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SNAKEBITE ANTIVENOM TREATMENT, CURRENT SITUATION, AND CHALLENGES IN BRAZIL AND OTHER HIGH-BURDEN COUNTRIES

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ABSTRACT

Snakebites affect around three million people a year worldwide. The World Health Organization (WHO) considers them a neglected tropical disease that affects tropical and subtropical countries and poor and rural populations. The WHO's strategy to reduce morbidity and mortality includes ensuring safe and effective antivenom treatment for victims and accelerating antivenom production through public policies and international agreements. Countries in Asia and Africa have recorded the highest number of cases and deaths. Brazil has been producing its antivenom for years and distributes it free of charge in the public health system; however, production is a current concern. This study aims to highlight the challenges in accessing adequate treatment for snakebite accidents in Brazil and other high-incidence countries in Asia and Africa. We conducted a review of the literature and official websites related to the problem. The review suggests that most countries in these areas do not have easy access to antivenom, or it is not effective; several countries have antivenom as part of their public health system, such as India, Thailand and Brazil; however, challenges persist. There is an urgent need for global funding for research and production of snakebite antidotes.

Keywords: Antidote. Snakebite. Poisoning. Treatment.

TRATAMENTO COM ANTIVENENO PARA PICADA DE COBRA, SITUAÇÃO ATUAL E DESAFIOS DO NO BRASIL E EM OUTROS PAÍSES COM ALTA INCIDÊNCIA

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RESUMO
Acidentes ofídicos afetam cerca de três milhões de pessoas por ano em todo o mundo. A Organização Mundial da Saúde (OMS) os considera uma doença tropical negligenciada que afeta países tropicais e subtropicais e populações pobres e rurais. A estratégia da OMS para reduzir a morbidade e a mortalidade inclui garantir tratamento antiveneno seguro e eficaz para as vítimas e acelerar a produção do antiveneno por meio de políticas públicas e acordos internacionais. Os países da Ásia e da África registraram o maior número de casos e mortes. O Brasil produz seu antiveneno há anos e o distribui gratuitamente no sistema público de saúde; no entanto, a produção é uma preocupação atual. Este estudo tem como objetivo destacar os desafios no acesso ao tratamento adequado para acidentes ofídicos no Brasil e em outros países de alta incidência na Ásia e na África. Realizamos uma revisão da literatura e de sites oficiais relacionados ao problema. A revisão sugere que a maioria dos países nessas áreas não tem acesso fácil ao antiveneno, ou ele não é eficaz; vários países têm o antiveneno como parte de seu sistema público de saúde, como Índia, Tailândia e Brasil; no entanto, os desafios persistem. Há uma necessidade urgente de financiamento global para pesquisa e produção de antídotos contra picadas de cobra.

Palavras-chave: Antídoto. Picada de Cobra. Envenenamento. Tratamento.

TRATAMIENTO CON ANTIVENENO DE LA MORDEDURA DE SERPIENTE, SITUACIÓN ACTUAL Y RETOS DE EN BRASIL Y OTROS PAÍSES CON ALTA INCIDENCIA

RESUMEN
Las mordeduras de serpiente afectan a unos tres millones de personas al año en todo el mundo. La Organización Mundial de la Salud (OMS) las considera una enfermedad tropical desatendida que afecta a países tropicales y subtropicales y a poblaciones pobres y rurales. La estrategia de la OMS para reducir la morbilidad y la mortalidad incluye garantizar un tratamiento seguro y eficaz con antiveneno para las víctimas y acelerar la producción de antiveneno mediante políticas públicas y acuerdos internacionales. Los países de Asia y África han registrado el mayor número de casos y muertes. Brasil produce su antiveneno desde hace años y lo distribuye gratuitamente en el sistema público de salud; sin embargo, la producción es una preocupación actual. Este estudio pretende poner de relieve las dificultades para acceder a un tratamiento adecuado de los accidentes por mordedura de serpiente en Brasil y otros países de alta incidencia en Asia y África. Se realizó una revisión de la literatura y de los sitios web oficiales relacionados con el problema. La revisión sugiere que la mayoría de los países de estas zonas no tienen fácil acceso al antídoto, o éste no es eficaz; varios países tienen el antídoto como parte de su sistema de salud pública, como India, Tailandia y Brasil; sin embargo, los desafíos persisten. Existe una necesidad urgente de financiación mundial para la investigación y producción de antídotos contra las mordeduras de serpiente.

Palabras clave: Antídoto. Mordedura de Serpiente. Envenenamiento. Tratamiento.

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1 INTRODUCTION

It is estimated that around 2.7 million people globally suffer from accidents caused by snakes every year, around 100,000 to 138,000 people die, and another 400,000 become disabled as a result [1-10]. Approximately 5.8 billion people, or nearly the entire world's population, are at risk of developing this health issue [11,12].

In 2017, the World Health Organization (WHO) included snakebite in its list of Neglected Tropical Diseases. In 2019, the strategy “Snake Poisoning: A Strategy for Prevention and Control” was approved to reduce mortality and disability from snakebite poisoning by 50% by 2030 [4-6,13-17]. This comprehensive strategy suggests four main objectives: empowering and involving communities; partnership, coordination, and resource generation; strengthening health systems; and providing safe and effective treatments or antivenoms [14,18-22].

Snakebite envenoming (SBE) is a problem of global concern, [1,6-8,11,23-25] considered a medical emergency that requires immediate attention [26-29]. It occurs mainly in tropical and subtropical countries in Asia and sub-Saharan Africa, Latin America, and Oceania [3,8,21,30-32]. The country with the highest number of snakebites and deaths worldwide is India, with an estimated 2.8 million bites and 50,000 deaths per year [33]. Several other countries in this region, including Sri Lanka and Thailand, present a higher number of occurrences [74, 75]. Countries in Africa as Nigeria, also have a high number of snakebite envenoming [75]. In Brazil, around 30 thousand snakebite cases have been reported annually to the Ministry of Health [6, 34].

SBE mainly affects poor populations practicing agriculture or traditional extractives, with difficulties in accessing health services and adequate anti-venom treatment [6,21,23,24,26,30,31,35-39]. It is a common occupational injury for farmers and agricultural workers, indigenous populations, hunter-gatherers, shepherds, fishermen, people with limited access to education and health care, and children [6-9]. In addition to the risk of death, SBE can have physically, psychologically, and economically devastating consequences due to its high occurrence among individuals of working age and the high cost of care [40].

Epidemiological studies of SBE are scarce, which makes it difficult for governments to develop strategies to improve treatments to prevent death or morbidity [6-9]. There is little investment in research, epidemiological studies, information systems, the formulation of new antivenoms, and the training of health teams to care for people who have suffered accidents

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[41-47]. There are many obstacles to making this condition less of an impact on vulnerable populations [4-6,12,13,21,47].

Antivenom is the only treatment for snakebites [5,44,46,48]. They are specific and should be administered according to the type of venom and the severity of the case. The communities most at risk are generally far from health services, and the nearest health units rarely have the resources to treat snakebites effectively. Victims often must travel long distances to a hospital with the necessary clinical capacity. This delay increases the severity of the envenomation and the likelihood of death [26].

Patients who are treated within six hours of the accident have a better outcome [23,33]. Production protocols have remained almost unchanged since the 1800s [44,45]. Research gaps urgently need to be filled to develop new safe products and facilitate access to these life-saving products [6,48].

This study aims to highlight the challenges in accessing adequate treatment for snakebites in Brazil and other high-incidence countries in Asia and Africa. To better situate the problem, we have also included an overview of snakebite accidents.

2 METHODOLOGY

A literature review on accidents caused by venomous snakes was carried out of articles indexed on the platform of the Journal Portal of the Foundation for the Coordination of Improvement of Higher Education Personnel (In Portuguese: “Portal de Periódicos da Fundação Coordenação de Aperfeiçoamento de Pessoal de Nível Superior”; acronym in Portuguese CAPES) [49]. This portal is a virtual library of scientific information that hosts 48,038 full-text journal titles and many other references (Table S1). The following websites were also consulted: Snakebite Envenoming – WHO [21]; Brazilian Ministry of Health [34], Oswaldo Cruz Foundation [51], laboratories producing antivenom in Brazil (Vital Brazil Institute [52], Butantan Institute [53], Ezequiel Dias Foundation [54] and Immunobiological Research and Production Center [55]); Clodomiro Picado Institute [56], South African Vaccine Producers (SAVP) [57]; African Snakebite Institute [58].

The following words were chosen as descriptors: snakebite, Brazil, Asia, Africa, and treatment combined with the Boolean operator “AND”. Africa and Asia were chosen because they are the regions of the world with the highest incidence of snake-related accidents, a great diversity of species, and similar geographical characteristics, such as large areas of forest. The inclusion criteria were as follows: manuscript published between 2018 and 2024,

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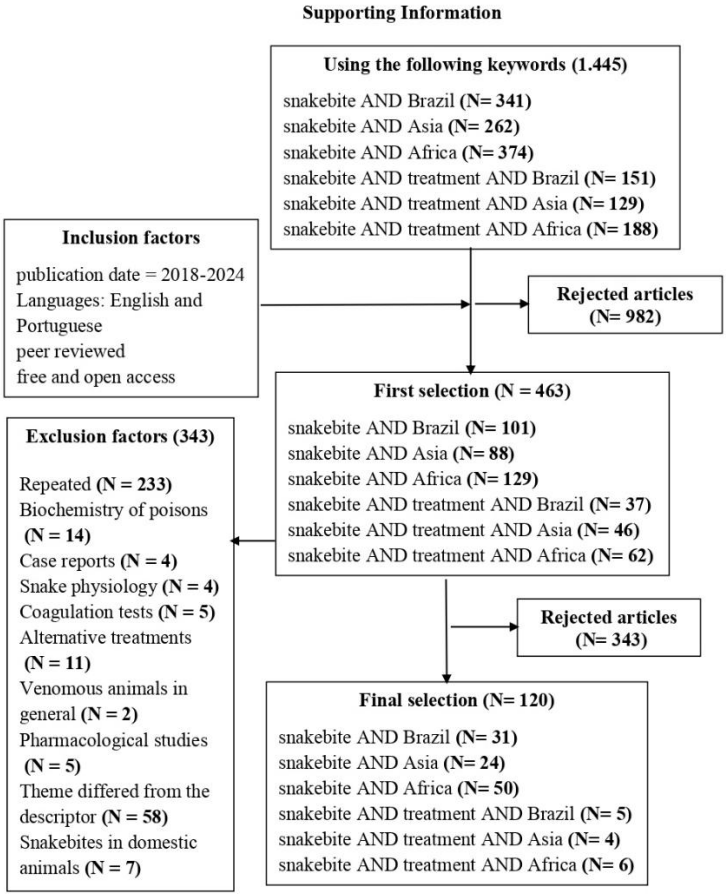
written in English or Portuguese, complete articles, open-access, and peer-reviewed. The exclusion criteria were repetition of articles in the databases, discordant abstracts, or those not relevant to the topic after reading. To analyze the information in the selected manuscript, we employed neither quantitative nor qualitative techniques; instead, we examined each article and its relevance to the objectives of this work. In the initial search, 1,445 articles were found. The selection was made in two stages: the first applying the inclusion criteria (463 manuscripts selected), and the second stage, we applied the exclusion criteria, resulting in the selection of 120 articles to be used in this study (Figure 1).

Figure 1

Flowchart of literature review, inclusion and exclusion criteria used in this study, with the number of manuscripts selected in each stage



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3 RESULTS

3.1 OVERVIEW OF SNAKEBITES

3.1.1 Snakes and their venom

Snakes are animals that generate curiosity and complex feelings, and, at the same time, they are venerated and feared, even though they are not part of the same food web; they have a close relationship with humans [59,60]. Although snakes play an important role in ecological balance, the economy, technology, medicine, and pharmacology, among others, humans still see these animals only as a threat, a risk to human life [61]. We can observe a human-snake conflict with the environment, climate, and anthropogenic activity acting as mediators [62]. Snakes avoid human contact by retreating or hiding. Many species have defensive mechanisms, such as a rattle or capel, to ward off threats [63].

They are a diverse group of vertebrates with great evolutionary success, found in diverse habitats and on almost every continent except Antarctica. With a varied diet and diurnal or nocturnal habits, they are the second most diverse group of reptiles with more than 3,700 known species, 17% of which are considered venomous [60,64]. Brazil, due to its climatic heterogeneity, large forest areas, and different biomes, is the country in Latin America with the greatest diversity of snakes and the richest in the number of venomous species described, which is why it is among the countries with the greatest risk of envenomation by these animals [6,23,64,65] (Table 1).

Table 1

A summary of the number of venomous snakes, envenomation, deaths, and manufacturers of antivenoms. Global data, in regions with a high incidence of snakebites, and Brazil.

Geographic area	Venom snake	Envenoming	Deaths/year	Antivenom producers
Global	373 species [1,21]	Around 3 million [1]	Around 100000 [1, 12, 41]	**46** [4, 66]
Asia	60 species (India) [2]	Around 1.5 million [3]	More than 100000 [3] India = 46.000 [4]	**15** [1, 3]
Africa	54 species [5]	Around 580000 [6,10]	· Around 50 (North Middle East) · Around 30000 [3,10]; · (Sub-Saharan) 32000 [7]	**8** [1,3,8,57]
Latin America	Not informed	Around 60000 [3]	Around 350 [3]	**16** [1,3,66]
Brazil	44 species [1]	Around 30000 [6,9,23,34,47]	Around 100 [9,23,47]	**4** [6,66,71]

Source: produced by the authors, 2025.

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The WHO has categorized highly venomous snakes into two groups based on the level of medical importance to guide the production of antivenom; Category 1 major medical importance, which are snakes that commonly cause bites with high levels of morbidity, disability, and mortality; and Category 2 secondary medical importance, which are snakes capable of causing morbidity, disability or death, but are less common or lack epidemiological and clinical studies. To achieve the global target of halving the burden of snakebite accidents by 2030, which is the goal of the WHO, it is necessary to understand the current situation of these accidents [4,29].

In the Middle East and North Africa, 17 species of snakes are found, and in sub-Saharan Africa, covering the Central, Eastern, Southern, and Western regions of the African continent, 26 species (Table 1). The snakes responsible for many bites and associated with serious or potentially fatal envenomation are vipers, African vipers, cytotoxic or neurotoxic snakes, and mambas [46,47,72,73]. Among these, the most medically relevant snakes belong to the genera *Echis spp., Naja spp., Dendroaspis spp*., and *Bitis spp*. [46].

In Asia, up to two million people are bitten by snakes every year (19). This number is high in several countries in the region, including India, with the highest number of occurrences, the Philippines, Thailand, Sri Lanka, and Indonesia, among others [72-75].

Epidemiological data on snakebites in Central, Western, and Northern Asia are limited, as well as in Eastern Asia, including China [72,73]. But *Cryptelytrops albolabris* is a common and clinically relevant snake that is distributed in the lowlands, hills, and lower mountain ranges of Nepal. *Talbolabris* is also distributed in South and Southeast Asian countries. Other vipers of medical importance in Asia are *Gloydius himalayanus*, *Ovophis monticola*, *Trimeresurus albolabris*, *Septentrionalis, Stejnegeri*, and *Tibetanus* [76].

Asia has widely distributed snakes of medical importance such as *Protobothrops mucrosquamatus, Viridovipera stejnegeri, Deinagkistrodon acutus, Bungarus multicinctus, Naja atra,* and *Daboia siamensis* [77]. India is home to 52 species of venomous snakes and has more snakebites and snakebite-related deaths per year than any other country in the world [72].

In South America, the most important snakes belong to the genus *Bothrops spp*. [46,47,78,79], with around 48 species distributed from Mexico to Argentina [25,79]. *Lachesis muta, Crotalus spp.,* and *Micrurus spp*. [46] distributed among the Viperidae and Elapidae families [37]. In the Viperidae family, the genera Bothrops, Crotalus, and Lachesis, popularly known as Jararacas, Cascavéis, and Surucucus, respectively, have specialized teeth for

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injecting venom [7,8,37,38]. The genera that stand out the most are *Bothrops spp.* and *Crotalus spp*., as they are responsible for more than 95% of reported accidents. Bothrops spp. is abundant, with a wide geographical distribution, since they have successfully colonized most of the south of the American territory and are responsible for most accidents in Brazil (Figure 2), around 85% [30,39,46,80].

In Brazil, notification of snake accidents is mandatory. Around 30,000 snake accidents are reported every year to the Ministry of Health's National System of Diseases (acronym in Portuguese, SINAN) [6,14,23,81,82] involving the four genera of snakes of interest to public health [1,6,37,38,81,83,84] (Figure 2). There are 405 known species of snake, 66 of which are venomous, divided into 4 genera [85] (Table 1). The Viperidae family has three genera, the Jararacas *(Bothrops spp*.), which are widely distributed throughout the country and can be found in forests and anthropized environments such as plantations or even urban centers. Rattlesnakes (*Crotalus spp.)* are mainly distributed in dry areas of the country. Surucucus (*Lachesis spp*.) are distributed in the Amazon and much of the Atlantic Forest, with some records in forests in the interior of Brazil. The Elapidae family has around 39 species of True Coral Snakes (*Micrurus spp*.). True Corals are distributed throughout the Brazilian territory, and several species adapt very well to anthropized areas. Micrurus corallinus and Micrurus frontalis are the two most frequent species [6,23,85-88].

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Figure 2

Snakes of medical importance in Brazil. A: B. jararaca; B: B. neuwiedi; C: B. alternatus; D: B. moojeni; E-F: Lachesis muta; G-H: B. jararacuçu; I-J: Crotalus durissus; K-L: Micrurus coralinus.

Source: Prepared by the authors, 2025. **Photos**: Ana Paula Amorim (A, I, K, L); Moana Ferreira (B, C, D, E, F, H, J); Ricardo Igreja (G).

3.1.2 The bite and the burden

Snakebite is an ecological, social, economic, cultural, and political phenomenon [2,89]. Snakes bite to defend themselves against a predator or to secure a meal. Snake bites in humans are usually defensive or mistaken [36,84]. Snake bites are triggered by the introduction of a complex cocktail of toxins by the animal's inoculating apparatus, known as fangs, which are solenoglyphic in viperids and proteroglyphic in elapids (Figure 3), into the victim's body, leading to local and/or systemic alterations [90,91]. There may be a seasonal effect, as the rainy seasons have been associated with an increase in the frequency of snakebite accidents [6,35].

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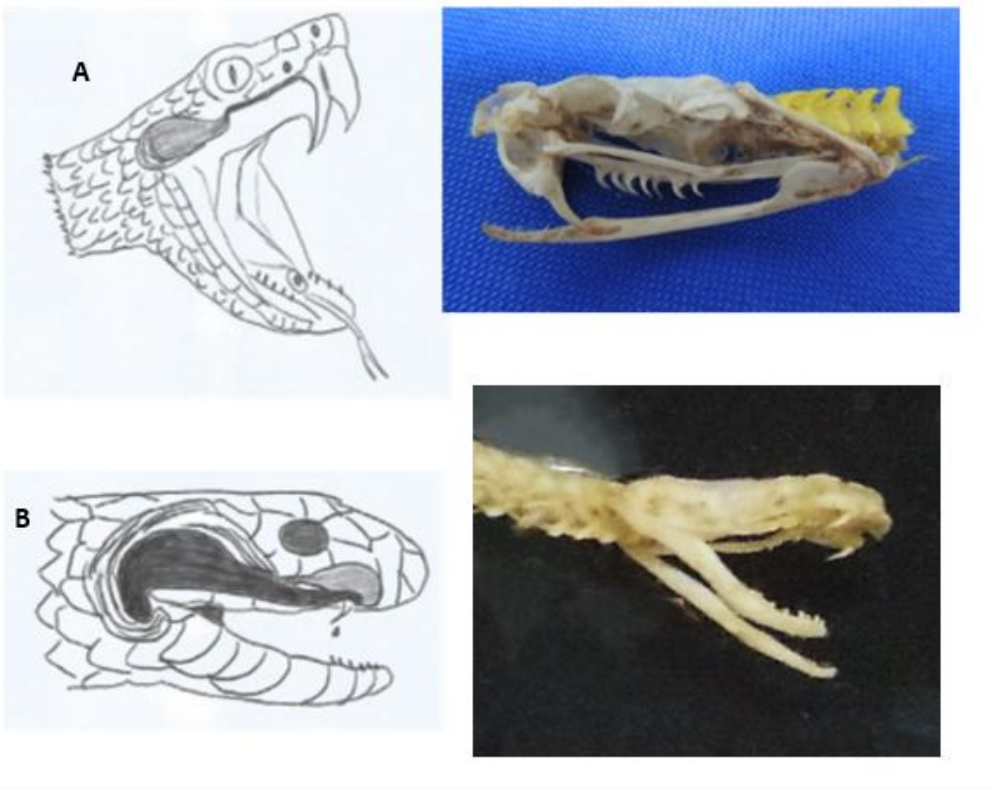
Figure 3

Venom inoculation device for venomous snakes. a) Viperids – Solenoglyphic Dentition; b) Elapides – Proteroglyphic Dentition.



Photos: Moana Ferreira. Illustrations: Ana Paula Amorim.

A person can be bitten for various reasons: rolling over the animal while sleeping, not realizing its presence, handling the animal by an inexperienced or confident person, and trying to capture or kill the animal [63]. Generally, the bite is on the extremities, the upper limbs first, due to rural work, or because the injured person tries to handle the animal [28]. Then the lower limbs, due to stepping on the animal or passing close to where it rests or nests [92]. In indigenous Brazilian populations, bites occur in greater numbers on the lower limbs, particularly the feet [23]. Men are the most affected and in the economically active age group between 15 and 49 [14,19,84].

It is a burden that causes social and economic damage, affecting people of working age in rural areas of tropical and subtropical countries where care is poor in terms of prophylaxis and adequate treatment [6,12,35-37,93]. They are the main cause of human poisoning in Brazil [94]. Late or inadequate treatment can lead to permanent disabilities [63] or psychological alterations [95].

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The burden of poisoning varies dramatically between regions, and disproportionately affects rural communities in the tropical zones of Africa, Asia, and Latin America [25,28,36,72], where doctors have long witnessed injuries, disabilities, and deaths from snakebite, which is a daily occurrence [6,37,96]. India is responsible for many deaths each year, around 50,000, due to the high prevalence of venomous snakes in a heavily populated region with poor living conditions, limited access to healthcare, and a lack of antivenom [33]. Geographical inaccessibility, distance, and traditional healing practices are factors that contribute to snakebite morbidity and mortality in Asia [61].

Snakebites are generally underreported [19,97,98]. Data on the incidence of bites is scarce in most countries [74,99]. The WHO is launching a new Snakebite Data and Information Platform. It comprises tools for managing, analyzing, and visualizing up-to-date data from various sources. It includes an up-to-date range of maps of all clinically important venomous snakes, other relevant information, and an integrated database of antivenom products. This will become a central space for collaboration, data sharing, and access to snakes and snakebites for Member States, the scientific community, industry, other stakeholders, and the public [21].

Medical care is not available for many victims in rural tropical regions. As a result, the epidemiology, clinical effects, consequences, and socioeconomic impact of this disease are not well understood [43,98]. Retrospective studies are also important for obtaining this information [47]. Identifying risk regions for mapping and surveillance can help in the diagnosis, monitoring, treatment, prevention, and reduction of these accidents [65].

Brazil's biodiversity facilitates the presence of snakes in all its biomes [14], and accidents occur in rural and urban areas, with serious cases leading to sequelae and death. It is an ever-present occupational and environmental risk, adding to the burden of poverty [6,96,100]. Brazil is the third country, next to Vietnam, in terms of the number of accidents involving venomous snakes in the world, behind only India and Sri Lanka [101,102]. They are an important cause of morbidity and mortality [103]. Many accidents are caused by snakes of the genus Bothrops, followed by the genus Crotalus. The Micrurus and Lachesis genera occur less frequently. When evaluating the highest incidences by Brazilian region, the North and the Center-West regions recorded the highest numbers of notifications. The months are hot and rainy, periods of great rural activity since it is in this area that we have the greatest occurrences [6,47]. In the Unified Health System (SUS, per its acronym in Portuguese), snakebite antivenom is provided free of charge. According to the Brazilian Ministry of Health

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[23], around 1,600 hospitals across the country provide five types of antivenom to treat different types of envenomation: pentavalent antibotropic, pentavalent antibotropic and antilacetic, pentavalent antibotropic and antilacetic, antilacetic and antielapidic [23,104]. However, in remote areas such as the Amazon region, access to antivenom is limited, and that leads to a delay in care or the absence of medical treatment, increasing the chances of a poor outcome [23].

The notification of cases of snakebite is compulsory in Brazil and part of the National Surveillance System (SINAN to its acronym in Portuguese) [81,82,102]. This system is an important source of surveillance data on poisonings by venomous animals. The information contained in the Information System for Notifiable Diseases (SINAN), although still underreported, can be used in epidemiological analyses and strategic research for SUS [9,81], guiding public policies and interventions, especially the distribution of antivenom. Due to the importance of these records, it is necessary to constantly assess the quality of the data reported in a system [94].

3.1.3 Symptoms and diagnostic

Patients usually report a history of snakebites with fear and anxiety. Some patients, especially children, may present cardiovascular collapse, unconsciousness, bleeding, paralysis, or respiratory failure and may not provide a clear history of snakebite [105].

A basic diagnosis requires a complete patient history, targeted examination, and appropriate laboratory investigations. As well as information on the circumstances of the accident such as geography, time of incident, activity, number of bites; details of the snake if seen, brought, or photographed; clinical manifestations of envenomation including time of onset; first aid applied and past medical history, for example, allergies, previous snake bites, relevant medications and pre-existing medical conditions [72,106].

On physical examination, there may be local tissue damage, such as ecchymosis, blistering, and necrosis. Neurotoxic effects can be generalized weakness, ptosis, and ophthalmoplegia; this can progress to paralysis of the facial muscles and respiratory failure. Significant bleeding at the puncture site, epistaxis, or evidence of spontaneous bleeding may indicate a hemotoxic effect with local or systemic coagulopathy [25,33,98,106,107]. Patients may show signs of shock and organ dysfunction [108]. Symptoms that may suggest systemic effects of the poisoning include nausea, vomiting, abdominal pain, lethargy, muscle weakness, muscle fasciculation, and severe headache. It is important to recognize these

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symptoms early to start anti-venom [25,33,35,64,98,106,109]. With a physical examination, the patient's history, and laboratory tests, trained professionals may be able to infer the species of snake being attacked and guide the choice of treatment [33,72,98].

Another important piece of information is the identification of the animal, as it is common to be uncertain about the offending species. Identification helps with diagnosis and enables knowledge of regional species of medical importance and the serotherapy indicated [47,72,84,99]. Correct identification of the causative animal helps with treatment and care, mainly by reducing the time it takes to decide and apply the antidote, which results in fewer consequences for the injured person [110]. Knowledge of snake distributions is fundamental to understanding where vulnerable human populations are exposed to snake bites, the degree of exposure, and where the antidote for each species is needed [111] and is also important for health education and public health strategies [112].

3.2 TREATMENT AND ANTI-VENOM PRODUCTION

Antivenom is the only safe treatment for snakebite [5,44,46,48], has been available for 120 years, and is highly effective [6,8,101]. It should be administered within 3 to 6 hours of the occurrence, according to the type of accident and the severity of the case, to offer the best results and the lowest risk of surgical interventions, disability, and death. [14,42,47,102]. Patients who seek care in the first 6 hours after the bite have significantly lower morbidity and mortality [23,33]. On the other hand, delaying care worsens the prognosis and can increase the risk of injury and acute renal failure, and the severity of the envenomation [9,72,113].

By 2022, there were 31 antivenoms available worldwide for treatment [46]. But their production protocols have remained essentially unchanged since the 1800s: purification of immunoglobulins (IgG) from horses or sheep hyper-immunized with sublethal and subtoxic doses of snake venom. The effectiveness of conventional antivenom is restricted to the immunogenic potential of the venoms used in its manufacture [44,45] (Table 2). Research efforts have been made to overcome these problems in the production of antivenoms. When injected into a poisoned human bitten by a snake, it mainly neutralizes the toxins of the venom used in its production [46]. Once in the hospital, further assessment, additional resources, and treatment options can be offered [44].

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Table 2

Scheme to produce anti-ophidian sérum

Step	Description
1	Extraction of snake venom, which is transformed into an antigen
2	Horses receive the antigen in small doses to produce antibodies against the venom.
3	Blood tests are used to see if there are enough antibodies in the animal's body. When this happens, the blood is collected and separated from the plasma, which is where the antibodies are
4	The plasma undergoes industrial processing for purification and formulation.
5	The serum is ready

Source: Instituto Butantan (53); adapted by authors, 2025.

However, the lack of attention to this public health problem and the crises in the production of antivenoms around the world have left millions of people vulnerable, with less chance of treatment and of reducing the likelihood of death and occupational disability [36,38,114]. Production inefficiencies with poorly structured systems, little incentive for innovation or investment in new technological processes, inadequate market demand, low manufacturing volumes, storage limitations, and distribution problems have combined with inadequate funding for procurement, poor training of health professionals, and a local tendency towards traditional cures to create a fragile market at risk of collapse in many parts of the world [42,114].

According to Chippaux [1], in 2019 there were 46 antivenom manufacturers in the world, of which 16 (35%) were in the Latin American region and 15 (33%) in Asia; in the Sub-Sharan Africa region, where there are an estimated 500,000 accidents, there is only one antivenom producing laboratory (Table 1).

The high costs of antivenoms are largely the result of the cost of maintaining the serpentarium; venoms; breeding animals such as horses; immunizing them for 15 to 18 months; IgG purification; IgG digestion; quality control tests, preferably on mice, carried out at each stage of production and for each batch produced; bottling; sometimes freeze-drying; distribution and clinical studies. Above all, there is the risk of poor sales of a product that expires very quickly, especially with liquid formulation, further perpetuating price increases [18].

There is an urgent need to improve the availability, geographical, and financial accessibility of antivenom at a global level to guarantee safe and effective pharma-cotherapeutic treatments for snakebite victims [70,115-117]. It should therefore ensure the development of high-quality guidelines on the treatment of snakebites, including accessibility, epidemiological, demographic, and ecological studies [72,116,118,119].

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The distribution and maintenance of antivenoms in remote areas is crucial. There is an urgent need for research into new types of antivenoms with a longer shelf life without the need for refrigeration [6,48], and countries affected by snakebites must increase their budgetary expenditure on interventions in accidents and on the acquisition of antivenoms [18]. The treatment of SBE is challenging and requires innovation [69,120].

In Africa, SBE is underestimated, and the reliable supply of effective antivenom for snakebites is challenging [40,69,108]. Despite the high number of snakebites, there has been a decline in production and a loss of confidence in antivenom products [40], which long ago became unaffordable for all victims, as effective treatment usually re-quires 2 to 10 vials of antivenom and these costs are hardly subsidized, which makes antivenom treatment, if available and effective, unaffordable for many African victims. In other words, snakebite victims in sub-Saharan Africa have been abandoned for decades by the lack of adequate responses from governments and international health agencies [26]. In addition, victims face geographical access difficulties, and health professionals lack information [69].

In Eswatini, a country in southern Africa, treatment depends on the SAIMR Polyvalent antivenom, which, although effective, is difficult to find outside the country of manufacture (South Africa) and frighteningly expensive. The alternatives being tested have been the antivenoms 'Panafrican' manufactured by the Clodomiro Picado Institute and 'PANAF' manufactured by Premium Serums & Vaccines - the Panafrican and PANAF antivenoms offer effective alternatives to SAIMR Polyvalent for snakebite treatment that could be a hope in Eswatini and neighboring countries [31]. In Cameroon, Inoserp® PAN-AFRICA (IPA), manufactured by Inosan Biopharma, is widely used. Panaf-Premium ® (manufactured in India) and Equitab® (manufactured in Great Britain) have been in the process of being regularized since 2023 [32,121]. North Africa has been producing MENA-Vip-ICP®, which aims to unify all snake antivenoms in the Middle East and North Africa (MENA) but is still in the validation phase [122]. Also in North Africa, more specifically in Tunisia and Morocco, a treatment based on nanobodies or VHHs from camelids has been developed, which seems to be promising in the treatment of SBE by *Naja haje* [123].

Small-molecule toxin inhibitors have also received limited attention to date as potential alternatives to immunoglobulin-based snakebite therapies. Perhaps the most promising is the PLA 2 inhibitor, 'Varespladib', which has been widely explored for repurposing as a snakebite therapy and has shown substantial promise in preclinical models against a range of elapid and viper venoms [24].

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When it comes to the security of supply, it is important to remember that dependence on imports of antivenoms puts African countries at permanent risk of supply [18,43]. In addition, some African countries have registered antivenoms that are epidemiologically unsuitable due to the most prevalent snake species [124]. In many African and Asian countries, the production of antivenoms is paralyzed or completely stopped [19]. Many factors such as late arrival at health facilities, negatively affecting the treatment and outcome of snakebite victims, availability of ineffective or unsafe antivenoms, restricted access, and high costs are crucial challenges in the care of accident victims, making supportive measures often the only therapeutic options for patients presenting with snakebite envenomation in many African countries [108]. It is important to note that snakebite envenomation also causes long-term health effects and can have strong social and economic impacts that are little researched globally in the affected communities [68].

Despite the importance of knowledge and awareness about SBE, several studies have found that many health professionals in endemic regions have little general knowledge about the snakebite crisis and the complexity of accident management. A study of medical care in Nigeria showed little knowledge about venomous snakes, first aid, snakebite treatment, and prevention. Similar gaps in initial knowledge and treatment confidence regarding the treatment of snakebite patients were found in doctors in Hong Kong, Laos, Nepal, and West Bengal [36,75].

According to 45 clinically important venomous snakes found in Asia identified by the WHO, only 22 (49%) have been tested and confirmed to have antivenom-neutralizing capacity against their lethality. In addition, antivenoms were found to be ineffective against six (13%) clinically important venomous snakes [41].

More than a third of annual global deaths occur in India [68], even though it is a major manufacturer of antivenoms [125]. Polyvalent and monovalent antivenoms are available, but they do not cover all venomous species. In addition, there is a need for a standardized quality control process for the manufacture of antivenom to ensure that they are safe and effective [72]. The care provided to injured people is still very poor in India's public and private health systems [125]. In addition, in many regions, anti-venom is available free of charge in public hospitals, but the medical staff in these centers are not trained [109]. In other Asian countries, T. albolabris poisoning can be fatal due to the unavailability of antivenom [107].

On the other hand, the healthcare system in Thailand and Taiwan is well-developed, and expenses for SBE treatment are reimbursed by the universal healthcare coverage

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system. In Thailand, access to antidotes has greatly improved since the implementation of the Thai national antidote program in 2010 [126].

Geographical accessibility is part of the broader, diverse, and complex concept of access to healthcare. Assessing the quality of access to care involves the geographical accessibility of health services, their availability, the feasibility of obtaining them, and the acceptability of this care. Elements such as the spatial distribution of the population, the road network, the location of health centers and hospitals, and travel time must be considered to properly identify possible access to facilities that provide anti-ophidian serums. As with many other types of health care, access to health services and travel costs hinder access to the supply of anti-ophidian serum [14,117].

Brazil is a self-sufficient manufacturer of snake antivenom. Since 1986, the Ministry of Health has purchased all antivenom production from the four national producers: Butantan Institute,Vital Brazil Institute, Ezequiel Dias Foundation, and Immunobiological Production and Research Center [8,23]. Under current policies, most of the antivenom is distributed free of charge to various hospitals through the Unified Health System (SUS) [23,88,127]. There is good accessibility to high-quality antivenoms at the gender and intergender level, enabling the treatment of many of these poisonings [128,129]. But despite Brazil having a nationalized health system, many municipalities in the country do not have easy access to emergency care services [113]. There is an association between the distribution of the population, the routes, and the health facilities that can provide serum. More populous parts of the country have more widely distributed facilities and more significant availability of routes. The Amazon region, in the north of the country, has a spatially concentrated distribution of facilities and more complex circulation or transportation, since in many cases the only means available are waterways [14]. When the injured person is indigenous, they receive the anti-venom serum through the Indigenous Health Care Subsystem under the SUS. It should be noted that the indigenous population, especially in the northern region of Brazil, is more vulnerable to accidents and has a mortality rate 3.5% higher than the white population in the same region [23]. This is mainly due to the centralization of antivenom in more populated regions [22,23,128,130,131].

A set of 16 studies with 3,697 records carried out in 16 countries showed that socio-economic and cultural factors also influence treatment-seeking behavior and can lead people bitten by snakes to opt for traditional or unconventional practices rather than hospital care. Lack of money or transportation, or distrust of Western medicine, can influence the decision

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to go to the hospital. To compound this lack of trust, the staff at many health centers are not sufficiently trained to treat snake bites, and, even if medicines are available, they can be too expensive for many victims. In addition, many antivenoms need to be kept refrigerated to remain stable and effective. In environments with few resources and frequent power cuts, even in cities, keeping them refrigerated can be almost impossible [36]. [36]. It is therefore necessary to involve the population in this process of health education, through educational campaigns, about the areas with the highest incidence, the profile of the highest incidence, the period of the year of highest occurrence, and ways of preventing it [36,47].

As for follow-up after hospital discharge, after the acute effects have been resolved and they have been discharged, most patients rarely have any contact with the health system in relation to the snakebite accident. Although some acute pathological effects of envenomation can disappear completely within a few days of the bite, other effects or their consequences can last for months or years. However, due to the lack of clinical follow-up and clinical research studies, the long-term effects of ophidian poisoning are poorly defined. In addition, some psychological effects resulting from the accident are likely to have a delayed onset. The long-term sequelae that can be observed are local necrosis resulting in amputation, chronic ulcers, chronic local pain, and swelling, blindness due to the primary effects of the venom, chronic kidney dis-ease, neuromuscular paralysis, neurological effects secondary to toxic or ischemic events, neurological effects after intracranial hemorrhage, reduced parasympathetic activity, anosmia and changes in taste, hypopituitarism, psychological effects [98,132].

The hope for better treatment may lie in the recombinant production of broad-spectrum antivenoms. Neutralizing monoclonal antibodies have several advantages over conventional antivenoms. Although recombinant antivenoms offer a promising solution to solve SBE, there is a need for clinical validation, which seems unlikely to occur commercially over the next decade [133].

3.3 CHALLENGES TO BE OVERCOME

There are many challenges when it comes to addressing and treating snakebites around the world, and these need to be urgently addressed. Some challenges are similar in different places, others are specific to the locality or population affected, as shown in the table below (Table 3).

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Table 3

Description of the current challenges in snakebite accidents concerning geographical regions

Geographic area	Challenges
Global	Low production of antivenoms [1,12] Lack of data on snake bites [1,12] Lack of epidemiological data on snakebites [1,12,23,41] Inadequate health services, especially in remote communities [1,19,32,111] Underreporting of incidence and mortality [1] Difficulties in accessing antivenoms with a shortage of safe, affordable, and effective products [1,116,125] Socioeconomic and cultural factors that influence behavior and treatment [1,125] Socioeconomic vulnerability [16,119] Financial incentives for new laboratories producing antivenom [137] Many victims opt for traditional practices instead of hospital care [1,41]
Asia	Lack of information on access to antivenoms [10,12,41, 125] Difficulties in accessing antivenoms [10,19,125] Populations most vulnerable to snakebite: Pakistan and Indonesia (10); India, Sri Lanka, and Nepal [11] Highest mortality rate: India [11] Vulnerable populations [11,16,75] Low capacity of health systems [11,19,125] Inefficient access to supportive treatments [11,19,125] Insufficient financial support [41] Search for alternative treatments = increased mortality [11,19,41,125] Inadequate and insufficient production of antivenoms [11,125] High cost of available antivenoms [11,41] Underreporting [11] Difficulties for health staff in recognizing snakes of medical importance [12,19]
Africa	Underreporting [11,93] Vulnerable populations [16, 69, 75,116, 119] Populations most vulnerable to snakebite: Angola, Democratic Republic of Congo, and Ethiopia [10] Identifying venomous species in the most vulnerable locations [10] Most critical countries for treatment: Mali, Senegal, and Guinea [10] Lack of epidemiological studies to develop anti-venom coverage strategies [10,32,69,116,119] Difficulties in accessing antivenoms [32,116,117,119] Inadequate health services, especially in remote communities [1,32, 117] Need to improve medical care and transportation of the injured [10,116] Provide safe antivenoms, training for health teams, and public policies [10,116; 119] High cost of available antivenoms [11,116] Difficulties in recognizing snakes of medical importance on the part of the health team, or lack of training [122,135] Higher mortality rates in descending order [11]: Western Sub-Saharan Africa - Nigeria, Burkina Faso, Cameroon, Chad, The Marin Coast, Ghana, Mali, and Niger. Central Sub-Saharan Africa - Democratic Republic of Congo. Eastern Sub-Saharan Africa - Ethiopia and Kenya.

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Latin America	Difficulties in accessing antivenoms, especially in Colombia, Peru, and Northern Brazil [10]; Central America, Paraguay, and the Caribbean [136] Delay in seeking adequate medical care [13] Improving the quality of antivenoms [136] Financial incentives for new antivenom-producing laboratories [136,137] Shortage of human resources and equipment for anti-venom production [14] Vulnerable populations [6, 23,75] Improving the availability and accessibility of safe and effective antivenoms [136] Of the 20 countries that make up Latin America, only 9 countries produce serums [14]
Brazil	. Difficulties in accessing antivenoms, especially in the north of the country [10] . The Indigenous population has the highest accident and mortality rate [23] Despite mandatory reporting, there is still underreporting [6,9,11,14,15,23] Delay in seeking adequate medical care [9,13,23] Vulnerable populations [6, 23] Difficulties in accessing health facilities [6] Less populated regions have fewer health facilities, worse routes, and worse distribution of antivenoms [16]

Source: elaborated by the authors, 2025

4 CONCLUSIONS

Accidents involving venomous snakes have been a global public health problem for many years, affecting all continents, but mainly poor countries, with traditional agricultural and extractive practices, difficulties in accessing health systems and efficient antivenoms, with a lot of under-reporting, public health systems with little or no incentive for research and educational production in health or the environment. These aspects strengthen its status as a neglected tropical disease and reinforce the importance of investments in this sector and innovations in public policies for the care of vulnerable populations, the continuing education of health professionals, and the training of new professionals who can take a closer look at this disease that affects so many around the world.

The most important challenge to be filled to save the lives of people vulnerable to SBE is funding research into innovative approaches to discovering and developing state-of-the-art treatments for snakebites. There is an urgent need for global funding for antivenom research and production, similar to that for vaccines, which should be coordinated by the WHO. This effort would bring together international organizations, governmental and non-governmental agencies, research institutes, and sponsors. Such measures can succeed through robust epidemiological studies, analysis of large databases, and the provision of relationships between the incidence of accidents and environmental conditions. It is essential to envision a future with improved access to hospital units offering safe and effective treatments, where SBE is no longer a public health concern.

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We can also suggest that one of the gaps to be filled is the encouragement of research into snakebite envenomation, both from an ecological and public health perspective, which could serve as a tool for improving future estimates of the disease burden.

Improving the quality of information is another fundamental issue for epidemiological surveillance, particularly in drawing up strategies and public policies for health promotion and the prevention of SBE, based on evidence and with a transdisciplinary perspective. As with other neglected tropical diseases, the control of snakebite envenomation is hindered by inadequate epidemiological data and insufficient investment in diagnostic, intervention, and analytical tools. The WHO and several countries are working to close this gap. Knowledge about the epidemiology of accidents, their incidence rates, morbidity, lethality, and the distribution patterns of venomous snakes, as well as their physiological and behavioral characteristics, is essential for the prevention and proper treatment of snakebite accidents, so that any potential change in any of these items is of total concern for the control of this disease. A change in the distribution of these species could lead to a change in the way the specific serum is currently distributed, as well as identifying possible risk areas where greater attention is required from public authorities.

It is essential to strengthen health units, including continuous training of health teams, particularly in regions where the most vulnerable populations reside. It is also crucial to engage and educate communities to help them understand the dynamics, biology, and life cycles of these animals, and to prevent accidents, thereby enabling the world's poorest and most vulnerable communities to live healthy and productive lives.

Brazil is the largest country in Latin America and has demonstrated self-sufficiency in the production of anti-snake serums through four public laboratories, as well as in epidemiological studies, records on the ecology and biological knowledge of venomous snakes, and reporting of snake bites. It also has decentralized and free distribution logistics for antivenom based on records of occurrences. The country has a well-established snakebite treatment program and is a leader in toxicological research. The main shortcomings are the difficulties in accessing antivenoms, especially in the North of the country, mainly due to the low demographic density of the region and the distance from health units, and the Indigenous population, which has a higher mortality rate than the white population, due to ethnic and religious as-pects and failures in specific public policies for assisting these injured groups.

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INSTITUTIONAL REVIEW BOARD STATEMENT

This doctoral project in the Postgraduate Program in Infectious and Parasitic Diseases at the School of Medicine of the Federal University of Rio de Janeiro, entitled “Epidemiological aspects of accidents by venomous snakes reported in the municipality of Rio de Janeiro between 2008 and 2017”, was submitted, evaluated and approved by the Human Research Ethics Committee of the Clementino Fraga Filho University Hospital of the Federal University of Rio de Janeiro (CEP/HUCFF/FM/UFRJ), Brazil. It is registered under the protocol CAAE: 70667423.9.0000.5257.

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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