




Snakebite envenoming in Brazilian children: clinical aspects, management and outcomes

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ABSTRACT

Snakebite envenoming is currently considered a neglected tropical disease, which affects over 5 million people worldwide, and causes almost 150 000 deaths every year, as well as severe injuries, amputations and other sequelae. Snakebite envenoming in children, although proportionally less frequent, is generally more severe, and represents an important challenge for pediatric medicine, since they often result in worse outcomes. In Brazil, given its ecological, geographic and socioeconomic characteristics, snakebites are considered an important health problem, presenting approximately 30 000 victims per year, approximately 15% of them in children. Even with low snakebite incidence, children tend to have higher snakebite severity and complications due to the small body mass and same venom volume inoculated in comparison to adults, even though, due to the lack of epidemiological information about pediatric snakebites and induced injuries, it is difficult to measure the treatment effectiveness, outcomes and quality of emergency medical services for snakebites in children. In this review, we report how Brazilian children are affected by snakebites, describing the characteristics of this affected population, clinical aspects, management, outcomes and main challenges.

KEYWORDS: venom, snakebite, envenomation, infants, child, disabilities

INTRODUCTION

Snakebite envenoming (SBE) is a Category A neglected tropical disease that results from the inoculation of toxic venoms by a snake into humans, usually under accidental conditions [1, 2]. Snake venoms present high variability and complexity. Since they are rich sources of proteins and peptides targeting a wide range of tissue receptors, they result in a gamut of clinical effects [2, 3]. The events derived from SBEs range from local tissue damage, which eventually results in permanent sequelae, to systemic effects that include hemostatic abnormalities, acute kidney injury, rhabdomyolysis, neuromyopathy, hypotension, bradycardia and shock [1, 4–6]. Local and systemic alterations can be severe and require different health services, including hospitalization for long periods, surgical procedures and follow-up for rehabilitation [4, 7, 8]. In addition to the physical disabilities that can be permanent, SBE can lead to significant psychological trauma [9, 10].

SBEs prevail among young male adults from rural regions of low- and middle-income countries, with certain significant risks and poor access to medical care [8, 11–13]. However, children living in rural areas are also potential victims when participating in agricultural labor, or when exploring different environments while playing or walking around [14]. Indeed, the global burden of SBEs is large and, disproportionately, affects children living in low-income environments, resulting in long-term effects (e.g. amputations) and post-traumatic stress [4, 11–13]. Due to the smaller bodies and large proportional volume of injected venom, children have more severe presentations, such as faster and more severe neurotoxicity, coagulopathy and more severe local tissue damage even though, due to the lack of epidemiological information about pediatric snakebites and induced injuries, it is a challenge to measure the treatment effectiveness, outcomes and quality of emergency medical services for snakebites in children [14–19]. In this article, we review SBEs in Brazilian children and present information on clinical aspects, management and outcomes.

EPIDEMIOLOGY

Annually, approximately 5.4 million people worldwide are bitten by venomous snakes, which results in 2.7 million envenomings and up to 138 000 deaths [9]. As a problem

with global and widespread impact, in 2017, SBE was designated by the World Health Organization (WHO) as a Category A disease in its list of neglected tropical diseases [1, 20, 21]. Despite their importance, the real burden remains unknown due to a remarkable underreporting [22]. Studies suggest that the number of people suffering from permanent sequelae could be as high as 400 000, and the associated number of disability-adjusted life years may add up to over 6 million [1, 15, 23–26]. Moreover, there are significant changes in the incidence of snakebites between different regions, being the highest in rural areas.

Ninety-five percent of snakebites happen in Africa, Asia and Latin America [15]. Because of their characteristic ecology and biogeography, tropical and subtropical developing countries, such as those in Latin America, have high incidence and mortality rates [1]. In Brazil, since 2010, all envenomings caused by venomous animals have been considered mandatory notification events. From 2012 to 2020, 404 311 cases of SBEs were reported to the Ministry of Health (MoH) [27], with 63 869 (15.8%) occurring in children below 14 years old [27]. Although there is a lack of epidemiological studies, the Brazilian incidence of snakebites is similar to other reports in the world showing around 15–30% of the total occurs in children [14, 16, 28]. In Brazil, the SBE incidence is much higher in the Amazon region compared to the central and southern regions of the country [29]. Figure 1 shows SBEs spatial distribution in Brazil and its relation to severity and access to health facilities. Regardless of the noteworthy higher incidence observed in the Amazon region, the number of intensive care units (ICUs) and pediatricians is proportionately lower in this region [30]. These characteristics and variations within countries must be considered when formulating public health policies and priorities at the national, regional and local levels.

CIRCUMSTANCES OF SNAKEBITES AMONG CHILDREN

Although children are proportionally less exposed to snakebites than adult male individuals because of work-related exposure, records of envenomings in children occurred indoors, while playing or sleeping [31–33], and outdoors, when fishing or farming [34, 35]. Also, children are less likely to defend themselves or understand the potential risks of venomous snakes [36].

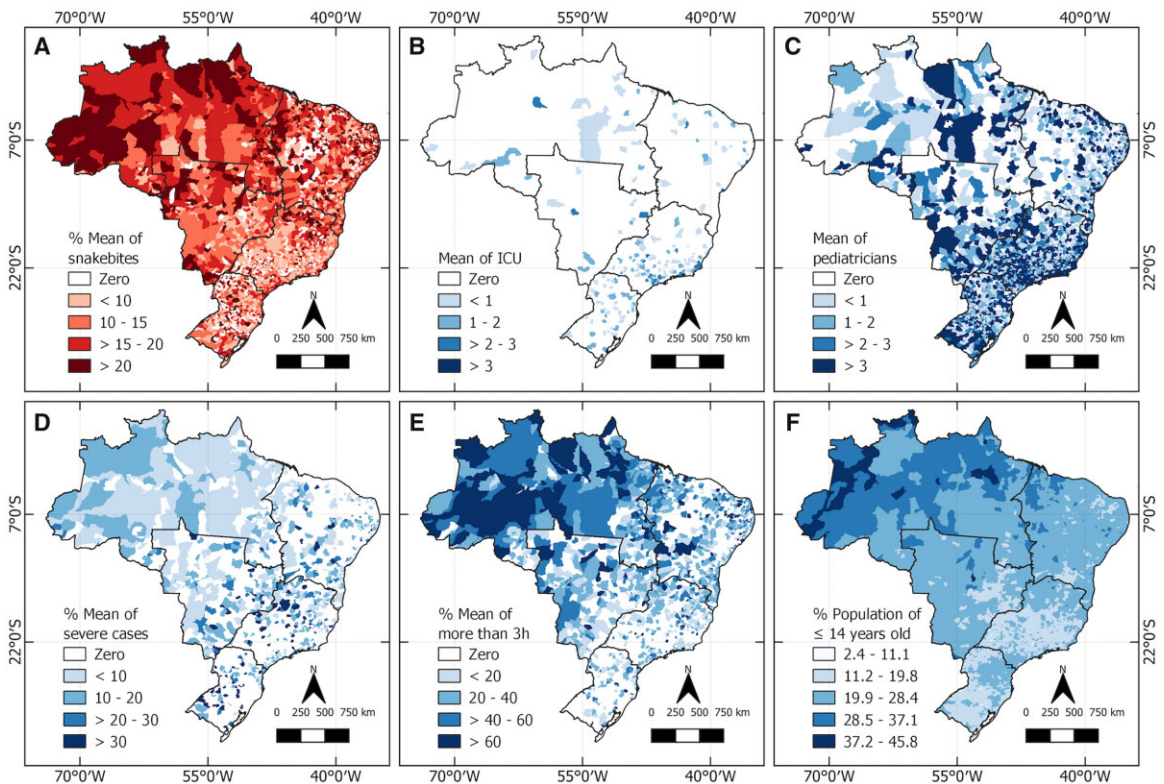


Figure 1. Snakebite envenomings in children and health facilities in Brazil. The mean percentage of snakebites (A), pediatric intensive care units (B), mean numbers of pediatricians (C), severe cases (D) and cases in which the patient took >3 h from health care to receive appropriate care were calculated (E). Finally, the distribution of the mean percentage of children up to 14 years old in Brazil was established (F). Data regarding the number of pediatricians and pediatric intensive care units (ICU-ped) in Brazil were obtained from the National Register of Health Establishments (CNES, <http://cnes.datasus.gov.br/>), while the estimated population up to 14 years old was obtained from the Department of Informatics of the Unified Health System (DATASUS, <https://datasus.saude.gov.br/>). Information regarding snakebites involving individuals aged up to 14 years old from 2012 to 2020, cases classified as severe, and time to reach health care facilities were collected from the Notifiable Diseases Information System [27]. The cartographic bases of Brazil and the macro-regions were obtained from the Brazilian Institute of Geography and Statistics (IBGE, <https://www.ibge.gov.br/geociencias/downloads-geociencias.html>). All descriptive analyses were performed using the R Studio software Version 1.4.1106, and the results were plotted on choropleth maps using the QGIS software version 3.18.

Children living in conservation units and indigenous lands are more susceptible to SBEs because of the overlap between these environments and those where venomous snakes are more prevalent [37, 38], leading to envenomation occurring in typical places and situations such as the backyards, routes to schools, forestry activities and fishing [34, 36, 39–42]. Moreno, *et al.* [41] reported that 18.7% of SBEs occurred in Rio Branco (Acre) students on their way to or from school, reflecting a permanent risk of being bitten by snakes during daily activities [37, 38].

Although more prevalent in rural areas, venomous snakes can also be found in certain places among the urban zones such as forest fragments, rivers, streams and

wasteland, where they benefit from finding natural prey such as rodents and amphibians [43–45]. In Rio Branco (Acre), as in many other municipalities in the Amazonian region, there was an increase in snakebites in households [46]. Oliveira, *et al.* [46] observed a higher incidence of cases in children under 10 years old in the urban (23.94% of cases) compared to the rural zones (8.5%) in this state [46].

SPECIES INVOLVED IN SNAKEBITE ENVENOMING

In Brazil, *Bothrops*, *Crotalus*, *Lachesis* and *Micrurus* are the medically important snake genera [47]. Envenomating

triggered by *Bothrops* genus corresponds to most cases of SBEs in Brazil due to the wide distribution of *Bothrops* snake genus throughout the national territory, represented by 29 species [48]. Moreover, of all snakes, *Bothrops* spp. appear to have a more defensive behavior, which makes them more likely to strike out, contributing to the high frequency of bites by this genus [34, 38, 47, 49]. Hence, the majority of clinical reports and case series studies of snakebites involving Brazilian children cite *Bothrops* as the cause (Table 1) [31, 34, 42].

Bothrops atrox species cause most of the SBEs in the Amazon region with a significant, detrimental, economic and public health impact on rural communities [50, 51]. Campbell and Lamar reported a case of a child bitten by *B. atrox* while fishing in Rio Branco (Acre) whose outcome was arm amputation [34]. A 5-year-old girl was bitten in the eye by a *Bothrops moojeni* while sleeping in her bed in Campina Verde (Minas Gerais) and the enucleation of her eyeball was needed [31]. Pardal, *et al.* [42] and Silva and Pardal [35] reported two boys (10 and 15 years old, respectively) who were bitten by *Bothrops marajoensis* in the foot and in the leg, respectively, while carrying out açai (the fruit from *Euterpe oleracea*—a palm tree) on Marajó Island (Pará). Another case of an SBE from an arboreal snake, *Bothrops bilineatus*, involved a 13-year-old boy bitten on the chest while climbing the açai palm tree at the height of 4 m [39].

Rattlesnake (*Crotalus durissus*) envenomings are less common than those from *Bothrops* snakes, probably due to their geographic distribution, more frequent in open areas such as Cerrado and Caatinga biomes. There are no reports of envenoming from this species in forested areas of most of the Amazon and Atlantic Forests, since they usually colonize deforested areas [47]. Compared to *Bothrops*, rattlesnakes are less aggressive and usually make a sound with their rattle at the tip of their tail, thus alerting people to their presence [47]. In a case series published by Bucarechi, *et al.* [52], in the region of Campinas (São Paulo), 31 cases involving children were described over a period of 16 years (1984–99). The authors reported rattlesnake envenoming involving children aged 1–14 years (mean age 8 years), mostly male [25], and in rural areas, including in backyards.

Bushmaster (*Lachesis muta*) envenoming is also less frequent due to the natural geographical distribution (Amazon and Atlantic Forests from the northeast of Brazil to Rio de Janeiro), overlapping with low population density forested areas. Also, their large size which is poorer to sight together with the less aggressive behavior contributes to the lower incidence [47]. Reports

in the literature show that envenoming by *Lachesis muta* occurs mainly in adults who are generally more exposed due to activities within forests or due to keeping specimens in captivity [53, 54]. However, caution must be taken with the underestimated envenoming induced by *Lachesis*, including in children (3.9%) [55]. Because of the popular names, health professionals mistakenly attribute to *B. atrox*, envenoming possibly caused by *L. muta* [56, 57]; only one proven case of a 13-year-old child bitten in Recife (Pernambuco) is available in the literature [58], with no details on the circumstances involved.

Coral snakes (*Micrurus* and *Leptomicrurus*) present aposematic (warning) colors and secretive habits. Although the species are widely found in Brazil [47], elapid-derived envenomings represent less than 1% of Brazilian SBEs. The smallmouth and their proteroglyph dentition (functional tooth in front of their jaws) make it challenging to inoculate toxins, and most bites occur when these snakes are handled [47, 59, 60]. However, their color can be attractive [58], especially for younger children unaware of the danger. Mota-da-Silva, *et al.* [55] observed elapid envenoming in children in 6% of envenoming cases under 4 years old in Brazil, which corresponds to twice that recorded for other groups of snakes (*Bothrops*, *Crotalus* and *Lachesis*) in the same age group.

SBEs caused by Colubridae and Dipsadidae families, with opistoglyph dentition (functional tooth behind in their jaws), are less frequent and are generally milder cases, even though they may account for 40–56% of snakebites in some regions [45, 61]. In Brazil, snakes of the genus *Philodryas* (mainly *Philodryas olfersii* and *Philodryas patagoniensis*) are among the main species causing snakebites and can cause pain and edema like *Bothrops* envenoming [61–65]. Because of that and the likeness with that species, snakebites by Colubridae and Dipsadidae are sometimes mistakenly reported as *Bothrops*-derived envenoming [66]. The brown-banded water snake (*Helicops angulatus*) is the most involved in snakebites in urban areas in Rio Branco [41] and in Cruzeiro do Sul (Acre). There is scarce literature on details to understand the circumstances of SBEs in children (Table 1).

CLINICAL ASPECTS AND OUTCOMES

Overall clinical aspects

The snake venom inoculated by snakes induces a variety of pathophysiological events in victims. In Brazil, envenoming caused by the Viperidae family (i.e. *Bothrops* and *Lachesis*) is characterized by exacerbated local

Table 1. Snakebite envenoming involving children according to snake species

Snake	Age	Gender	Location of bite	State	Symptoms	Outcome	Reference
<i>Boiruna maculata</i>	1.3	F	Ankle	RS	Sub-family Dipsadidae Pain, swelling, local erythema and mild cyanosis	Discharged	[33]
<i>Helicops angulatus</i>	8	M	Foot	AC	No	Discharged	[66]
<i>Helicops angulatus</i>	9	F	Foot	AC	No	Discharged	[66]
<i>Philodryas olfersii</i> (11 cases, 25.6%)	<9	?	?	SP	?	?	[64]
<i>Philodryas patagoniensis</i>	5	M	Leg	MG	Swelling and warmth on the bitten limb	?	[62]
<i>Philodryas patagoniensis</i> (60 cases)	<9	?	?	SP	?	No sequelae	[65]
<i>Micrurus averyi</i>	7	F	Foot	AM	Sub-family Elapidae Intense local pain, paresthesia, edema, erythema, nausea and drooling	Discharged	[89]
<i>Micrurus corallinus</i>	1	M	Finger	RS	Acute myasthenia, ptosis, salivation and muscular weakness	?	[36]
<i>Micrurus corallinus</i>	2	M	Forearm	SP	?	?	[60]
<i>Micrurus corallinus</i>	4	M	Finger	SP	?	?	[60]
<i>Micrurus corallinus</i>	6	M	Foot	SP	?	?	[60]
<i>Micrurus corallinus</i>	11	M	Hand	SP	?	?	[60]
<i>Micrurus frontalis</i>	9	M	Finger	SP	?	?	[60]
<i>Bothrops</i> spp. (73 cases)	–	–	–	SP	Sub-family Viperidae Edema, pain, ecchymosis, blisters, necrosis, local and/or systemic bleeding, local infection, compartment syndrome, gangrene and acute renal failure	Two fibular nerve palsy and one amputation	[90]
<i>Bothrops atrox</i>	10	M	Arm	AC	?	?	[34]
<i>Bothrops bilineatus</i>	13	M	Chest	AC	?	?	[39]
<i>Bothrops</i> sp.	13	M	Foot	AC	?	?	[39]
<i>Bothrops</i> sp.	14	M	Foot	AC	?	?	[39]
<i>Bothrops jararaca</i>	13	M	Leg	SP	?	?	[34]

(continued)

Table 1. (continued)

Snake	Age	Gender	Location of bite	State	Symptoms	Outcome	Reference
<i>Bothrops jararaca</i> (11 cases)	–	–	–	SP	?	?	[90]
<i>Bothrops jararacuçu</i>	3	F	Thigh	SP	?		[34]
<i>Bothrops jararacuçu</i>	11	M	Foot	SP	?	?	[34]
<i>Bothrops marajoensis</i>	10	M	Foot	PA	Local pain edema, ecchymosis, blisters, somnia, and hematuria and a comatose state	Sequelae, right side flaccid hemiplegia	[42]
<i>Bothrops marajoensis</i>	15	M	Leg	PA	Intense local pain, edema, ecchymosis, local bleeding, nausea, vomiting, epigastralgia and altered urine color	Discharged	[35]
<i>Bothrops moojeni</i>	5	F	Eye	MG	Gross facial swelling, bilateral periorbital ecchymosis, exophthalmus and local bleeding	Eye enucleation	[31]
<i>Bothrops neuwiedi</i>	–	–	–	SP	?	?	[90]
<i>Crotalus durissus</i> (31 cases)	1–14	25 M/6 F	Feet 12, legs 9 and ankles 7	SP	Palpebral ptosis, myalgia, weakness, slight edema and erythema	?	[52]
<i>Crotalus durissus</i>	12	M	?	SP	?	?	[34]
<i>Crotalus durissus</i>	13	M	?	SP	?	?	[34]

?, unknown information.

symptoms (swelling and pain) and coagulopathies [67, 68]. Also, envenoming from the Brazilian *Crotalus* genus has mostly systemic myotoxic and pre-synaptic neurotoxic action, with mild local symptoms. On the other hand, the Elapidae family-derived venom presents neurotoxins that affect the neuromuscular junction causing acute neuromuscular weakness with respiratory involvement [69]. Since the severity classification depends on medical assessment and snake identification, the clinical management depends on health professional's ability to recognize them.

Differences between adults and children

The global burden of snakebite disproportionately affects low-income children and often leads to significant permanent physical and psychological sequelae [16, 17, 20, 26, 70, 71]. Although long-term sequelae in a child's life are relevant, few studies describe the type of sequelae, details of causes, and frequency [71]. Bites to the hands or feet cause more disabilities in children than adults due to local tissue necrosis associated with compartment syndrome [72]. Edema causes blood vessel compression preventing extremity vascularization (compartment syndrome), exacerbated by vascular lesions caused by hemorrhages, inadequate treatments (e.g. tourniquets, which are commonly used in Brazil) or severe anemia caused by bleeding [71]. Amputation or loss of limb in children after snakebite is commonly caused by suspected compartment syndrome [73]. Capillary occlusion can occur at a pressure lower than that of the axial artery, so the diagnosis requires monitoring of intra-tissue pressure [74]. The interruption of the micro-circulation in children causes a drop in blood pressure that can sometimes occur with compartment pressure thresholds higher than those observed in adults [75].

Lethality

Brazilian MoH data from 2007 to 2020 show that lethality and clotting abnormalities are similar between adults and children, except for children under 3 years old, for whom lethality rates are higher and unclottable blood is more usual. Other studies also show higher lethality rates in children and the elderly than adults [55].

Risk factors for severity

Severity and antivenom underdosing are more frequent in children over 7 and 11 years, respectively; however, it is less prevalent between 12 and 14 years. Local complications prevail among children of all ages, and delayed medical care is more frequent in children aged 4–14. Systemic bleeding is relevant in children between 8 and 11 years old but is significantly less frequent in children

under three years old. Acute kidney injury is considerably less frequent in children (Figure 2 and Table 2).

In Brazil, surveillance data from 2007 to 2020 show that living in rural areas (OR 1.56, $p < 0.001$), unclottable blood (OR 3.72, $p < 0.001$), antivenom underdosing (OR 5.61, $p < 0.001$) and time to care > 3 h (OR 1.61, $p < 0.001$) are considered risk factors for children envenoming severity following *Bothrops* accidents (Table 2). Nonetheless, the age group 12 to 14 years old presented a lower risk for severity compared to ≤ 3 -year-old children. Living in rural areas, which is probably a proxy for insufficient access to the health system and antivenom unavailability, is considered a risk factor for snakebite severity. In addition, younger ages and male sex are risk factors for severity and more adverse outcomes. It is believed that young men are more prone to try to catch, kill or otherwise interfere with snakes while exploring the environments, which poses greater exposure to various snakes [76].

The time between the bite and medical care is a well-known risk factor for complications and fatalities. In Brazil, delays in medical assistance greater than 6 h after envenoming are frequent. Child mortality was approximately 3-times higher regardless of that time and the snake genera [27]. According to a study in Australia, 20% of children treated with antivenom with a confirmed SBE have not seen the snake [77].

Sequelae in children

In Brazil, there is a massive shortage of data regarding the disabilities in children caused by SBEs, mainly because the mandatory Notifiable Diseases Information System (SINAN) notification is filled out during hospitalization, and some sequelae can appear later. Of the few articles reporting SBE involving children in Brazil (Table 1), the main outcomes and sequelae were peroneal nerve palsy, amputation, flaccid hemiplegia and eye enucleation. A study in Costa Rica documented these sequelae in children who had suffered snakebites deforming scars, skin grafts, limited functional mobility, affected limb and amputation [21]. In India, long-term complications and sequelae in children related to hemotoxic snakebite include amputations and limb deformities, hypopituitarism, osteomyelitis, squamous cell carcinoma in non-healing ulcer sites, sequelae of acute coronary syndromes, such as left ventricular dysfunction and stroke sequelae, such as limb weakness or cognitive impairment [78].

Disabilities, ranging from hypertrophic scars to amputations, translate into long-term transient or permanent disability [73]. In children, the physical and psychosocial implications are difficult to define, but

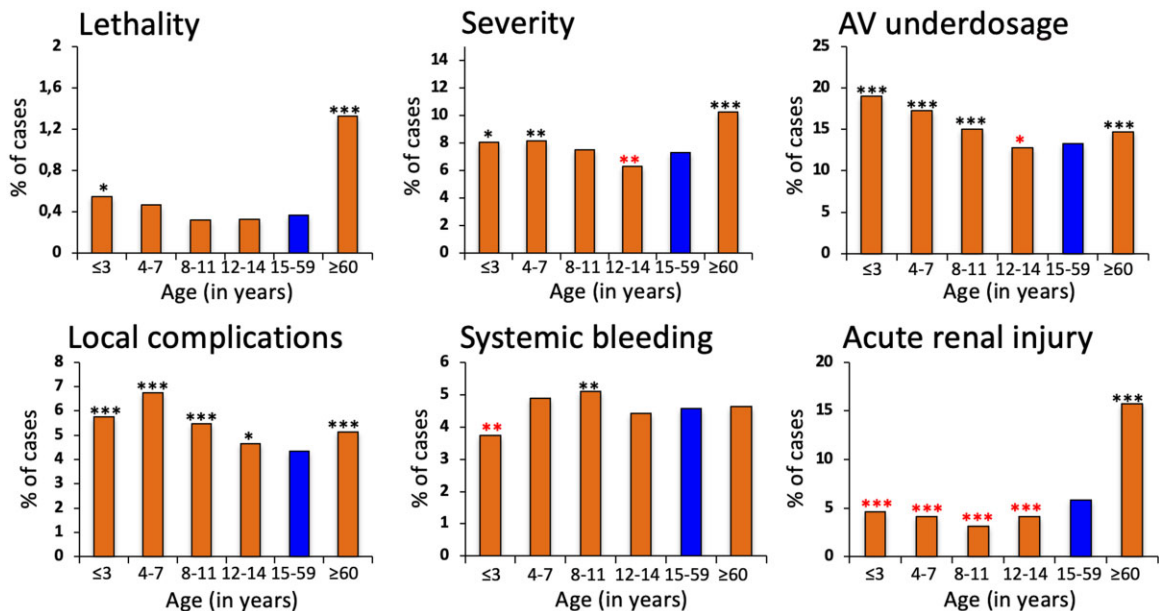


Figure 2. Distinct clinical aspects compared between children (under 14 years old), adults (between 15 and 59 years old) and the elderly (over 60 years old) in Brazil from 2007 to 2020. Comparison of outcome rates between age groups was made using Chi-square test, corrected by Fisher's exact test if necessary. Group of adults (15–59 years old, in blue) was the reference for comparisons. Statistical significance was considered if $p < 0.05$ in statistical tests. The analysis was performed using STATA software (StataCorp. 2013: Release 13. College Station, TX, USA). Red asterisks indicate that the group had a significantly lower frequency than the reference group. Black asterisks indicate that the group had a significantly higher frequency than the reference group. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

children who develop sequelae, as well as their families, undergo suffering and limitations, not only physical but also psychological. Children have reported that SBE impacts community, social and civic life, self-care, education, activities of daily living and their ability to communicate [79]. In addition, the costs of monitoring and the consequences of envenoming are high, both for health services and for the injured person [71, 80]. When it comes to children, it is necessary to consider the economic and educational impacts. SBEs with severe sequelae, such as amputations, cause the individual's impairments, preventing work and school activities. This seems to have a more significant impact on children than adults, given their longer life expectancy.

THERAPY

The World Health Organization (WHO) recommends the same protocol for adults and children under the same circumstances, although the amount of inoculated venom is not proportionally equal [81]. In Brazil, no specific guideline is available for snakebite envenoming in children.

Mainly in the Amazon rural areas, incisions, suction, tourniquets and other traditional therapies are typical, which can delay adequate clinical management and worsen the case, especially in children. Thus, it is essential to alert and educate the population about the risks associated with these practices. In addition, parents must be able to recognize the snake by bringing part of it or a photograph to the hospital to help the medical staff provide the appropriate management [69].

During the transfer to the health unit, the child must be kept calm and comfortable to reduce the hyperdynamic response that can accelerate the spread of the venom [82]. According to Parker-Cote and Meggs [82], immobilization of the bitten body part can lessen the lymphatic absorption of the venom. However, the clinical management is based on symptomatic medication, immunotherapy and adjuvant surgery. Symptomatic drugs include a range of analgesics, anti-inflammatory and antibiotics. Although the use of antibiotics is controversial, broad-spectrum antibiotics may be recommended for bacterial infections [83].

Antivenom serum is the specific treatment to reverse or prevent the effects of SBEs, being highly effective if administered promptly [82]. Essafti, *et al.* [84]

Table 2. Factors associated with 42 257 *Bothrops* envenoming affecting children in Brazil, from 2007 to 2021, according to the epidemiological surveillance database

Variable (completeness)	Total (%)	OR (95% CI)	<i>p</i>	aOR (95% CI)	<i>p</i>
Age (years) (100%)					
≤3	6034 (14.3)	1		1	
4–7	8295 (19.6)	1.01 (0.89–1.14)	0.828
8–11	13 720 (32.5)	0.93 (0.83–1.04)	0.189	0.90 (0.71–1.14)	0.393
12–14	14 208 (33.6)	0.77 (0.68–0.86)	<0.001	0.71 (0.56–0.92)	0.008
Gender (99.9%)					
Male	29 198 (69.1)	1		1	
Female	13 051 (30.9)	0.89 (0.82–0.97)	0.007	0.90 (0.75–1.06)	0.207
Area of occurrence (98.1%)					
Urban	6453 (15.6)	1		1	
Rural	35 001 (84.4)	1.56 (1.38–1.75)	<0.001	1.31 (1.03–1.67)	0.030
Ethnicity (93.2%)					
White	8305	1		1	
Black	2735	0.71 (0.60–0.84)	<0.001	1.06 (0.75–1.51)	0.730
Asian	371	0.88 (0.60–1.29)	0.505
Brown	24 943	0.67 (0.61–0.73)	<0.001	1.03 (0.83–1.29)	0.766
Amerindian	3015	1.11 (0.96–1.28)	0.140	1.27 (0.91–1.77)	0.158
Site of the bite (99%)					
Lower limbs	36 047	1		1	
Upper limbs and trunk	5796	1.38 (1.25–1.52)	<0.001	1.16 (0.93–1.43)	0.167
Blood clottability (49.4%)					
Clottable blood	12 422	1		1	
Uncloable blood	8467	3.71 (3.35–4.11)	<0.001	2.17(1.84–2.56)	<0.001
Antivenom dosage ^a (99.9%)					
Correct dosage	35 792	1		1	
Underdosage	6458	5.61 (5.20–6.06)	<0.001	2.24 (2.16–2.32)	<0.001
Time to care (94.6%)					
<3 h	25 388	1		1	
>3 h	14 590	1.61 (1.49–1.73)	<0.001	1.56 (1.32–1.84)	<0.001

Proportions of severe cases and deaths were compared using a Chi-square test (corrected by Fisher's test if necessary); differences were considered statistically significant for $p < 0.05$. The crude odds ratio (OR) with its respective 95% confidence interval (95% CI) was determined considering severity as the dependent variable. Logistic regression was used for the multivariable analyses and the adjusted OR with 95% CI was also calculated. All variables associated with the outcomes at a significance level of $p < 0.20$ in the univariate analysis were included in the multivariate analysis. Statistical significance was considered if $p < 0.05$.

aOR, adjusted odds ratio.

Bold values indicate significant differences.

^a According to the recommendations of the Brazilian MoH.

demonstrated the benefit of antivenom therapy in children, decreasing the need for blood transfusion, fasciotomy and length of stay at ICU. Mortality and systemic complications were lower with specific immunotherapy but were not statistically significant due to the small sample size.

Antivenom should be administered intravenously by infusion or slow intravenous impulse. For intravenous infusion, pediatric burettes of 100 ml normal saline infusion bags are useful for dose dilution and volume-controlled administration in the absence of mechanical infusion pumps. If clinical manifestations do not resolve after antivenom infusion, a second dose should be considered [83]. However, acute allergic reactions are associated with antivenom occurring in 2–50% of cases

depending on the type of antivenom and dose. Acute hypersensitivity reactions to Crotalidae Polyvalent Immune Fab (CPIF) are rare with the use of CPIF in pediatric patients. Two studies showed a prevalence of 7 and 19% of acute hypersensitivity reactions [85]. The frequency of hypersensitivity reaction in adults and children to antivenoms produced in Brazil is not known.

The treatment of early reactions in children includes interrupting antivenom (AV) infusion and administration of an initial dose of 0.01 mg/kg of epinephrine via the intramuscular route. In addition, hydrocortisone, at a dose of 4 mg/kg every 6 h, and promethazine are often used following epinephrine. To treat late reactions, oral antihistamine for 5 days, or a corticosteroid, such as prednisone, at a dose of 1 mg/kg per day for 5–7 days

are recommended [69]. Thus, clinical trials are needed to better understand the appropriate treatment for children, due to their particularities.

THE LONG WAY FORWARD

As a medical emergency, SBEs require a quick response, with treatment using antivenoms within the first 6 h after the bite [11, 86]. However, for populations living in rural areas of Brazil, especially in the Amazon region, access to health centers and the antivenom can take days, with consequent complications and increased morbidity and lethality. In addition to the poor availability of antivenom, patients' families may opt to search for traditional healers for first aid and treatment [37]. Traditional measures to deal with SBE include local incision(s), herbal medicine(s), tourniquet and suction application to the bite site; all of which are ineffective and can be harmful, leading to tendon, nerve or vascular injury, tissue necrosis, bleeding or infection. In addition, such measures can further delay access to antivenoms, thus resulting in increased severity and amputations, which can be more significant in children, and even death [14].

In Brazil, Butantan Institute is one of the institutions that manufactures antivenoms used to treat SBEs. The Institute has been recently modernized and currently produces five different antivenoms. However, there is still great difficulty in getting the antivenom for places far from the large cities, where most SBEs happen. In addition, antivenom preservation demands refrigerated storage, requiring electrical energy, which is not always available in rural healthcare units. Health professionals must be trained to diagnose SBE correctly, prescribe the proper type and amount of antivenom, and monitor adverse reactions. Considering the difficulties for patients to access the treatment, the antivenom supply system must be decentralized to reach the people who need it [87], which poses one of the biggest challenges in Brazil for managing and treating snakebites.

Prevention of SBEs is better than treating once a patient is envenomed. Therefore, SBEs must be avoided. Childhood is a period of life when knowledge and skills are learned, and the social context in which children are living can determine knowledge transmission and acquisition [1, 2]; thus, there is a need to educate children not to approach snakes and not to put their hands in holes or nests where snakes could be. Additionally, children must be taught preventive measures such as shoe use and the need to use lights in dark environments and at work. Although these are important

recommendations, it is worth noting that they are not always in line with the socio-economic reality of some communities, as well as their cultural context. Therefore, recommendations for managing snakebites, including pediatric cases, must consider socio-economic, demographic, and cultural aspects. As a strategy for snakebite prevention and control, the WHO has used community involvement in the development of solutions for SBEs as well as ensure that programs instill community empowerment [14, 76, 81].

In rural and riverine communities, hunting and food gathering skills are essential for survivorship, especially for the poor. Children and adolescents constitute a necessary workforce within the family context of riverine populations that economically depend on the extraction of piassava (*Attalea funifera*). Therefore, these children are constantly exposed to a higher risk for malaria, leishmaniasis and SBEs [4, 71]. Child labor in Brazil is a harmful reality far from eradication, and such work activities generally occur in rural areas, the leading site of SBEs. Thus, it is necessary to combat this practice in addition to promoting personal protective equipment use, which is sometimes less frequently used by children.

In addition to socioeconomic issues, another critical point is the geographic distribution of physicians in Brazil. In November 2020, Brazil reached the historic milestone of having 500 000 physicians, thus representing a ratio of 2.4 physicians per 1000 inhabitants. However, the inequalities in the distribution of those professionals persist and are evident. As seen in Figure 1, the number of pediatricians and ICU beds in the northern region is lower, although the number of children and SBEs is much more significant. Thus, more equity of health professional's distribution in different regions is necessary. Pediatricians are essential in the Amazon region, especially for managing snakebites in children [88].

CONCLUSIONS

SBEs in children tend to have higher severity and complications due to the small body mass and same venom volume inoculated in comparison to adults. In Brazil, well-identified risk factors for severity of envenomation include envenoming caused by pit vipers (e.g. *Bothrops* spp.), living in rural areas, bites occurring in upper limbs and trunk, having unclottable blood, receiving less than the required amount of antivenom and being more than 3 h away from health system facilities. Since they cause significant lethality, morbidity, and physical and psychological sequelae, SBEs have drastic economic and social

impacts and further foster the vicious cycle of poverty and disease, especially in children affected at the very beginning of their lives.

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