne, S.F., Isbister, G.K., Dawson, A., Giorgi, E., Diggle, P.J., Lalloo, D.G., de Silva, H.J., 2016. Mapping the risk of snakebite in Sri Lanka - a national survey with geospatial analysis. PLoS Neglected Trop. Dis. 10 https://doi.org/10.1371/journal.pntd.0004813 e0004813.

Fan, H.W., Vigilato, M.A.N., Pompei, J.C.A., Gutiérrez, J.M., 2019. Situación de los laboratorios públicos productores de antivenenos en América Latina. Rev. Panam. Salud Pública 43, e92. https://doi.org/10.26633/RPSP.2019.92.

Federal Ministry of Health, N.H.P, 2016. Promoting the health of Nigerians to accelerate socio-economic development. https://naca.gov.ng/wp-content/uploads/2019/10/National-Health-Policy-Final-copy.pdf.

Fernández, P., Gutiérrez, J.M., 2008. Mortality due to snakebite envenomation in Costa Rica (1993-2006). Toxicon 52, 530–533. https://doi.org/10.1016/j.toxicon.2008.06.018.

Fox, S., Rathuwithana, A.C., Kasturiratne, A., Lalloo, D.G., de Silva, H.J., 2006. Underestimation of snakebite mortality by hospital statistics in the Monaragala District of Sri Lanka. Trans. R. Soc. Trop. Med. Hyg. 100, 693–695. https://doi.org/10.1016/j.trstmh.2005.09.003.

Gutiérrez, J.M., 2010a. Los Orígenes del Instituto Clodomiro Picado. Instituto Clodomiro Picado, San José, Costa Rica.

Gutiérrez, J.M., 2010b. Snakebite envenomation in Central America. In: Mackessy, S. (Ed.), Handbook of Venoms and Toxins of Reptiles. CRC Press, Boca Raton, FL, USA, pp. 491–507.

Gutiérrez, J.M., 2016. Understanding and confronting snakebite envenoming: the harvest of cooperation. Toxicon 109, 51–62. https://doi.org/10.1016/j.toxicon.2015.11.013.

Gutiérrez, J.M., 2019. Reflexiones desde la Academia. Universidad, Ciencia y Sociedad. Editorial Arlekín, San José, Costa Rica.

Gutiérrez, J.M., 2021. Snakebite envenomation as a neglected tropical disease: new impetus for confronting an old scourge. In: Mackessy, S. (Ed.), Handbook of Venoms and Toxins of Reptiles, second ed. CRC Press, Boca Raton, FL, USA (in press).

Gutiérrez, J., Arias-Rodríguez, J., Alape-Girón, A., 2020. Envenenamiento ofídico en Costa Rica: logros y tareas pendientes. Acta Méd. Costarric 62, 102–108.

Gutierrez, J.M., Calvete, J.J., Habib, A.G., Harrison, R.A., Williams, D.J., Warrell, D.A., 2017. Snakebite envenoming. Nat. Rev. Dis. Prim 3. https://doi.org/10.1038/nrdp.2017.63, 17063.

Gutiérrez, J.M., Escalante, T., Rucavado, A., 2009a. Experimental pathophysiology of systemic alterations induced by *Bothrops asper* snake venom. Toxicon 54, 976–987. https://doi.org/10.1016/j.toxicon.2009.01.039.

Gutiérrez, J.M., Higashi, H.G., Wen, F.H., Burnouf, T., 2007. Strengthening antivenom production in Central and South American public laboratories: report of a workshop. Toxicon. https://doi.org/10.1016/j.toxicon.2006.09.005.

Gutiérrez, J.M., Rojas, E., Quesada, L., León, G., Núñez, J., Laing, G.D., Sasa, M., Renjifo, J.M., Nasidi, A., Warrell, D.A., Theakston, R.D.G., Rojas, G., 2005. Pan-African polyspecific antivenom produced by caprylic acid purification of horse IgG: an alternative to the antivenom crisis in Africa. Trans. R. Soc. Trop. Med. Hyg. 99, 468–475. https://doi.org/10.1016/j.trstmh.2004.09.014.

Gutiérrez, J.M., Rucavado, A., Chaves, F., Díaz, C., Escalante, T., 2009b. Experimental pathology of local tissue damage induced by *Bothrops asper* snake venom. Toxicon 54, 958–975. https://doi.org/10.1016/j.toxicon.2009.01.038.

Gutiérrez, J.M., Whyte, E., 2019. South-south cooperation for confronting the neglected problem of snakebite envenoming: the role of Costa Rica. South 178.

Habib, A.G., Abubakar, S.B., 2011. Factors affecting snakebite mortality in north-eastern Nigeria. Int. Health 3, 50–55. https://doi.org/10.1016/j.inhe.2010.08.001.

Habib, A.G., Abubakar, S.B., Abubakar, I.S., Larnyang, S., Durfa, N., Nasidi, A., Yusuf, P. O., Garnvwa, J., Theakston, R.D.G., Salako, L., Warrell, D.A., 2008. Envenoming after carpet viper (*Echis ocellatus*) bite during pregnancy: timely use of effective antivenom improves maternal and foetal outcomes. Trop. Med. Int. Health 13, 1172–1175. https://doi.org/10.1111/j.1365-3156.2008.02122.x.

Habib, A.G., Kuznik, A., Hamza, M., Abdullahi, M.I., Chedi, B.A., Chippaux, J.-P., Warrell, D.A., 2015. Snakebite is under appreciated: appraisal of burden from West Africa. PLoS Neglected Trop. Dis. 9 https://doi.org/10.1371/journal.pntd.0004088 e0004088.

Halilu, S., Iliyasu, G., Hamza, M., Chippaux, J.-P., Kuznik, A., Habib, A.G., 2019. Snakebite burden in Sub-Saharan Africa: estimates from 41 countries. Toxicon 159, 1–4. https://doi.org/10.1016/j.toxicon.2018.12.002.

Hansson, E., Sasa, M., Mattisson, K., Robles, A., Gutiérrez, J.M., 2013. Using geographical information systems to identify populations in need of improved accessibility to antivenom treatment for snakebite envenoming in Costa Rica. PLoS Neglected Trop. Dis. 7, e2009. https://doi.org/10.1371/journal.pntd.0002009.

Harrison, R.A., Hargreaves, A., Wagstaff, S.C., Faragher, B., Lalloo, D.G., 2009. Snake envenoming: a disease of poverty. PLoS Neglected Trop. Dis. 3, e569. https://doi.org/10.1371/journal.pntd.0000569.

Iliyasu, G., Tiamiyu, A.B., Daiyab, F.M., Tambuwal, S.H., Habib, Z.G., Habib, A.G., 2015. Effect of distance and delay in access to care on outcome of snakebite in rural north-eastern Nigeria. Rural Rem. Health 15, 3496.

Instituto Nacional de Estadística y Censos, 2003. Estadísticas Vitales 2000. Costa Rica. https://www.inec.cr/wwwisis/documentos/INEC/Estadisticas_Vitales/Estadisticas_Vitales_2000.pdf.

Instituto Nacional de Estadística y Censos, 2015. Estadísticas Vitales 2014. Costa Rica. https://www.inec.cr/sites/default/files/documetos-biblioteca-virtual/repoblacev2014.pdf.

Isbister, G.K., Maduwage, K., Shahmy, S., Mohamed, F., Abeysinghe, C., Karunathilake, H., Ariaratnam, C.A., Buckley, N.A., 2013. Diagnostic 20-min whole blood clotting test in Russell's viper envenoming delays antivenom administration. QJM 106, 925–932. https://doi.org/10.1093/qjmed/hct102.

Jayawardana, S., Arambepola, C., Chang, T., Gnanathasan, A., 2018. Long-term health complications following snake envenoming. J. Multidiscip. Healthc. 11, 279–285. https://doi.org/10.2147/JMDH.S126648.

Kasturiratne, A., Pathmeswaran, A., Fonseka, M.M.D., Lalloo, D.G., Brooker, S., de Silva, H.J., 2005. Estimates of disease burden due to land-snake bite in Sri Lankan hospitals. Southeast Asian J. Trop. Med. Public Health 36, 733–740.

Kasturiratne, A., Pathmeswaran, A., Wickremasinghe, A.R., Jayamanne, S.F., Dawson, A., Isbister, G.K., de Silva, H.J., Lalloo, D.G., 2017. The socio-economic burden of snakebite in Sri Lanka. PLoS Neglected Trop. Dis. 11 https://doi.org/10.1371/journal.pntd.0005647 e0005647.

Kasturiratne, A., Wickremasinghe, A.R., de Silva, N., Gunawardena, N.K., Pathmeswaran, A., Premaratna, R., Savioli, L., Lalloo, D.G., de Silva, H.J., 2008. The global burden of snakebite: a literature analysis and modelling based on regional estimates of envenoming and deaths. PLoS Med. 5, e218. https://doi.org/10.1371/journal.pmed.0050218.

Kularatne, S.A.M., 2002. Common krait (*Bungarus caeruleus*) bite in Anuradhapura, Sri Lanka: a prospective clinical study, 1996-98. Postgrad. Med. 78, 276–280. https://doi.org/10.1136/pmj.78.919.276.

Kularatne, S.A.M., 2000. Reactions to snake venom antisera: study of pattern, severity and management at General Hospital, Anuradhapura. Sri Lanka J. Med 9, 8–13.

Kularatne, S.A.M., Budagoda, B.D.S.S., Gawarammana, I.B., Kularatne, W.K.S., 2009. Epidemiology, clinical profile and management issues of cobra (*Naja naja*) bites in Sri Lanka: first authenticated case series. Trans. R. Soc. Trop. Med. Hyg. 103, 924–930. https://doi.org/10.1016/j.trstmh.2009.04.002.

Kularatne, S.A.M., Hettiarachchi, R., Dalpathadu, J., Mendis, A.S.V., Appuhamy, P.D.S.A. N., Zoysa, H.D.J., Maduwage, K., Weerasinghe, V.S., De Silva, A., 2014. *Enhydrina schistosa* (Elapidae: Hydrophiinae) the most dangerous sea snake in Sri Lanka: three case studies of severe envenoming. Toxicon 77, 78–86.

Lomonte, B., 2014. Snake venoms: from research to treatment. Acta Méd. Costarric 54, 20–29.

Lomonte, B., Fernández, J., Sanz, L., Angulo, Y., Sasa, M., Gutiérrez, J.M., Calvete, J.J., 2014. Venomous snakes of Costa Rica: biological and medical implications of their venom proteomic profiles analyzed through the strategy of snake venomics. J. Proteomics 105, 323–339. https://doi.org/10.1016/j.jprot.2014.02.020.

Maduwage, K., Isbister, G.K., Silva, A., Bowatta, S., Mendis, S., Gawarammana, I., 2013. Epidemiology and clinical effects of hump-nosed pit viper (Genus: hypnale) envenoming in Sri Lanka. Toxicon 61, 11–15.

Maduwage, K.P., Gawarammana, I.B., Gutiérrez, J.M., Kottege, C., Dayaratne, R., Premawardena, N.P., Jayasingha, S., 2020. Enzyme immunoassays for detection and quantification of venoms of Sri Lankan snakes: application in the clinical setting. PLoS Neglected Trop. Dis. 14 https://doi.org/10.1371/journal.pntd.0008668.

Martínez-Franzoni, J., Sánchez-Ancochea, D., 2019. La Búsqueda de una Política Social Universal en el Sur: Actores, Ideas y Arquitecturas. Editorial UCR, San José, Costa Rica.

Michael, G.C., Grema, B.A., Aliyu, I., Alhaji, M.A., Lawal, T.O., Ibrahim, H., Fikin, A.G., Gyaran, F.S., Kane, K.N., Thacher, T.D., Badamasi, A.K., Ogwuche, E., 2018. Knowledge of venomous snakes, snakebite first aid, treatment, and prevention among clinicians in northern Nigeria: a cross-sectional multicentre study. Trans. R. Soc. Trop. Med. Hyg. 112, 47–56. https://doi.org/10.1093/trstmh/try028.

Munasinghe, D.R., Kulasinghe, P., 1965. Snake-bite-a case report. Ceylon Med. J. 10, 140–143.

National Snakebite Guidelines, 2019. Sri Lanka Medical Association.

Onoka, C.A., Hanson, K., Hanefeld, J., 2015. Towards universal coverage: a policy analysis of the development of the National Health Insurance Scheme in Nigeria. Health Pol. Plann. 30, 1105–1117. https://doi.org/10.1093/heapol/czu116.

Onuaguluchi, G.O., 1960. Clinical observations on snakebite in Wukari, Nigeria. Trans. R. Soc. Trop. Med. Hyg. 54, 265–269. https://doi.org/10.1016/0035-9203(60)90073-0.

OPS, 2019. Perfil del sistema y servicios de salud de Costa Rica con base al marco de monitoreo de la Estrategia Regional de Salud Universal. Organización Panamericana de la Salud, San José, Costa Rica.

Otero-Patiño, R., Segura, A., Herrera, M., Angulo, Y., León, G., Gutiérrez, J.M., Barona, J., Estrada, S., Pereañez, A., Quintana, J.C., Vargas, L.J., Gómez, J.P., Díaz, A., Suárez, A.M., Fernández, J., Ramírez, P., Fabra, P., Perea, M., Fernández, D., Arroyo, Y., Betancur, D., Pupo, Lady, Córdoba, E.A., Ramírez, C.E., Arrieta, A.B., Rivero, A., Mosquera, D.C., Conrado, N.L., Ortiz, R., 2012. Comparative study of the efficacy and safety of two polyvalent, caprylic acid fractionated [IgG and F(ab')$_2$] antivenoms, in *Bothrops asper* bites in Colombia. Toxicon 59, 344–355. https://doi.org/10.1016/j.toxicon.2011.11.017.

Palmer, S., 2003. From Popular Medicine to Medical Populism. Duke University Press, Durham & London.

Picado, C., 1931. Serpientes Venenosas de Costa Rica. Sus Venenos. Seroterapia Antiofídica. Imprenta Alsina, San José, Costa Rica.

Premawardhena, A.P., de Silva, C.E., Fonseka, M.M., Gunatilake, S.B., de Silva, H.J., 1999. Low dose subcutaneous adrenaline to prevent acute adverse reactions to antivenom serum in people bitten by snakes: randomised, placebo controlled trial. BMJ 318, 1041–1043. https://doi.org/10.1136/bmj.318.7190.1041.

Pugh, R.N., Bourdillon, C.C., Theakston, R.D., Reid, H.A., 1979. Bites by the carpet viper in the Niger Valley. Lancet 2, 625–627. https://doi.org/10.1016/s0140-6736(79)91677-5.

Pugh, R.N., Theakston, R.D., 1980. Incidence and mortality on snake bite in savanna Nigeria. Lancet 2, 1181–1183. https://doi.org/10.1016/s0140-6736(80)92608-2.

Pugh, R.N., Theakston, R.D., Reid, H.A., 1980. Malumfashi Endemic Diseases Research Project, XIII. Epidemiology of human encounters with the spitting cobra, *Naja nigricollis*, in the Malumfashi area of northern Nigeria. Ann. Trop. Med. Parasitol. 74, 523–530.

Ratnayake, I., Mohamed, F., Buckley, N.A., Gawarammana, I.B., Dissanayake, D.M., Chathuranga, U., Munasinghe, M., Maduwage, K., Jayamanne, S., Endre, Z.H., Isbister, G.K., 2019. Early identification of acute kidney injury in Russell's viper (*Daboia russelii*) envenoming using renal biomarkers. PLoS Neglected Trop. Dis. 13 https://doi.org/10.1371/journal.pntd.0007486 e0007486.

Ratnayake, I., Shihana, F., Dissanayake, D.M., Buckley, N.A., Maduwage, K., Isbister, G. K., 2017. Performance of the 20-minute whole blood clotting test in detecting venom induced consumption coagulopathy from Russell's viper (*Daboia russelii*) bites. Thromb. Haemostasis 117. https://doi.org/10.1160/TH16-10-0769.

Reading, C.J., Luiselli, L.M., Akani, G.C., Bonnet, X., Amori, G., Ballouard, J.M., Filippi, E., Naulleau, G., Pearson, D., Rugiero, L., 2010. Are snake populations in widespread decline? Biol. Lett. 6, 777–780. https://doi.org/10.1098/rsbl.2010.0373.

Rojas, G., Bogarín, G., Gutiérrez, J.M., 1997. Snakebite mortality in Costa Rica. Toxicon 35, 1639–1643. https://doi.org/10.1016/s0041-0101(97)00046-9.

Rojas, G., Jiménez, J.M., Gutiérrez, J.M., 1994. Caprylic acid fractionation of hyperimmune horse plasma: description of a simple procedure for antivenom production. Toxicon 32, 351–363. https://doi.org/10.1016/0041-0101(94)90087-6.

Rosero-Bixby, L., 2004. Spatial access to health care in Costa Rica and its equity: a GIS-based study. Soc. Sci. Med. 58, 1271–1284. https://doi.org/10.1016/S0277-9536(03)00322-8.

Sáenz, M., Bermúdez, J., Acosta, M., 2010. Universal Coverage in a Middle Income Country. World Health Report, background paper 11, Costa Rica.

Sasa, M., Segura-Cano, S., 2020. New insights into snakebite epidemiology in Costa Rica: a retrospective evaluation of medical records. Toxicon:X 7. https://doi.org/10.1016/j.toxcx.2020.100055, 100055.

Sasa, M., Vazquez, S., 2003. Snakebite envenomation in Costa Rica: a revision of incidence in the decade 1990-2000. Toxicon 41, 19–22. https://doi.org/10.1016/s0041-0101(02)00172-1.

Sasa, M., Wasko, D.K., Lamar, W.W., 2009. Natural history of the terciopelo *Bothrops asper* (serpentes: Viperidae) in Costa Rica. Toxicon 54, 904–922. https://doi.org/10.1016/j.toxicon.2009.06.024.

Seneviratne, S.L., Opanayaka, C.J., Ratnayake, N.S., Kumara, K.E., Sugathadasa, A.M., Weerasuriya, N., Wickrama, W.A., Gunatilake, S.B., de Silva, H.J., 2000. Use of antivenom serum in snake bite: a prospective study of hospital practice in the Gampaha district. Ceylon Med. J. 45, 65–68. https://doi.org/10.4038/cmj.v45i2.8003.

Silva, A., Hlusicka, J., Siribaddana, N., Waiddyanatha, S., Pilapitiya, S., Weerawansa, P., Lokunarangoda, N., Thalgaspitiya, S., Siribaddana, S., Isbister, G.K., 2020. Time delays in treatment of snakebite patients in rural Sri Lanka and the need for rapid diagnostic tests. PLoS Neglected Trop. Dis. 14 https://doi.org/10.1371/journal.pntd.0008914 e0008914.

Silva, A., Maduwage, K., Sedgwick, M., Pilapitiya, S., Weerawansa, P., Dahanayaka, N.J., Buckley, N.A., Johnston, C., Siribaddana, S., Isbister, G.K., 2016a. Neuromuscular effects of common krait (*Bungarus caeruleus*) envenoming in Sri Lanka. PLoS Neglected Trop. Dis. 10 https://doi.org/10.1371/journal.pntd.0004368.

Silva, A., Maduwage, K., Sedgwick, M., Pilapitiya, S., Weerawansa, P., Dahanayaka, N.J., Buckley, N.A., Siribaddana, S., Isbister, G.K., 2016b. Neurotoxicity in Russell's viper (*Daboia russelii*) envenoming in Sri Lanka: a clinical and neurophysiological study. Clin. Toxicol. (Phila) 54, 411–419. https://doi.org/10.3109/15563650.2016.1143556.

Solórzano, A., 2004. Serpientes de Costa Rica. INBio, San José, Costa Rica.

Theakston, R.D., Phillips, R.E., Warrell, D.A., Galagedera, Y., Abeysekera, D.T., Dissanayaka, P., de Silva, A., Aloysius, D.J., 1990. Envenoming by the common krait (*Bungarus caeruleus*) and Sri Lankan cobra (*Naja naja naja*): efficacy and complications of therapy with Haffkine antivenom. Trans. R. Soc. Trop. Med. Hyg. 84, 301–308. https://doi.org/10.1016/0035-9203(90)90297-r.

Uzochukwu, B.S.C., Ughasoro, M.D., Etiaba, E., Okwuosa, C., Envuladu, E., Onwujekwe, O.E., 2015. Health care financing in Nigeria: implications for achieving universal health coverage. Niger. J. Clin. Pract. 18, 437–444. https://doi.org/10.4103/1119-3077.154196.

Vargas, M., Segura, A., Herrera, M., Villalta, M., Estrada, R., Cerdas, M., Paiva, O., Matainaho, T., Jensen, S.D., Winkel, K.D., León, G., Gutiérrez, J.M., Williams, D.J., 2011. Preclinical evaluation of caprylic acid-fractionated IgG antivenom for the treatment of Taipan (*Oxyuranus scutellatus*) envenoming in Papua New Guinea. PLoS Neglected Trop. Dis. 5, e1144. https://doi.org/10.1371/journal.pntd.0001144.

Villalta, M., Sánchez, A., Herrera, M., Vargas, M., Segura, Á., Cerdas, M., Estrada, R., Gawarammana, I., Keyler, D.E., McWhorter, K., Malleappah, R., Alape-Girón, A., León, G., Gutiérrez, J.M., 2016. Development of a new polyspecific antivenom for snakebite envenoming in Sri Lanka: analysis of its preclinical efficacy as compared to a currently available antivenom. Toxicon 122, 152–159. https://doi.org/10.1016/j.toxicon.2016.10.007.

Voorend, K., 2016. A Welfare Magnet in the South? Migration and Social Policy in Costa Rica. Erasmus University Rotterdam, The Netherlands.

Waiddyanatha, S., Silva, A., Siribaddana, S., Isbister, G.K., 2019. Long-term effects of snake envenoming. Toxins 11. https://doi.org/10.3390/toxins11040193.

Warrell, D.A., Arnett, C., 1976. The importance of bites by the saw-scaled or carpet viper (*Echis carinatus*): epidemiological studies in Nigeria and a review of the world literature. Acta Trop. 33, 307–341.

Warrell, D.A., Davidson, NMcD., Greenwood, B.M., Ormerod, L.D., Pope, H.M., Watkins, B.J., Prentice, C.R., 1977. Poisoning by bites of the saw-scaled or carpet viper (*Echis carinatus*) in Nigeria. Q. J. Med. 46, 33–62.

Warrell, D.A., Ormerod, L.D., Davidson, N.M., 1975. Bites by puff-adder (*Bitis arietans*) in Nigeria, and value of antivenom. Br. Med. J. 4, 697–700. https://doi.org/10.1136/bmj.4.5998.697.

WHO, 2019. Snakebite Envenoming – A Strategy for Prevention and Control. World Health Organization, Geneva.

WHO, 2010. Guidelines for the Prevention and Clinical Management of Snakebite in Africa. World Health Organization. Regional Office for Africa.

WHO, 2007. Rabies and Envenomings ;: a Neglected Public Health Issue ;: Report of a Consultative Meeting. World Health Organization, Geneva.

WHO, 2017. WHO Guidelines for the Production, Control and Regulation of Snake Antivenom Immunoglobulins. World Health Organization, Geneva.

Williams, S.S., Wijesinghe, C.A., Jayamanne, S.F., Buckley, N.A., Dawson, A.H., Lalloo, D.G., de Silva, H.J., 2011. Delayed psychological morbidity associated with snakebite envenoming. PLoS Neglected Trop. Dis. 5, e1255. https://doi.org/10.1371/journal.pntd.0001255.