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New insights into snakebite epidemiology in Costa Rica: A retrospective evaluation of medical records

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A R T I C L E I N F O

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A B S T R A C T

Continuous monitoring of the snakebite envenoming allows elucidating factors that affect its incidence at spatial and temporal scales, and is a great tool to evaluate the proper management of snakebite in health centers. To determine if there have been changes over time in snakebite epidemiology in Costa Rica, we conducted a retrospective study using medical records from six hospitals for the years 2012–2013. A total of 475 snakebite patients were treated at the selected hospital during this period. Most bites occurred during the rainy season and primarily affected young men, mainly farm workers and schoolchildren. About 55% of bites occur in peri-domiciliary environments, although its prevalence varies geographically. *Bothrops asper* generates the vast majority of envenoming in the country, which is why the main local symptoms registered are edema, pain, and bleeding disorders. The time elapsed until treatment did not explain the degree of severity at admission. However, complications were observed more frequently in patients who took longer to receive treatment. The primary complications were bacterial infections, whereas kidney failure and compartment syndrome documented at very low frequencies. Only one death was recorded, reflecting the low fatality rate exhibited in the country. Hospital treatment included the rapid administration of antivenom and complementary treatment of antibiotics, analgesics, and antihistamines. The application of the latter as prophylactic does not seem to prevent the appearance of mild early adverse reactions, registered in 22.5% of the cases. Morbidity and mortality rates from snakebite have continued to decrease in the country, as a result of the efforts that Costa Rica has made to improve its public health system. Among those efforts, the creation of primary care centers (EBAIS) has reduced the time to treatment in many regions of the country. The Costa Rican experience of using antivenom in primary health care centers and maintaining good medical records could be considered for application in other countries where snakebite is a major health problem.

1. Introduction

Snakebite envenoming is a relevant public health problem that affects around 2 million people worldwide, resulting in more than 100,000 deaths and close to 400,000 permanent disabilities per year (Kasturiratne et al., 2008; Harrison et al., 2009; Chippaux, 2011). Despite its significant impact, snakebite was long ignored by the global and regional health policies even in the most affected regions (Chippaux, 1998; Gutiérrez et al., 2006, 2010; Warrell, 2010). It was not until 2017 that the World Health Organization (WHO) added snakebite envenoming to its list of category A Neglected Tropical Diseases (World Health Organization, 2019; Williams et al., 2019), urging a comprehensive strategy to reduce global mortality and disability from snakebite envenoming (Gutiérrez et al., 2017; World Health Organization, 2019).

An essential aspect of WHO's comprehensive snakebite approach is epidemiological monitoring, which enables crucial information to promote knowledge-based public health decisions and campaigns (Harrison and Gutiérrez, 2016). In addition to the valuable knowledge on the incidence of snakebite and the factors that could affect it, epidemiological studies provide relevant information on clinical manifestations and complications, so they could be used to evaluate the appropriate use of antivenoms and auxiliary therapies in the clinic, and to allow

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adjustments in treatment protocols.

Widely used procedures in snakebite epidemiological monitoring include: prospective studies (Kularatne, 2003; Spiller and Bosse, 2003), community-based surveys (Rahman et al., 2010; Mohapatra et al., 2011), analysis of statistical reports from health government agencies (Kasturiratne et al., 2008), and retrospective studies of the medical records from health centers (Kalantri et al., 2006; Eslamian et al., 2016). Each of these approaches has its advantages and disadvantages, and often combining several of them provides a complete picture of the situation and the determinants of snakebite in a region.

In Costa Rica, a country with a long tradition of fighting snakebite through research, the production of antivenom, and improvements in the clinical management of those affected (Gutiérrez and Rojas, 1999), retrospective studies carried out periodically provide the baseline information for epidemiological surveillance of snakebite (Alfaro-Brianso and Boza-Mora, 1983; Montalván et al., 1983; Saborío et al., 1998; Arroyo et al., 1999). Overall, about 500 cases of snakebites are recorded in health centers in Costa Rica each year (Sasa and Vázquez, 2003). The incidence of snakebite affects impoverished communities and fluctuates with regard to climatic phenomena (Chaves et al., 2015). The relatively high incidence is explained in part by Costa Rica's tremendous biological diversity, which includes more than 140 species of snakes, 24 of them being medically important (Solórzano, 2004). Among the latter, the terciopelo *Bothrops asper* is the cause of the vast majority of accidents in Costa Rica and Middle America. This species adapts well to environments with a certain degree of human disturbance (Sasa et al., 2009). Recent research has shown that the distribution and relative abundance of *B. asper* are good predictors of the overall incidence of snakebites in the country (Bravo-Vega et al., 2019). Therefore, it is not surprising that prominent local tissue damage (edema, blisters, bleeding, and necrosis) and systemic effects (hemorrhage, coagulopathy, cardiovascular shock, and acute renal failure) in more severe cases are part of the repertoire of signs and symptoms that are generally manifested. Meanwhile, less than 2% of accidents involved coral snakes (genus *Micrurus*) and the neurotoxic symptoms that result from their bites (Arroyo et al., 1999). Despite all these effects, a substantial reduction in mortality rate occurred in the last fifty years in the country: decreasing from 4.8 to less than 0.2/10, 000 people (Rojas et al., 1997; Fernández and Gutiérrez, 2008).

Snakebite treatment in Costa Rica involves two equine antivenoms: polyvalent antivenom (effective against all pitviper species in the region) and anticoral (effective against Micrurus clarki, *M. nigrocinctus* and M. mosquitens, Lomonte et al., 2016s), both manufactured by Instituto Clodomiro Picado at Universidad de Costa Rica (Gutiérrez, 2010). Additional treatment is often provided, especially antibiotics, analgesics, and antihistamines (Avila-Agüero et al., 2001).

Although the general epidemiological profile in this country is known, there are still challenges to our understanding of snakebite in Costa Rica. These include the need to assess the circumstances in which snakebites occur; to evaluate the clinical manifestations of the accident by lesser-known venomous species in the region and how the antivenom neutralizes them; and whether the clinical use of antivenoms is adequate in the country (Gutiérrez, 2014). In addition, the last review of medical records was made in 1996 (Arroyo et al., 1999), and there have been notable demographic and social changes in the country, in addition to growth in primary care in the Costa Rican public health system. These amendments require an updated assessment of the epidemiology of snakebite in the country. Here, we present a retrospective analysis of the medical records of six of the most important hospitals for snakebite in Costa Rica. Our goal is to portray the current situation in the incidence and treatment of snake bite envenoming, and to assess complications and adverse reactions during treatment.

2. Methods

2.1. Medical records

We reviewed the clinical records of snakebite patients admitted by to six regional hospitals in Costa Rica during the period from January 2012 to January 2014. We included the following hospitals (locality, Province): Fernando Escalante Pradilla (San Isidro de Pérez Zeledón, San José); Manuel Mora Valverde (Golfito, Puntarenas); Ciudad Neily (Ciudad Neily, Puntarenas); Guápiles (Guápiles, Limón), William Allen (Turrialba, Cartago), San Carlos (Ciudad Quesada, Alajuela) (Fig. 1). Criteria for inclusion of these health centers were: (1) account for the majority of snakebites registered in the country, based in Costa Rican public health system statistics; (2) location in wet lowland regions that overlap with the distribution of *Bothrops asper*, the species responsible for the majority of accidents in the region; (3) variation in size and services offered.

For each report, we retrieved the following variables: personal data of the patient (age, gender, occupation); circumstance of the accident (place, date, time, activity that was performed when the bite occurred); anatomical site of the bite; antivenom treatment (type and volume of antivenom administered, the time elapsed between bite and treatment, adverse reactions to antivenom); clinical and laboratory data; medical and/or surgical treatment (including information on a drug allergy history); and complications and possible sequelae.

The severity of envenoming was classified following Arroyo et al. (1999) as: (a) mild (local pain, discrete edema at the bite site, erythema but no bleeding; (b) moderate: pain, progressive edema at the bite site, local bleeding, alteration in coagulation tests; (c) severe: pain, edema covers a large part of the affected limb, local bleeding, necrosis, coagulation disorders, systemic bleeding, hypotension and other systemic disorders (cardiovascular shock, acute renal failure).

In addition to the information collected in the medical records, we obtained information on snakebite envenoming corresponding to the study period of the registry of the Statistics Department of the Caja Costarricense de Seguro Social (CCSS, Costa Rican Public Health System).

2.2. Statistical analysis

We employed descriptive statistics to document the main factors explored. Snakebites occur mainly in the upper or lower extremities (Arroyo et al., 1999), so we used logistic regression to evaluate factors that could potentially explain the differential incidence in both types of limbs. We assessed the following factors: month, circumstance during the bite, offending snake species, age, sex, and geographic location of the accident. We also used binary logistic regression to determine the odds ratios associated with risk factors related to early and late adverse reactions.

To evaluate factors that could predict the severity of envenoming, we used a multinomial ordinal logistic regression (OLR, Abreu et al., 2008). In this model, severity is a three-stage ordinal response variable. Distances between the stages are not consistent (i.e., the relationship is in term of mild $<$ moderate $<$ severe stage, but their differences are not numerically identical). The stage order shows the probability of a case falling into a particular category, and the event being modeled is having an outcome in a particular category or any previous category (Hedeker, 2003). In OLR, the regression coefficient β denotes that for a one-unit increase in the predictor variable (i.e., going from category 0 to category 1 if categorical, or a one-unit increase if a continuous variable) we expect a "β" increase in the ordered log odds of being in a higher level of the response variable, given all of the other variables in the model are held constant.

Since hospitalization time is recorded as counts of days, we used a negative binomial regression model (Ver Hoef and Boveng, 2007) to evaluate if the observed stay differs between hospitals and to assess

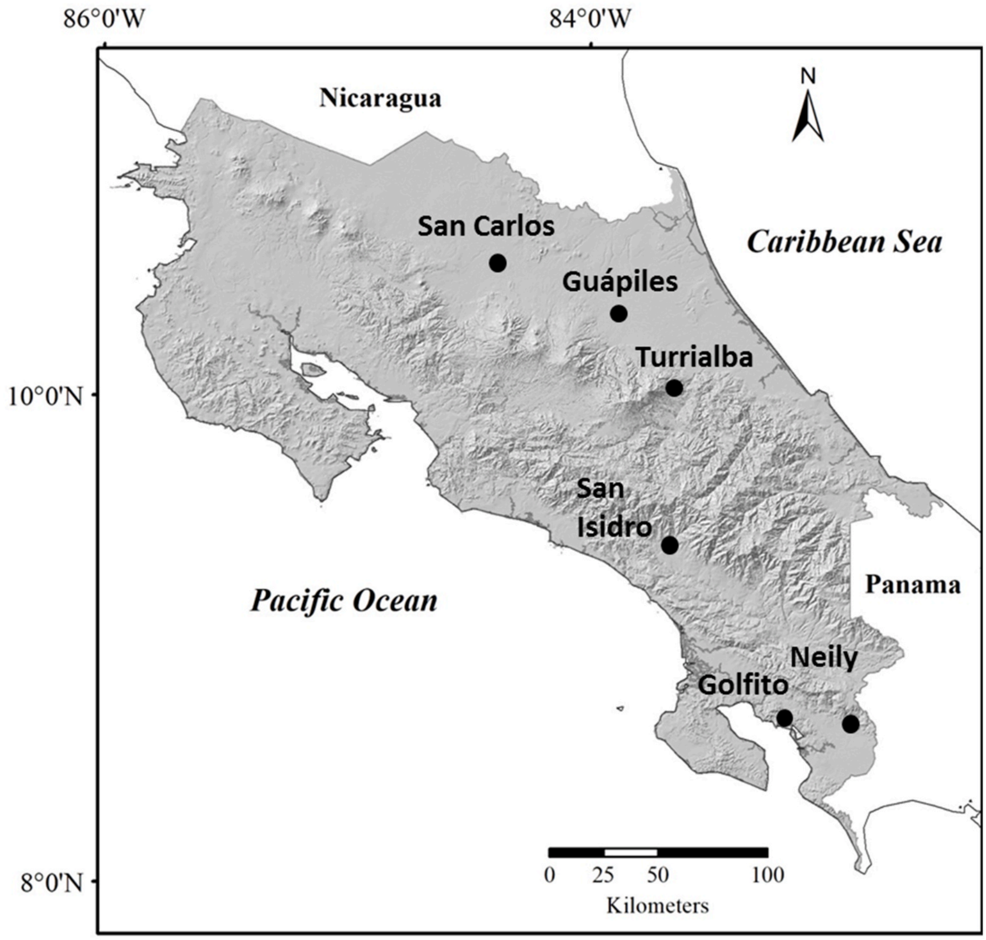

Fig. 1. Geographical locations of the six hospitals studied in Costa Rica.

whether it is affected by the degree of severity of envenoming. All analyzes were implemented in the statistical package SPSS 22 (IBM Corp, 2013).

3. Results

3.1. Snakebite epidemiology

A total of 475 snakebites were attended in the selected hospitals during the study period: San Isidro and Turrialba reported the highest incidence with 24% and 30% of the total number of cases, respectively (Fig. 2). Our sample represents 50% of the total number of snakebites reported for the entire country by the CCSS Statistics Department during the study period (annual mean ± sd = 473 ± 39.6 cases). The incidence rate for the country during the two studied years was 9.44 and 10.76 per 100,000 inhabitants per year.

There were small, but significant ($\chi^2 = 41.45$, df = 5, P < 0.005) differences between the number of medical records retrieved in our hospitals and the number of cases reported by CCSS for the same medical centers (Fig. 2). Most patients were admitted directly to the hospitals, although 38% of the patients received initial attention in primary care units (EBAIS, its Spanish acronym). The proportion of patients first attended in EBAIS differs among hospitals ($\chi^2 = 123.03$, df = 5, P < 0.001): from 12% (in Ciudad Neily) to 75% (in San Carlos). Of these patients, 74% received antivenom treatment at the primary care units, before admission to selected hospitals.

The risk of suffering snakebite in Costa Rica is more than double in men (70%) than in women (30%), and the incidence is higher in age groups under 30 years of age (Fig. 3). In general, the number of

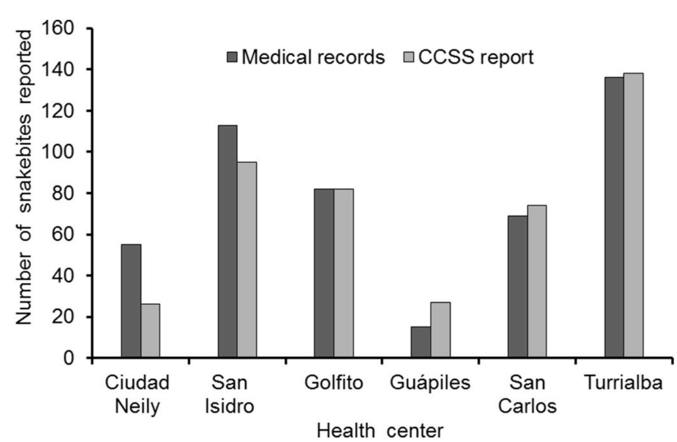

Fig. 2. The number of patients treated for snakebite from January 2012 to January 2014. Dark bars: number of cases according to the number of medical records reviewed. Light bars: numbers of cases reported for these medical centers in the statistics of the Costa Rican public health system (CCSS) during the study same period.

admissions for snakebite to selected hospitals remained constant in the two years of study ($\chi^2 = 14.43$, df = 14, P = 0.21), with a mean of 224 cases per year. However, the incidence of the snakebite differs between months ($\chi^2 = 30.93$, df = 11, P < 0.001), showing a peak between May–July and another in October–November (Fig. 4).

Almost 39% of the bites occurred in the upper limb, 58% in the lower

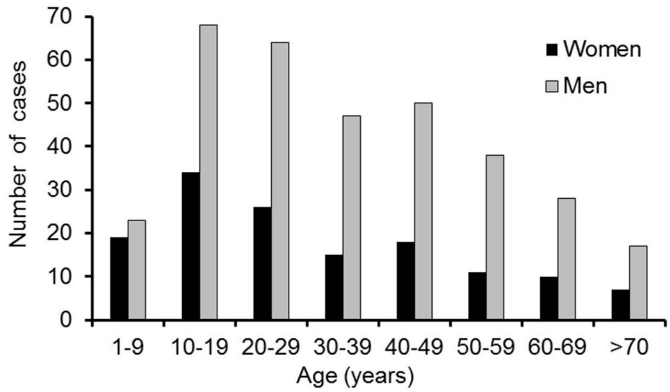

Fig. 3. Snakebite by gender and age group in six hospitals of Costa Rica. January 2012 to January 2014.

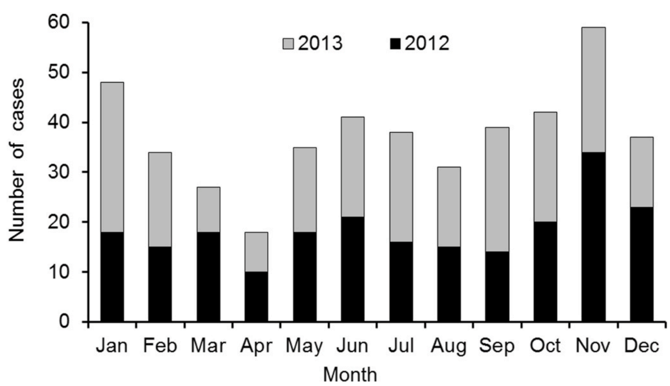

Fig. 4. The number of monthly cases admitted to six hospitals in Costa Rica during the study period.

limb, 0.5% in both limbs (bitten twice), and 3% in the trunk or head. Our logistic regression analysis supports that both: circumstance during bite ($T_{Wald} = 13.12$, df = 2, P = 0.01) and the offending snake species ($T_{Wald} = 15.96$, df = 4, P = 0.03) affect the anatomical site of the bite, but this variable is not affected by location, month, age, or gender of the patient, (P > 0.1 in all cases).

3.2. Species involved

The presumptive snake identity was reported in 295 of the cases. Based on the descriptions of the snake reported in the records, we identified *Bothrops asper* in 84.5% of the cases with available information. The public quickly identifies another pitviper, the green palm pitviper *Bothriechis lateralis*, for its intense emerald green color. This species is arboreal and inhabits mid-elevation regions: it was registered in 7.3% of the snakebites attended in Turrialba, which partly explains the high incidence of bites in upper extremities observed there (Fig. 5). A few cases (<8% from total) were attributed to other pitviper species (*Bothriechis schlegelii, Porthidium nasutum*, *Metlapilcoatlus mexicanus*) but since no descriptions were provided and their common names are not unique, it was not possible to elucidate their true identity. Of the total records, six cases (2.1%) were attributed to coral snakes (genus *Micrurus*), while in three reports it is mentioned that the bite resulted from non-venomous snakes (all attributed to *Boa imperator*).

3.3. Circumstances of the bite

From 215 records with available information on the location and circumstance when the accident occurred, 55% indicated that the snakebite took place in the domiciliary or peri-domiciliary environments (including houses, and public roads), and 40% recorded bites during activities in agricultural areas. Only 5% of bites occurred during recreational activities in wild environments (rivers or mountains). Snakebite circumstances vary in different regions of the country (Fig. 5). Thus, while in Turrialba and Ciudad Neily the highest frequency of bites occurs in agriculture sites (associated with coffee and African oil-palm plantations, respectively), in the rest of hospitals the proportion of bites in peri-domiciliary environments seems to be higher (Fig. 5). In the peri-domiciliary environments, feet and legs were bitten more frequently, while a relatively higher proportion of upper extremity bites was recorded during agricultural activities in Turrialba, San Isidro, and Ciudad Neily (Fig. 5). Even though these figures represent only 46% of the reviewed records, these results reveal that the risk of snakebite is also high in situations other than agriculture as has traditionally been visualized.

3.4. Envenoming severity and antivenom treatment

Pain and edema at the bite site were the most common clinical signs at admission, recorded in more than 80% of the cases. Alterations in blood coagulation (47.80%), gingival bleeding (6.42%), bleeding at the site of the bite (3.21%), and flictenae (2.40%), were also common. Less common manifestations included local necrosis (1.20%), and acute kidney injury (2.70%). Based on their symptoms, 33.4% of cases were classified as mild cases, 55.20% were considered moderate, and 11.4% were severe cases (Fig. 6).

The severity of the snakebite is not associated with the elapsed time until receiving medical attention, as retrieved from the OLR analysis: less than 1 h ($\beta = -0.538$, P = 0.38); between 1 and 3 h ($\beta = -0.552$, P = 0.36); more than 3 h ($\beta = -0.91$, P = 0.29), more than 5 h ($\beta < 0.01$, reference group) (Fig. 5). Nor is it related to the age of the patient ($\beta = -0.004$, P = 0.50) or with the anatomical site of the bite: upper limb ($\beta = -0.335$, P = 0.73), lower limb ($\beta = 0.186$, P = 0.04), trunk ($\beta = -0.442$, P = 0.18, reference group).

Seven patients presented no symptoms of envenoming and therefore did not receive treatment, presumably due to dry bites or bytes by non-venomous species. In four other cases, there were no clear local or systemic symptoms of envenoming, but patients were treated with polyvalent antivenom. The rest of the patients were treated with antivenom therapy: 98.5% of them received polyvalent antivenom, while 1.3% received anticoral antivenom. In one case, the patient was treated with both antivenoms; apparently it was a pitviper envenoming.

The dose of antivenom used varied between 5 and 35 ampoules (10 ml vials), although in most cases, 10 (52%) and 15 (24%) vials were used. The infusion of antivenoms was carried out diluted in physiological saline solution in all cases, with administration times ranging between 10 and 240 min. As expected, the volume of antivenom used increased with the level of envenoming severity (Spearman r = 0.43, P < 0.001) but was not related to the time of the treatment (P = 0.48).

3.5. Ancillary therapeutic interventions

Complementary treatment to antivenom therapy was evidenced in all cases, especially by the use of antibiotics, analgesics, and anti-inflammatory drugs (Fig. 7). However, the selection of drugs used in additional treatments was not homogeneous and seemed to follow specific protocols in some medical centers. This premise is supported by a principal component analysis (PCA) performed on the complementary treatment followed by each patient. The PCA allows determining if there is structure in the combination of drugs supplied by different hospitals considered here. The first two principal components explain 36% of the variance. Despite this low contribution, PC1 allows separating the treatment combination followed in Turrialba from that observed in the Golfito, Ciudad Neily, and San Isidro hospitals (Fig. 8). This component is related to the use of Clindamycin, Chlorpheniramine, Dexamethasone, Gentamicin, and Tramadol as a regular complementary treatment. PC2

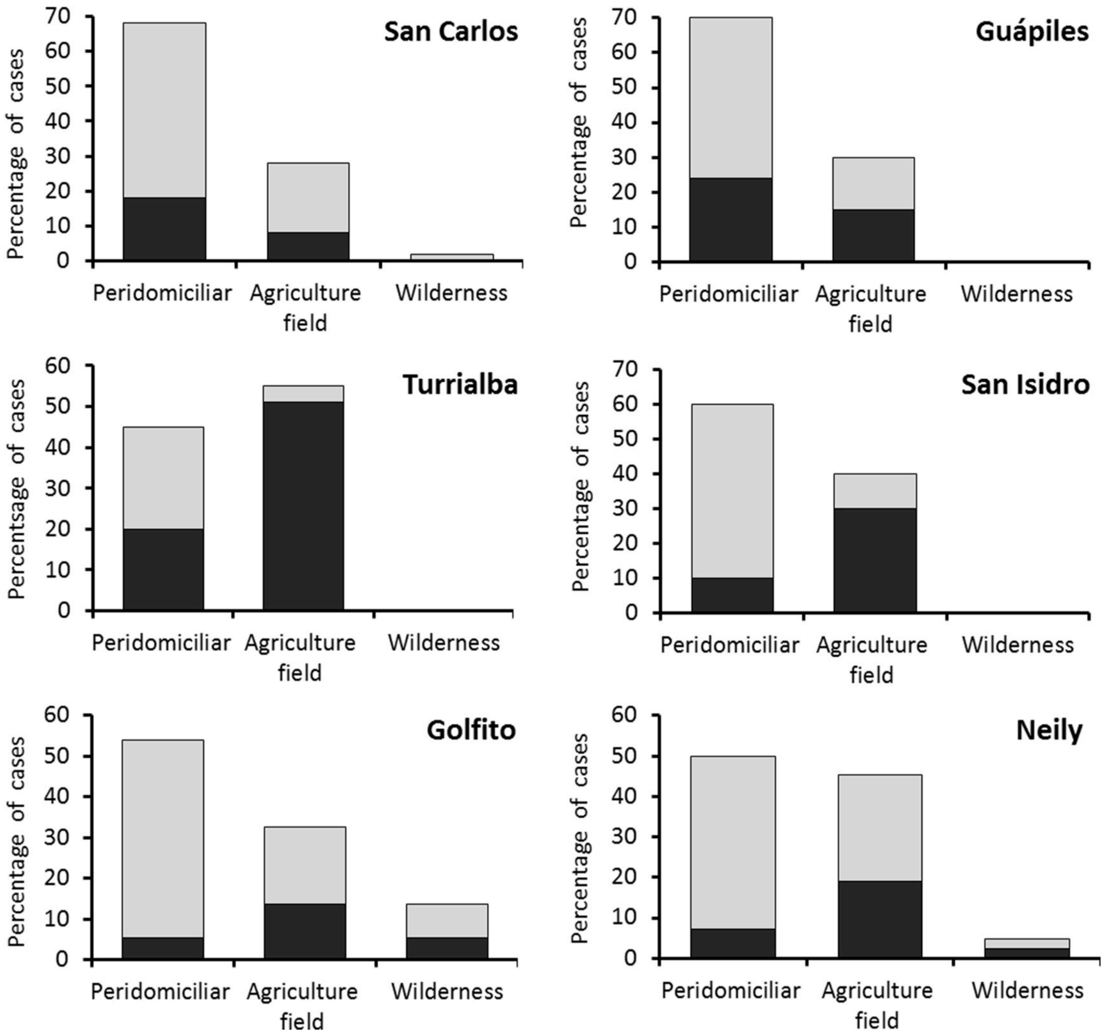

Fig. 5. Percentage of snakebite cases occurring in peri-domiciliary, agricultural, or wilderness environments registered in different hospitals in Costa Rica. The proportion of bites in the lower limbs (gray) and upper limbs (black) is shown.

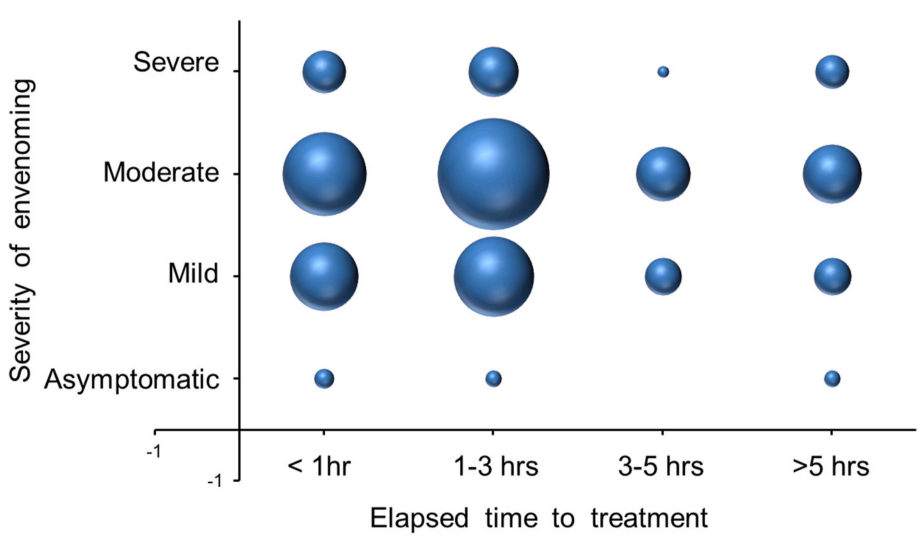

Fig. 6. Elapsed time to treatment and severity of snakebite. Sphere volume relates to the proportion of reviewed cases. The degree of severity is independent of the time to access treatment ($Chi^2 = 10.08$, df = 9, P = 0.344).

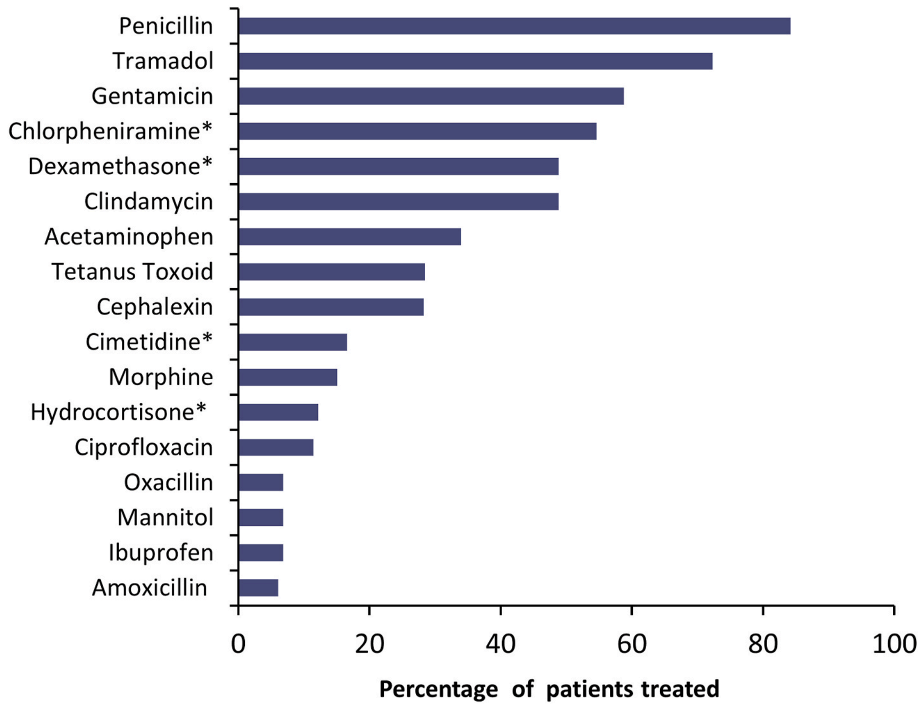

Fig. 7. Main drugs used in the complementary treatment of snakebite in studied Costa Rican hospitals. * Drugs administered as premedication.

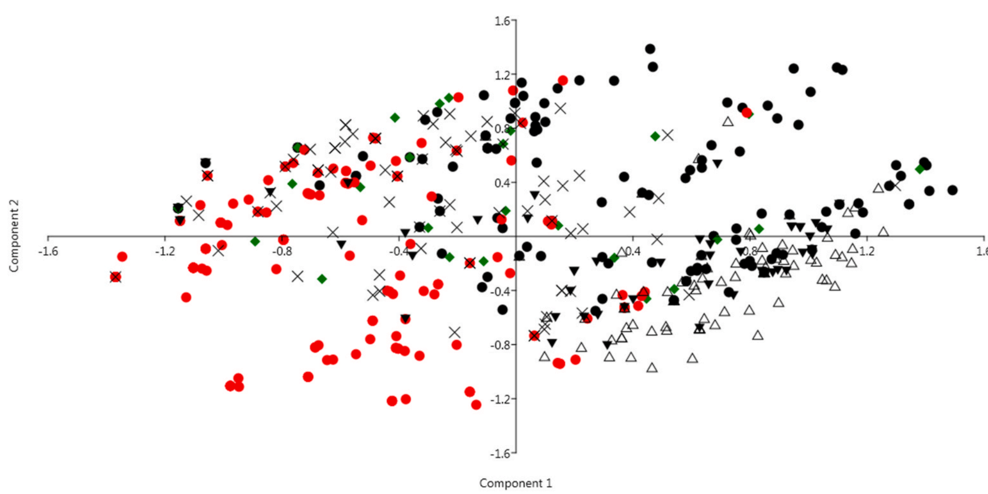

Fig. 8. Principal components of complementary treatment in patients admitted for snakebite envenoming to studied hospitals: San Isidro (black dot), Guápiles (Green diamond), Turrialba (red dot), Golfito (open triangle), Ciudad Neily (black inverted triangle), and San Carlos (Xs). See text for elaboration. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

mainly separates the treatments followed in Golfito and Ciudad Neily hospitals from that of San Carlos, and it is related to the use of Acetaminophen, Chlorpheniramine, Dexamethasone and tetanus toxoid (Fig. 8; factor loads >0.3 in all cases).

3.6. Clinical complications

Sixty-five patients (14%) experienced some complications during treatment, the most frequently derived from bacterial infections (Table 1). The percentage of cases that developed compartment syndrome, as well as disseminated intravascular coagulation, was low (<0.5% in both cases). Similarly, only 3.16% of the patients required surgical intervention (Table 1). Functional limitation of limb movement due to muscle retractions was the most recorded sequela. From the reviewed records, three pregnant women (>18 weeks) received antivenom treatment. Two of these cases were uneventful, and another developed cellulitis. A fourth pregnant woman (4 weeks) suffered loss of the fetus, but an anembryonic pregnancy was suspected. Lethality was low in our sample: only one patient died, a 22-year-old man bitten by a *B. asper* who was admitted to the San Isidro hospital where his situation got complicated with hypoxic encephalopathy, acute kidney injury, and required assisted mechanical ventilation.

3.7. Adverse reactions

Adverse reactions to antivenom treatment were reported as either early reactions or late reactions in 234 patients: 111 patients (22.5%) manifested early adverse reactions (EAR, within the first 24 h of treatment), whereas 160 (32.3%) developed late adverse reactions (LAR); the proportion of patients experiencing both types of reactions differ (χ^2

Table 1
Complications reported in snakebite patients from six hospitals in Costa Rica, from January 2012 to January 2014.

Complications	Total (%)
No complications	410 (86.0)
Bacterial infections (total)	33 (6.90)
Abscess	4 (0.84)
Cellulitis	29 (6.10)
Sepsis	1 (0.21)
Disseminated intravascular coagulation	2 (0.42)
Compartment syndrome	2 (0.42)
Fasciotomy	8 (1.68)
Surgical debridement	3 (0.63)
Amputations	4 (0.84)
Ulcers	3 (0.63)
Encephalopathy	2 (0.42)
Renal dysfunction	3 (0.63)
Sequelae	4 (0.84)
Abortion	1 (0.21)
Death	1 (0.21)

$_{\text{McNemar}} = 7.85$, $P = 0.05$). Thirty-seven patients (7.5%) experienced both early and late reactions.

Eighty-two percent EARs occurred within the first 3 h of antivenom administration. Mild EARs, characterized by cutaneous manifestations, i.e. urticarial and pruritus, were observed in 51 patients. Moderate EARs were recorded in 38 cases and included periorbital edema, dyspnea, and vomit. Severe reactions, including hypoxia and hypotension, were recorded in 22 patients with EARs. Twenty-five of these cases evolved from mild to severe EAR.

Late adverse reactions (LAR) were recorded in almost a third of all the studied cases (32.3%). The majority of them (>40%) developed urticaria and itching, but fever and ecchymosis were also recorded in a few cases. Elapsed time from antivenom treatment to LARs varied between 2 and 14 days (mean 7.01 days), but two records of serum sickness were reported after 42 and 55 days.

We evaluated the risk of developing adverse reactions for different factors, using binary logistic regression (Table 2). For early reactions, both the elapsed time to treatment above 3 h and the use of Chlorpherinamine showed significantly odd ratios (OR); while for late reactions, the number of vials of antivenom administered, and complementary treatments with Clindamycin, Cephalexin and Dexamethasone showed significant OR (Table 2).

3.8. Hospitalization time

Hospitalization time ranged from 1 to 42 days, with a median of 4 days. Almost a third of the patients were hospitalized for one or two days (Fig. 9), although about 9% of them were transferred to other hospitals, and thus we lost their follow-up.

The variance in hospitalization time (25.54) exceeds its mean (4.99), suggesting over dispersed data (Ver Hoef and Boveng, 2007). Thus, we use a negative binomial model to assess factors that influence the stay.

Table 2
Risk factors to adverse reactions to snakebite treatment.

Early adverse reactions			Late adverse reactions		
Risk factor	OR	*P*	Risk factor	OR	*P*
Elapsed time to treatment (3–5 h)	2.97	0.001	Dose of antivenom	1.07	0.003
			Clindamycin	1.89	0.005
Chlorpheniramine (Protection factor)	0.52	0.042	Cephalexin	0.56	0.016
			Dexametasone (Protection factor)	0.43	0.001
Factors with no effect: Age, Site of bite, Previous reactions, Type of antivenom, Dose, Other treatments	>0.05		Factors with no effect: Age, Site of bite, Early adverse reactions, Previous reactions to drugs, Type of antivenom, Other treatments	>0.05	

The median hospitalization time differs between the different medical centers studied, with the San Carlos, San Isidro, and Golfito hospitals showing longer stays (Table 3, $\chi^2_{\text{wald}} = 21.23$, df = 4, $P < 0.001$).

As we expected, the severity of the envenoming significantly affected the length of the hospital stay. ($\chi^2_{\text{wald}} = 50.30$, df = 2, $P < 0.001$). Mild cases required a shorter hospitalization time ($\bar{x} \pm \text{sd} = 2.27 \pm 1.77$). In contrast, moderate cases required twice as long (5.78 ± 3.64, $\chi^2_{\text{wald}} = 25.09$, df = 1, $P < 0.001$); while severe cases required four times more than mild cases ($\chi^2_{\text{wald}} = 43.03$, df = 1, $P < 0.001$) (Fig. 9).

4. Discussion

4.1. Snakebite epidemiology

Snakebite envenoming continues to be a relevant health problem in Costa Rica. Although we only included a portion of the country's hospitals in this analysis, we consider that our results reflect well the snakebite situation in Costa Rica. First, our data represents almost half of the snake bite cases recorded during the study period. Besides, three hospitals (Turrialba, Neily, and San Isidro) receive patients from both lowlands and highlands, exposed to different venomous snake communities. Finally, hospitals located in regions outside the *B. asper* distribution range (such as the dry region in the northwestern part of the country) received only 28 snakebite admissions, which represents less than 3% of total registrations during the study period (Department of Statistics, CCSS).

We found that several epidemiological traits, including the age and sex of the people affected, the geographic and chronological distribution of envenoming throughout the year, and the low lethality, are similar to those reported in a previous study for the year 1996 (Arroyo et al., 1999). As a dynamic disease, however, other attributes of snakebites in the country have changed, and deserve further examination.

During the study period, the total annual number of snake bites remained close to that reported in the previous decade, but the estimated incidence rate was lower than previous accounts, confirming the decreasing trend in the incidence of snakebite in Costa Rica (Sasa and Vázquez, 2003). The simplest explanation for this reduction is population growth in the last two decades, which exceeds 28% in both rural and urban areas of the country (INEC, https://www.inec.cr/poblacion/).

Our assessment confirms that *Bothrops asper* is responsible for the vast majority of snakebites in the country, although we acknowledge that the identification of the offending snake based on the description *a posteriori* is not always accurate. In regions where monovalent or bivalent antivenoms are used, knowing the identity of the biting snake is essential to provide adequate treatment; and various methodologies for identifying the offending snake have been implemented (Eng and Gopalakrishnakone, 2004; Hung et al., 2014; Dhananjaya et al., 2015; Sharma et al., 2016a, 2016b). In contrast, in the case of Costa Rica, the identity of the offending species is not so relevant for the choice of antivenom, since a clear difference in signs and symptoms exist between viperid species (where polyvalent antivenom is indicated) and elapid species (where coral antivenom is used), thus allowing the selection of the type of antivenom((Bolaños, 1982).

While it might not be necessary for treatment selection, the correct identification of the biting snake can provide insights about the course of the envenoming and the ecology of the snakebite, and could provide valuable information for its prevention (Ruíz de Castañeda et al., 2019). With the advent and popularity of cameras in mobile phones, it is now possible to photograph the biting snake, even in rural regions of tropical countries like Costa Rica. This procedure is being used in poison control centers in several countries (see review in Bolon et al., 2020). In Costa Rica, several informal groups already provide snake identification services on social networks, and in the coming years, this service is expected to be formalized at the clinical practice level. The use of these procedures in the clinic will allow us to determine more precisely the

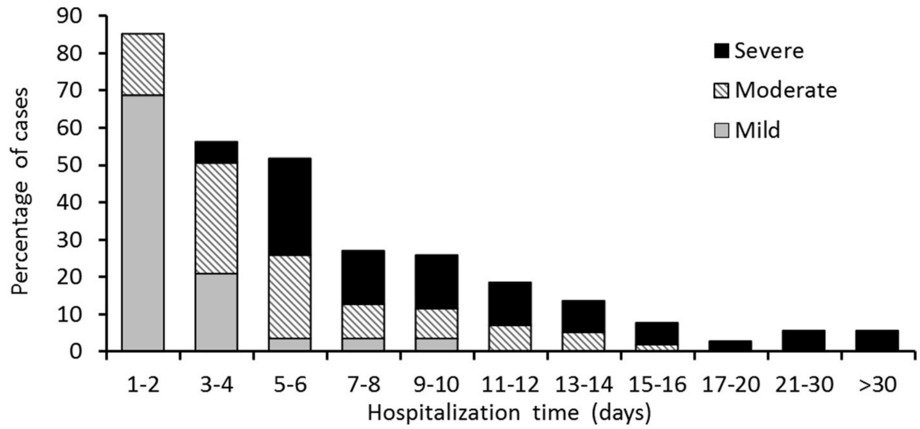

Fig. 9. Frequency distribution of hospitalization time due to snakebite envenoming. Proportion of mild, moderate, and severe envenoming cases are shown.

Table 3
Descriptive statistics of the distribution of hospitalization time for snakebite envenoming in Costa Rican hospitals.

Hospital	n	$\bar{x}$	σ^2	range	Percentiles		
					25	50	75
San Carlos	70	7.10	17.55	1–20	3.75	6.00	10.00
Guápiles	15	7.00	76.84	1–40	2.00	2.00	11.00
Turrialba	141	3.35	8.57	1–24	1.50	3.00	4.00
San Isidro	113	7.64	52.03	1–42	3.00	5.00	10.50
Ciudad Neily	55	2.52	5.36	1–14	1.00	2.00	4.00
Golfito	82	6.90	24.79	1–37	4.00	6.00	8.00

contribution of each species in the snakebite burden in the country.

The onset of the rainy season coincides with a higher frequency of accidents; a situation that parallels that reported in other tropical regions (Currie et al., 1991; Mustapha, 2003; González-Andrade and Chippaux, 2010). Although it is difficult to interpret the causes of this increase, it should be noted that this period coincides with the birth season of numerous snake species, including *Bothrops asper* (Sasa et al., 2009). Snake demography affects snakebite epidemiology, as has been observed for *Daboia russelli* in Myanmar were most envenoming cases resulted from snakes less than one-year-old, about 65% of them hatchlings (Tun-Pe et al., 1991). Although we do not have records of the size of the snake, several patients refer to small *B. asper* individuals, probably hatchlings, as responsible for the bites. Additionally, it is precisely at the beginning of the rainy seasons when the activities for agricultural production increase (land preparation, weeding, sowing; Boucher et al., 1983), which would suppose a greater exposure of people in the field. Recently, epidemiological compartmental models confirm that the incidence of snakebite depends on the relationship between the relative abundance of snakes and the human population (Bravo-Vega et al., 2019), so it is highly likely that the peaks observed at the beginning of the rainy season resulted from such interaction.

Worldwide, snakebite is considered an occupational hazard for farmers due to its high prevalence in this labor group and to the fact that it occurs mainly during daylight hours, when conducting agricultural work (Da Silva et al., 2003; Alirol et al., 2010; Habib and Abubakar, 2011; Gutiérrez, 2014). For Costa Rica, Arroyo et al. (1999) found that 47% of accidents recorded in 1996 occurred in farmers, whereas 27% involved children; most of them while doing agricultural work. In contrast, for the 2012–2013 period, our data shows 40% of accidents involving people doing agricultural work, while 55% of cases occurred in the domiciliary or peri-domiciliary settings. The latter figure includes 77% of cases in children. Although based on a fraction of the medical records, these statistics reveal changes in the pattern of the snakebite in the country, at least within some localities. The socioeconomic development promoted in districts with rural prevalence, largely associated with increased tourism activity in Costa Rica in the last two decades (Mok, 2005; Rojas-Alvarado, 2009), could explain the change in the proportion of cases in circumstances other than agricultural activity.

A large proportion of snakebites occurring in the immediate vicinity of housing or in activities other than agricultural work has been noticed in other tropical sites (Pandey et al., 2016; Rahman et al., 2010), affecting students and housewives (Alirol et al., 2010). In fact, numerous cases of neurotoxic envenoming caused by kraits (*Bungarus* spp.) in Southeastern Asia occur while the victims sleep on the floor in their homes (Mondal et al., 2012; Sharma et al., 2016a, 2016b), an example of the close relationship between some venomous snake species and anthropic environments. Not surprisingly, *B. asper* is one of the most frequent snake species encountered in environments close to human dwellings in Costa Rica (Sasa et al., 2009).

4.2. *Snakebite envenoming treatment*

Most envenoming cases were classified as mild or moderate according to their clinical features. Arroyo et al. (1999) suggested that the prevalence of mild and moderate cases result from an early attendance and treatment (<3 h from the bite), stressing that the early administration of antivenom prevents the escalation of local and systemic effects. In our analysis, more than three-quarters of the patients received treatment in less than 3 h; however, the severity of the envenoming was independent of the time elapsed between bite and treatment. In fact, the proportion of cases at each severity level is maintained, even in cases where the elapsed time exceeds 5 h. The unexpected absence of a positive relationship between the degree of severity and the time to treatment has also been reported in few other studies. In India, Shuchithra et al. (2008) found that the severity of snakebite at the local level was higher in patients who received early treatment (<6 h) than in those who took longer to receive it, although the most severe complications occurred in patients admitted later. The degree of snakebite severity is also mediated by other factors, including the amount of venom that is injected, the route and anatomical site of injection, and the physiological and anatomical characteristics of the victim (Gutiérrez, 2010). For example, Faiz et al. (2017) found that the severity of neurotoxicity in the monocled cobra *Naja kauthia* envenomation is dependent on the amount of venom antigen in the circulation; a similar relation was observed in snakebites by *Bothrops lanceolatus* in Martinique (Bucher et al., 1997). In children, bites tend to be more complicated than in adults, presumably due to their lower body mass and the faster absorption (De Franco-Montalván et al., 1983). Therefore, some other factors, besides time to treatment, may better explain the severity observed in our records.

The main complications observed, i.e., those derived from bacterial infections, compartment syndrome, and renal alterations, coincide with envenoming involving pitvipers in other Neotropical regions (Otero-Patiño, 2009; Roriz et al., 2018). However, less than a sixth of the total number of patients experienced some type of complication, a relatively low proportion in relation to other studies in the area (De Franco-Montalván et al., 1983; López et al., 2008). Furthermore, we observed a significant decrease in the frequency of abscesses, necrosis, and cellulitis compared to the previous decade in the country (Saborío et al., 1998; Arroyo et al., 1999). Infections are largely the result of the inoculum of high bacterial and fungal loads present in the oral cavity, venom-delivery apparatus, and snake venom (Dehghani et al., 2016a,b). In addition to the bacteria coming from the snake, bacteria present in the skin or in the environment can enter the wound, thus aggravating the situation. Arroyo et al. (1980) and Bolaños and Brunker (1983) reported the presence of anaerobic bacteria (eight *Clostridium* species) as well as aerobic (genera *Aeromonas*, *Proteus*, *Escherichia*, *Providencia*, *Morganella*, *Klebsiella*, *Pseudomonas*, and *Micrococcus*) in the oral cavity and venom of several pitviper species of Costa Rica, including the *Bothrops asper*. Some of these same bacteria were isolated in cultures from snakebite patients from different parts of the country (Avila-Agüero et al., 2001).

Since the most frequent pathogens include known gram-positive and gram-negative bacteria, the practice in Costa Rican hospitals is to start antimicrobial therapy with clindamycin or penicillin plus some aminoglycoside. This pretreatment could explain the reduction in the frequency of abscesses and cellulitis observed in our analysis. On the other hand, resistance to antibiotics in bacteria found in infections of snakebite patients (López et al., 2008; Sachett et al., 2017) opens the debate on whether antibiotic treatment should be supplemented prophylactically, or whether instead, the infection should be confirmed first and antibiotic resistance testing requested in all cases before trying antibiotics (Tagwireyi et al., 2001; Wagener et al., 2017). The prophylactic use of antibiotics has been recommended in cases when (a) there is objective evidence of infection, or (b) there is marked local tissue damage, which greatly favors infection (Resiere et al., 2020).

Another complication inherent to antivenom treatment is the appearance of adverse reactions, early or late, to this product (Schaeffer et al., 2012). Incidence of early adverse reactions in our assessment was similar to those reported in other studies using antivenom from the same manufacturer (Abubakar et al., 2010; Otero et al., 1999). However, most EARs were mild, characterized mainly by cutaneous manifestations, i.e., rashes, redness, and itching. The occurrence of EARs is not related to a history of sensitivity to other medications, nor to differences in the initial dose delivered to the patient (Alirol et al., 2017). Instead, they are explained either by IgE-mediated reactions, or –more often– antivenom anticomplement activity and the presence of heterophilic antibodies (León et al., 2013; Stone et al., 2013).

Previous exposure to animal immunoglobulins is considered a potential risk factor for IgE-mediated reactions to antivenom proteins (León et al., 2013). However, 17 patients who had received antivenom for a previous snakebite did not show a statistically higher frequency of EARs ($\chi^2 = 1.04$, df $= 1$, $P = 0.309$), which leads us to conclude that IgE-mediated reactions may not explain the EARs recorded.

In all the health centers included in our study, the protocol includes pretreatment with antihistamines to prevent early reactions. This practice is not universally advised: several studies noted insufficient evidence that pretreatment with corticosteroids or antihistamines can reduce EARs (Bucaretchi et al., 1994; Fan et al., 1999; de Silva et al., 2011). In contrast, subcutaneous epinephrine administration seems to prevent the development of EAR (Premawardhena et al., 1999; Williams et al., 2007; Habib and Abubakar, 2011; de Silva et al., 2011) and is recommended in cases where the use of antivenom is associated with a high rate of allergic reactions and where resources to treat an eventual reaction are limited. Once the early reactions appear, slow infusion, or temporary suspension of antivenom, and an auxiliary treatment with a combination of antihistamines and corticosteroids are recommended (Warrell, 1999; Gutiérrez et al., 2006). Given its widespread use in the clinic as prophylaxis, and considering that current recommendations are based on limited evidence, the routine premedication with antihistamines and corticosteroids used in Costa Rican hospitals should be reconsidered.

On the other hand, serum sickness was recorded in one out of three cases in our analysis. Serum sickness is a type III hypersensitivity (Johansson et al., 2001) that occurs due to an IgG-based antibody response of the patient to horse proteins recognized as foreign. Although it is usually a mild condition, the incidence of serum sickness is poorly known, especially since patients do not return to medical centers or do not associate the manifestations with a reaction to antivenom treatment (Abubakar et al., 2010; Meregildo-Rodriguez et al., 2020). In our records, the mean elapsed time to the appearance of serum sickness was seven days, longer than the time in the hospital for many of the patients. Furthermore, LARs treatment is not always included in the patient's medical history. This situation may be resolved shortly with the application of a unique digital file in the Costa Rican health system (see below). LoVecchio et al. (2003) suggested that the incidence of late reactions increases with the amount of heterologous protein administered, so it is believed that the dosage of antivenom determines the probability of late adverse reaction. If so, the volume of antivenom delivered (usually more than 100 ml) possibly explains the high incidence of LARs in our study.

Only four of the reviewed cases involved pregnant women, one ending in abortion. Langley (2010) points to an overall rate of fetal mortality due to snakebite envenomation of around 20%, whereas maternal mortality can be as high as 5%. Although these figures included studies conducted at different sites, involving envenoming by different species, under different treatments and health systems, they highlight the idea that snakebite envenoming during pregnancy should be managed as a delicate condition.

The low lethality observed in our sample reflects the drastic reduction in the mortality rate in recent decades in Costa Rica (<0.1 per 100,000 persons per year, Fernández and Gutiérrez, 2008). The reduction in overall mortality has been attributed to: (1) the local production of effective antivenoms and their availability in medical centers; (2) the development of homogenous treatment protocols used in these centers; and (3) an improvement in the country's health systems that guarantee better access to medical care (Fernández and Gutiérrez, 2008).

Although the elapsed time to treatment did not explain the degree of severity on admission, time is an essential factor in reducing snakebite complications, as has been pointed out in several studies (Warrell, 1999). The complications were more frequently observed in patients who took longer to receive treatment: 20.4% of patients with complications lasted more than 5 h in receiving treatment. Our analysis suggests a marked reduction of time to treatment in the country. Between 1985 and 1995, 50% of children who suffered a snakebite in the Costa Rican Caribbean received medical treatment in 3 h, although the average time to receive care was 6.8 h (Saborío et al., 1998). Arroyo et al. (1999) conclude that approximately 61% of snakebite patients received treatment in 3 h or less, while approximately 20% of patients did so after more than 5 h of the bite. Hansson et al. (2013) used GIS geographic information systems and the CCSS bite records for the period 2003–2007 to estimate the time needed to reach the medical center. According to their assessment, about 92% of the population in high-risk areas required less than 2 h to access hospitals or clinics, whereas 2.5% would have transportation times greater than 3 h. These projections are somewhat optimistic: in our data, 77% of the patients received treatment less than 3 h after the bite, and about 22% of them took more than 3 h to receive it. The reason for these differences may be because Hansson et al. (2013) model is based on an analysis of the distances to medical centers and the possible speeds on different types of road, but do not take into account the delays caused by the idiosyncrasies of the accident (for example, time to seek help, get transportation, and transfer).

4.3. Snakebite management in the Costa Rican health system

The early care of snakebite in Costa Rica results from the advent of the basic teams of integrated health care (EBAIS), primary care centers established as part of a significant reform of the health sector started in the mid-nineties (Rosero-Bixby, 2004a). The more than 1014 EBAIS have managed to decentralize the large medical centers and provide primary health services in the least developed areas of the country, improving the equity for medical access and increasing life expectancy and other health indicators (Rosero-Bixby, 2004a). Based on a GIS spatial analysis, Rosero-Bixby (2004b) estimated that half of the Costa Rican population resides within a short distance of a primary care center (<1 km) or a hospital (<5 km). In contrast, about 10% of the population has inadequate or inequitable access to health services, according to several indicators. Our data support these estimates: almost 40% of patients received antivenom treatment at these primary care centers before reaching the focal hospitals, highlighting the efficacy of EBAIS in early emergency care. The Costa Rican experience of using antivenom in primary health care facilities could be considered for application in other settings.

Another important reason for the early treatment of patients is the trust that Costa Rican population has in their public health system, as indicated by the fact that empirical pre-hospital treatments based on traditional medicine or beliefs have been drastically reduced in the country. In the mid-1990s, about 3% of snakebite patients underwent empirical treatments before entering the medical center, mainly tourniquets, bite-site incisions, attempted suctioning of the venom, use of medicinal plants, and cold compresses (Arroyo et al., 1999). A single case recorded use of traditional medicine in our analysis. This situation differs markedly from other countries in tropical regions where pre-hospital empirical treatments are much more frequent (Alirol et al., 2010). Confidence in the public health system and refraining from empirical practices facilitate the rapid transportation of the affected person to a health facility.

Recorded hospitalization times for snakebite envenoming in Costa Rican hospitals were similar to those reported in other studies in the region (Bucher et al., 1997; Praba-Egge et al., 2003). However, the mean length of stay for our patients was slightly higher than previously reported for the country (Arroyo et al., 1999); and even higher than the overall mean length of stay (4.7 $\pm$ 7.64 days) reported for all conditions in Costa Rican hospitals during 2014 (Morera-Salas, 2016). This last author analyzed the length of stay for different treatments, and compared them with estimates of the expected stays, suggesting that hospitalization times in Costa Rica are longer than expected according to the caseloads attended, an issue that deserves further analyses.

The release of patients from a health center should be done when their well-being can be guaranteed, ensuring that their health, or the health of their family, is not compromised. However, delaying hospital stay is considered a vital management problem, since it may highlight a lack of efficiency in the flow of patients, compromise the availability of resources, increase attention costs, and increase the risks of adverse outcomes (Ceballos-Acevedo et al., 2014). The factor that most frequently prolongs the stay in the CCSS hospitals is the delay in performing surgical and diagnostic procedures (Morera-Salas, 2016; Calderón-Sánchez and Villegas-León, 2019). Although our data do not allow us to assess potential biases in the length of stay, the high frequency of snakebite patients transferred to other health centers is noticeable; mainly to solve inaccessibility of some services within the studied hospitals. Besides, some snakebite cases are considered labor accidents, and so the patients referred to the National Insurance Institute clinic, allowing them to continue their recovery there and to opt for rehabilitation programs if necessary. In the short term, there is no doubt that these transfers solve the needs of attention for particular health services, but in the long term they could represent higher economic costs, as has already been pointed out by several researchers (Calderón-Sánchez and Villegas-León, 2019).

Despite these difficulties, Costa Rica is proud of its public health system administered by the Caja Costarricense de Seguro Social (CCSS), an autonomous institution in charge of financing, purchasing medicines, and delivering most of health services in the country (Sáenz et al., 2011). CCSS is a solidarity system financially supported by taxpayers, but it extends its services even to people who are not affiliated. In this way, the state ensures the universal right to health of all citizens. The patient's history records have been an indisputable bulwark to understand various pathologies at the national level and to support the approach of reforms and developments to the same system. Although we show some discrepancies between snakebite records in medical centers and those reported by the CCSS, our study was carried out months before the implementation of the single digital health medical record (EDUS, Spanish acronym), perhaps the most important innovation in the health system in recent years. The individual digital file in EDUS allows the registration and storage of the clinical history of each patient, and in Costa Rica, it began to be implemented in some centers since 2012. However, it took several years before the digital records were automated in all the health network of the country (Varela, 2017). The effectiveness of this system for capturing and centralizing information on the snakebite envenoming has yet to be evaluated. However, the expectation is that the traceability of the patient and having the information in real-time will contribute for a more accurate report.

5. Conclusion

Epidemiological surveillance of the snakebite is a necessary practice to determine its trend over space and time, and examine its effects and consequences on populations at risk. This praxis is also a valuable tool for assessing the treatment protocols followed in health centers. As in other countries with a long history of epidemiological studies, snakebite in Costa Rica shows similar patterns in its essential aspects through time, although there are conditions that have varied in recent decades, mostly in response to the development of rural regions.

In addition to farmers, other groups at risk are affected by snakebite in the country, and they must be monitored, especially in locations where domiciliary or peri-domiciliar envenomings is high. Both the morbidity and mortality rates due to snakebite have continued to decrease in the country. The reduction in the impacts of snakebites is a consequence of the efforts that Costa Rica has made to improve its public health system, with the CCSS in the lead (Sáenz et al., 2011). The creation of the EBAIS has allowed the reduction of the time to treatment in many regions of the country. Besides, antivenom availability, which results from local production and the CCSS's effective acquisition and distribution mechanisms to health centers, constitutes another essential ingredient for the success of snakebite management.

The monitoring and homogenization of hospital protocols must continue to ensure the quality and universality of the treatments followed. Also, CCSS must continue evaluating possibilities to secure relevant medical services in the country's health centers (Rojas-Barahona, 2014; Calderón-Sánchez, and Villegas-León, 2019), which would reduce patient transfers and –perhaps– their hospitalization time. The implementation of the single electronic record system will undoubtedly facilitate and accelerate many of these analyzes aimed at improving health care in the country.

CRediT authorship contribution statement

Mahmood Sasa: Conceptualization, Formal analysis, Writing - original draft. **Sofía E. Segura Cano:** Conceptualization, Methodology, Data curation, Writing - original draft.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Mahmood Sasa is a researcher at Instituto Clodomiro Picado, the center that produces the snake-antivenom used in Costa Rican hospitals.

Agknowlegements

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References

Abreu, M.N.S., Siqueira, A.L., Cardoso, C.S., Caiaffa, W.T., 2008. Ordinal logistic regression models: application in quality of life studies. Cad. Saúde Pública 24, s581–s591.

Abubakar, I.S., Abubakar, S.B., Habib, A.G., Nasidi, A., Durfa, N., Yusuf, P.O., Larnyang, S., Garnvwa, J., Sokomba, E., Salako, L., Theakston, R.D.G., Juszczak, E., Alder, N., Warrel, D.A., 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 (7), e767.

Alfaro-Brianso, B., Boza-Mora, A., 1983. Ofidismo en hospital rural del Pacifico Sur durante 1981. Acta Med. Costarric. 26 (1), 24–27.

Alirol, E., Sharma, S.K., Bawaskar, H.S., Kuch, U., Chappuis, F., 2010. Snake bite in South Asia: a review. PLoS Neglected Trop. Dis. 4 (1), e603.

Alirol, E., Sharma, S.K., Ghimire, A., Poncet, A., Combescure, C., Thapa, C., Paudel, V.P., Adhikary, K., Taylor, W.R., Warrell, D.A., Kuch, U., Chappuis, F., 2017. Dose of antivenom for the treatment of snakebite with neurotoxic envenoming: evidence from a randomised controlled trial in Nepal. PLoS Neglected Trop. Dis. 11 (5), e0005612.

Arroyo, O., Bolaños, R., Muñoz, G., 1980. The bacterial flora of venoms and mouth cavities of Costa Rican snakes. Bull. Pan Am. Health Organ. 3, 280–285.

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 (4), 23–29.

Avila-Agüero, M.L., Valverde, K., Gutiérrez, J., París, M.M., Faingezicht, I., 2001. Venomous snakebites in children and adolescents: a 12-year retrospective review. J. Venom. Anim. Toxins 7 (1), 69–84. https://doi.org/10.1590/S0104-79302001000100006.

Bolaños, R., 1982. Las serpientes venenosas de Centroamérica y el problema del ofidismo. Primera parte. Aspectos zoológicos, epidemiológicos y biomédicos. Rev. Costarric. Ciencias Med. 3 (2), 165–184.

Bolaños, R., Brunker, T., 1983. Bacteriología del veneno y de las glándulas veneníferas de Bothrops asper y Crotalus durissus durissus de Costa Rica. Rev. Costarric. Ciencias Med. 4 (1), 27–29.

Bolon, I., Durso, A.M., Botero-Mesa, S., Ray, N., Alcoba, G., Chappuis, F., Ruiz de Castañeda, R., 2020. Identifying the snake: first scoping review on practices of communities and healthcare providers confronted with snakebite across the world. PloS One 15 (3), e0229989.

Boucher, D.H., Hansen, M., Risch, S., Vandermeer, J.H., 1983. Agriculture. In: Janzen, D. H. (Ed.), Costa Rican Natural History. University of Chicago Press, Illinois, pp. 66–73.

Bravo-Vega, C.A., Cordovez, J.M., Renjifo-Ibáñez, C., Santos-Vega, M., Sasa, M., 2019. Estimating snakebite incidence from mathematical models: a test in Costa Rica. PLoS Neglected Trop. Dis. 13 (12), e0007914.

Bucaretchi, F., Douglas, J.L., Fonseca, M.R., Zambrone, F.A., Vieira, R.J., 1994. Snake bites in children: antivenom early reaction frequency in patients pretreated with histamine antagonists H1 and H2 and hydrocortisone. Rev. Inst. Med. Trop. Sao Paulo 36 (5), 451–457.

Bucher, B., Canoge, D., Thomas, L., Tyburn, B., Robbe-Vincent, A., Choumet, V., Bon, C., Ketterlé, J., Lang, J., 1997. Clinical indicators of envenoming and serum levels of venom antigens in patients bitten by *Bothrops lanceolatus* in Martinique. Trans. R. Soc. Trop. Med. Hyg. 91, 186–190.

Calderón-Sánchez, I., Villegas-León, A.M., 2019. Análisis de factores relacionados con el pago de horas extra a médicos generales del Servicio de Urgencias, por traslados de pacientes programados del salón de Medicina Interna del Hospital Carlos Luis Valverde Vega, durante el periodo 2015. Acta Acad. 63 (Noviembre), 145–160.

Ceballos-Acevedo, T., Velásquez-Restrepo, P.A., Jaén-Posada, J.S., 2014. Duración de la estancia hospitalaria. Metodologías para su intervención. Rev. Gerenc. Polít. Salud 13 (27), 274–295. https://doi.org/10.11144/Javeriana.rgyps13-27.dehm2.

Currie, B.J., Smith, A.M., Sutherland, S.K., Hudson, B.J., 1991. An epidemiological study of snakebite envenomation in Papua New Guinea. Med. J. Aust. 154 (4), 266–268.

Chaves, L.F., Chuang, T.W., Sasa, M., Gutiérrez, J.M., 2015. Snakebites are associated with poverty, weather fluctuations, and El Niño. Science advances 1 (8), e1500249.

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

Chippaux, J.P., 2011. Estimate of the burden of snakebites in sub-Saharan Africa: a meta-analytic approach. Toxicon 57, 586–599.

Da Silva, C.J., Jorge, M.T., Ribeiro, L.A., 2003. Epidemiology of snakebite in a central region of Brazil. Toxicon 41, 251–255.

Dehghani, R., Sharif, M.R., Moniri, R., Sharif, A., Kashani, H.H., 2016a. The identification of bacterial flora in oral cavity of snakes. Comp. Clin. Pathol. 25, 279–283.

Dehghani, R., Sharif, A., Assadi, M.A., Kashani, H.H., Sharif, M.R., 2016b. Fungal flora in the mouth of venomous and non-venomous snakes. Comp. Clin. Pathol. 25, 1207–1211.

De Franco-Montalván, D., Alvarez-Trejos, I., Mora, L.A., 1983. Mordedura de ofidios venenosos en niños en la región Pacifico Sur. Análisis de ciento setenta casos. Acta Med. Costarric. 26 (2), 61–70.

de Silva, H.A., Pathmeswaran, A., Ranasinha, C.D., Jayamanne, S., Samarakoon, S.B., Hittharage, A., Kalupahana, R., Ratnatilaka, G.A., Uluwatthage, W.W., Aronson, J.K., Armitage, J.M., Lalloo, D.G., de Silva, H.J., 2011. Low-dose adrenaline, promethazine, and hydrocortisone in the prevention of acute adverse reactions to antivenom following snakebite: a randomised, double-blind, placebo-controlled trial. PLoS Med. https://doi.org/10.1371/journal.pmed.1000435.

Dhananjaya, B.L., Menon, J.C., Joseph, J.K., Raveendran, D.K., Oommen, O.V., 2015. Snake venom detection kit (svdk): update on current aspects and challenges. In: Gopalakrishnakone, P., Faiz, A., Fernando, R., Gnanathasan, C.A., Habib, A.G., Yang, C.C. (Eds.), Clinical Toxinology in Asia Pacific and Africa, pp. 379–400.

Eng, K.H., Gopalakrishnakone, P., 2004. Optical immunoassay for snake venom detection. Biosens. Bioelectron. 19, 1285–1294.

Eslamian, L., Mobaiyen, H., Bayat-Makoo, Z., Piri, R., Benisi, R., Naghavi-Behzad, M., 2016. Snake bite in Northwest Iran: a retrospective study. J. Anal. Res. Clin. Med. 4 (3), 133–138. https://doi.org/10.15171/jarcm.2016.022.

Faiz, M.A., Ahsan, M.F., Ghose, A., Rahman, M.R., Amin, R., Hossain, M., Tareq, M.N.U., Jalil, M.A., Kuch, U., Theakston, R.D.G., Warrell, D.A., Harris, J.B., 2017. Bites by the monocled cobra, *Naja kaouthia*, in Chittagong division, Bangladesh: epidemiology, clinical features of envenoming and management of 70 identified cases. Am. J. Trop. Med. Hyg. 96 (4), 876–884.

Fan, H.W., Marcopito, L.F., Cardoso, J.L.C., França, F.O., Malaque, C.M., Ferrari, R.A., Theakston, R.D.G., Warrell, D.A., 1999. Sequential randomized and double blind trial of promethazine prophylaxis against early anaphylactic reactions to antivenom for *Bothrops* snake bites. B M.J. 318 (7196), 1451–1452.

Fernández, P., Gutiérrez, J.M., 2008. Mortality due to snakebite envenomation in Costa Rica (1993–2006). Toxicon 52, 530–533.

González-Andrade, F., Chippaux, J.P., 2010. Snake bite envenomation in Ecuador. Trans. R. Soc. Trop. Med. Hyg. 104 (9), 588–591.

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

Gutiérrez, J.M., 2014. Current challenges for confronting the public health problem of snakebite envenoming in Central America. J. .Venom. Anim. Toxins inc. Trop. Dis. 20 (1), 7. http://www.jvat.org/content/20/1/7.

Gutiérrez, J.M., Rojas, G., 1999. Instituto Clodomiro Picado: ciencia y tecnología endógenas en la solución de un problema de salud pública en Centroamérica. Interciencia 24 (3), 182–186.

Gutiérrez, J.M., Theakston, R.D.G., Warrell, D.A., 2006. Confronting the neglected problem of snakebite envenoming: the need for a global partnership. PLoS Med. 3, e150.

Gutiérrez, J.M., Williams, D., Fan, H.W., Warrell, D.A., 2010. Snakebite envenoming from a global perspective: towards an integrated approach. Toxicon 56, 1223–1235.

Gutiérrez, J.M., Calvete, J.J., Habib, A.G., Harrison, R.A., Williams, D.J., Warrell, D.A., 2017. Snakebite envenoming. Nature Rev. Dis. Primers 3 (1), 1–21.

Habib, A.G., Abubakar, S.B., 2011. Factors affecting snake bite mortality in north-eastern Nigeria. Int. Health 3 (1), 50–55.

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 (1), e2009.

Harrison, R.A., Gutiérrez, J.M., 2016. Priority actions and progress to substantially and sustainably reduce the mortality, morbidity and socioeconomic burden of tropical snakebite. Toxins 8 (12), 351.

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.

Hedeker, D., 2003. A mixed-effects multinomial logistic regression model. Stat. Med. 22, 1433–1446.

Hung, D.Z., Lin, J.H., Mo, J.F., Huang, C.F., Liau, M.Y., 2014. Rapid diagnosis of *Naja atra* snakebites. Clin. Toxicol. 52 (3), 187–191.

IBM Corp, 2013. IBM SPSS Statistics for Windows, Version 22.0. IBM Corp, Armonk, NY.

Johansson, S.G., Hourihane, J.O., Bousquet, J., Bruijnzeel-Koomen, C., Dreborg, S., Haahtela, T., Kowalski, M.L., Mygind, N., Ring, J., van Cauwenberge, P., van Hage-Hamsten, M., Wuthrich, B., EAACI (the European Academy of Allergology and Clinical Immunology nomenclatres task force, 2001. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. Allergy 56, 813-824. https://doi.org/10.1034/j.1398-9995.2001.t01-1-00001.x.

Kalantri, S., Singh, A., Joshi, R., Malamba, S., Ho, C., Ezoua, J., Morgan, M., 2006. Clinical predictors of in-hospital mortality in patients with snake bite: a retrospective study from a rural hospital in central India. Trop. Med. Int. Health 11 (1), 22–30.

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.
Kularatne, S.A.M., 2003. Epidemiology and clinical picture of the Russell's viper (*Daboia russelii russelii*) bite in Anuradhapura, Sri Lanka: a prospective study of 336 patients. Southeast Asian J. Trop. Med. Publ. Health 34 (4), 855–862.
Langley, R.L., 2010. Snakebite during pregnancy: a literature review. Wilderness Environ. Med. 21 (1), 54–60.
León, G., Herrera, M., Segura, A., Villalta, M., Vargas, M., Gutiérrez, J.M., 2013. Pathogenic mechanisms underlying adverse reactions induced by intravenous administration of snake antivenoms. Toxicon 76, 63–76.
Lomonte, B., Rey-Suárez, P., Fernández, J., Sasa, M., Pla, D., Vargas, N., Bérnard-Valle, M., Sanz, L., Correa-Neto, C., Núñez, V., Alape-Girón, A., Alagón, A., Gutiérrez, J.M., Calvete, J.J., 2016. Venoms of Micrurus coral snakes: evolutionary trends in compositional patterns emerging from proteomics analyses. Toxicon 122, 7–25.
López, N., Lopera, C., Ramírez, A., 2008. Características de los pacientes con accidente ofídico y complicaciones infecciosas atendidos en el Hospital Pablo Tobón Uribe entre los años 2000 y 2006. Acta Méd. Colomb. 33 (3), 127–130.
LoVecchio, F., Klemens, J., Roundy, E.B., Klemens, A., 2003. Serum sickness following administration of antivenin (Crotalidae) polyvalent in 181 cases of presumed rattlesnake envenomation. Wilderness Environ. Med. 14 (4), 220–221.
Meregildo-Rodriguez, E.D., Vásquez-Tirado, G.A., Asmat-Rubio, M.G., 2020. Enfermedad del suero secundaria a suero antiofídico. Rev. Peru. Med. Exp. Salud Pública 37 (1), 176–177.
Mohapatra, B., Warrell, D.A., Suraweera, W., Bhatia, P., Dhingra, N., Jotkar, R.M., Rodriguez, P.S., Mishra, K., Whiteker, R., Jha, P., Million Death study collaborators, 2011. Snakebite mortalilty in India: a nationally representative mortality survey. PLoS Neglected Trop. Dis. 5 (4), e1018.
Mok, S.C., 2005. Turismo y ambiente: un potential para el desarrollo económico para Costa Rica. Reflexiones 84 (2), 25–37.
Mondal, R.N., Chowdhury, F.R., Rani, M., Mohammad, N., Islam, M., Haque, M.A., Faiz, M.A., 2012. Pre-hospital and hospital management practices and circumstances behind venomous snakebite in northwestern part of Bangladesh. Asia Pac. J. Med. Toxicol. 1, 18–21.
Montalván, F., Alvarez-Trejos, I., Mora-Watler, L.A., 1983. Mordedura de ofidios venenosos en niños en la Región Pacífico Sur. Análisis de ciento sesenta casos. Acta Med. Costarric. 26 (2), 61–70.
Morera-Salas, M., 2016. Índice de internación ajustado por riesgo en hospitales públicos de Costa Rica. Rev. Gerenc. Polít. Salud 15 (31), 202–214. https://doi.org/10.11144/Javeriana.rgyps15-31.iiar.
Mustapha, S.K., 2003. Snake bite in gombe. Highl. Med. Res. J. 1 (4), 22–27.
Otero, R., Gutierrez, J.M., Rojas, G., Nuñez, V., Diaz, A., Miranda, E., Uribe, A.F., Silva, J.F., Ospina, J.G., Medina, Y., Toro, M.F., García, M.E., León, G., García, M., Lizano, S., 1999. A randomized blinded clinical trial of two antivenoms, prepared by caprylic acid or ammonium sulphate fractionation of IgG, in *Bothrops* and *Porthidium* snake bites in Colombia. Correlation between safety and biochemical characteristics of antivenoms. Toxicon 37, 895–908.
Otero-Patiño, R., 2009. Epidemiological, clinical and therapeutic aspects of *Bothrops asper* bites. Toxicon 54, 998–1011.
Pandey, D.P., Vohra, R., Stalcup, P., Shrestha, B.R., 2016. A season of snakebite envenomation: presentation patterns, timing of care, anti-venom use, and case fatality rates from a hospital of southcentral Nepal. J. Venom Res. 7, 1–9.
Praba-Egge, A.D., Cone, S.W., Araim, O., Freire, I.L., Paida, G.V., Escalante, J.T., Carrera, F.M., Chavez, M.R., Merrell, R.C., 2003. Snakebites in the rainforests of Ecuador. World J. Surg. 27, 234–240.
Premawardhena, A.P., De Silva, C.E., Fonseka, M.M.D., 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 (7190), 1041–1043.
Rahman, R., Faiz, M.A., Selim, S., Rahman, B., Basher, A., Jones, A., d'Este, C., Hossain, M., Islam, Z., Ahmed, H., Milton, A.H., 2010. Annual incidence of snake bite in rural Bangladesh. PLoS Neglected Trop. Dis. 4 (10), e860.
Resiere, D., Gutiérrez, J.M., Névière, R., Cabié, A., Mehdaoui Hossein Hossein, M., Kallel, H., 2020. Antibiotic therapy for snakebite envenoming. J. Venom. Anim. Toxins Incl. Trop. Dis. https://doi.org/10.1590/1678-9199-JVATITD-2019-0098.
Rojas, G., Bogarín, G., Gutiérrez, J.M., 1997. Snakebite mortality in Costa Rica. Toxicon 35, 1639–1643.
Rojas-Alvarado, L.D., 2009. Evolución e importancia del turismo en Costa Rica. Decimoquinto Informe Estado de la Nación en Desarrollo Humano Sostenible. Consejo Nacional de Rectores, p. 34. San José, Costa Rica.
Rojas-Barahona, R., 2014. Análisis de las Necesidades de Formación y Capacitación en la Especialidad de Endocrinología, Caja Costarricense de Seguro Social proyección 2015-2025. https://repositorio.binasss.sa.cr/xmlui/bitstream/handle/20.500.11764/369/Endocrinolog%C3%ADa_2015_2025.pdf?sequence=1&isAllowed=y.
Roriz, K.R.P.S., Zaqueo, K.D., Setubal, S.S., Katsuragawa, T.H., Silva, R.R.D., Fernandes, C.F.C., Cardoso, L.A.P., Rodriguez, M.M.S., Soares, A.M., Stábeli, R.G., Zuliani, J.P., 2018. Epidemiological study of snakebite cases in Brazilian Western Amazonia. Rev. Soc. Bras. Med. Trop. 51, 338–346.
Rosero-Bixby, L., 2004a. Evaluación del impacto de la reforma del sector de la salud en Costa Rica mediante un estudio cuasi-experimental. Rev. Panam. Salud Públic 15 (2), 94–103.
Rosero-Bixby, L., 2004b. Spatial access to health care in Costa Rica and its equity: a GIS-based study. Soc. Sci. Med. 58 (7), 1271–1284.
Ruíz de Castañeda, R., Durso, A.M., Ray, N., Fernández, J.L., Williams, D.J., Alcoba, G., Chappuis, F., Salathé, M., Bolon, I., 2019. Snakebite and snake identification: empowering neglected communities and health-care providers with AI. The Lancet Digital Health 1 (5), e202–e203.
Saborío, P., González, M., Cambronero, M., 1998. Accidente ofídico en niños en Costa Rica: epidemiología y detección de factores de riesgo en el desarrollo de absceso y necrosis. Toxicon 36, 359–366.
Sachett, J.A., da Silva, I.M., Alves, E.C., Oliveira, S.S., Sampaio, V.S., do Vale, F.F., Romero, G.A.S., Dos Santos, M.C., Marques, H.O., Colombini, M., da Silva, A.M.M., Fan, H.W., Lacerda, M.V.G., Monteiro, W.M., Ferrerira, L.C.L., 2017. Poor efficacy of preemptive amoxicillin clavulanate for preventing secondary infection from Bothrops snakebites in the Brazilian Amazon: a randomized controlled clinical trial. PLoS Neglected Trop. Dis. 11 (7), e0005745.
Sáenz, M.D.R., Acosta, M., Muiser, J., Bermúdez, J.L., 2011. Sistema de salud de Costa Rica. Salud Publica Mex. 53, s156–s167.
Sasa, M., Vázquez, S., 2003. Snakebite envenomation in Costa Rica: a revision of incidence in the decade 1990-2000. Toxicon 41, 19–22.
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.
Schaeffer, T.H., Khatri, V., Reifler, L.M., Lavonas, E.J., 2012. Incidence of immediate hypersensitivity reaction and serum sickness following administration of crotalidae polyvalent immune Fab antivenom: a meta-analysis. Acad. Emerg. Med. 19 (2), 121–131.
Sharma, R., Dogra, V., Sharma, G., Chauhan, V., 2016a. Mass awareness regarding snake bite induced early morning neuroparalysis can prevent many deaths in North India. Int. J. Crit. Illn. Inj. Sci. 6 (3), 115–118. https://doi.org/10.4103/2229-5151.190652.
Sharma, S.K., Kuch, U., Höde, P., Bruhse, L., Pandey, D.P., Ghimire, A., Chappuis, F., Alirol, E., 2016b. Use of molecular diagnostic tools for the identification of species responsible for snakebite in Nepal: a pilot study. PLoS Neglected Trop. Dis. 10 (4), e0004620 https://doi.org/10.1371/journal.pntd.0004620.
Suchithra, N., Pappachan, J.M., Sujathan, P., 2008. Snakebite envenoming in Kerala, South India: clinical profile and factors involved in adverse outcomes. Emerg. Med. J. 25 (4), 200–204.
Solórzano, A., 2004. Serpientes de Costa Rica: distribución, taxonomía e historia natural. Editorial INBio.
Spiller, H.A., Bosse, G.M., 2003. Prospective study of morbidity associated with snakebite envenomation. J. Toxicol. Clin. Toxicol. 41 (2), 125–130.
Stone, S.F., Isbister, G.K., Shahmy, S., Mohamed, F., Abeysinghe, C., Karunathilake, H., Ariaratnam, A., Jacoby-Alner, T.E., Cotterell, C.L., Brown, S.G., 2013. Immune response to snake envenoming and treatment with antivenom; complement activation, cytokine production and mast cell degranulation. PLoS Neglected Trop. Dis. 7 (7), e2326 https://doi.org/10.1371/journal.pntd.0002326.
Tagwireyi, D.D., Ball, D.E., Nhachi, C.F., 2001. Routine prophylactic antibiotic use in the management of snakebite. BMC Clin. Pharmacol. 1, 4. https://doi.org/10.1186/1472-6904-1-4.
Tun-Pe, Ba-Aye, Aye-Aye-Myint, Tin-Nu-Swe, Warrell, D.A., 1991. Bites by Russell's vipers (*Daboia russelii siamensis*) in Myanmar: effect of the snake's length and recent feeding on venom antigenaemia and severity of envenoming. Trans. R. Soc. Trop. Med. Hyg. 85, 804–808. https://doi.org/10.1016/0035-9203(91)90464-a.
Varela, J.C., 2017. Análisis de la implementación del Expediente Digital Único en Salud y su impacto en el cumplimiento de las metas en el Primer Nivel de Atención del Área de Salud Buenos Aires durante el año 2016. Thesis. Instituto Centroamericano de Administración Pública. ICAP. http://biblioteca.icap.ac.cr/BLIVI/TESIS/2017/91.%20Calderon,%20Jorge%20.pdf.
Ver Hoef, J.M., Boveng, P.L., 2007. Quasi-Poisson vs. negative binomial regression: how should we model overdispersed count data? Ecology 88, 2766–2772.
Wagener, M., Naidoo, M., Aldous, C., 2017. Wound infection secondary to snakebite. S. Afr. Med. J. 107, 315–319.
Warrell, D.A., 1999. WHO/SEARO guidelines for the clinical management of snake bites in the Southeast Asian region. Southeast Asian J. Trop. Med. Publ. Health 30 (Suppl. 1), 1–85.
Warrell, D.A., 2010. Snake bite. Lancet 375 (9708), 77–88.
World Health Organization, 2019. Snakebite Envenoming. A Strategy for Prevention and Vontrol. WHO, Geneva, p. 50. Available at: https://www.who.int/snakebites/resources/9789241515641/en/. (Accessed 16 February 2020).
Williams, D.J., Jensen, S.D., Nimorakiotakis, B., Müller, R., Winkel, K.D., 2007. Antivenom use, premedication and early adverse reactions in the management of snake bites in rural Papua New Guinea. Toxicon 49 (6), 780–792.
Williams, D.J., Faiz, M.A., Abela-Ridder, B., Ainsworth, S., Bulfone, T.C., Nickerson, A.D., Habib, A.G., Junghanss, T., Fan, H.W., Turner, M., Harrison, R.A., Warrell, D.A., 2019. Strategy for a globally coordinated response to a priority neglected tropical disease: snakebite envenoming. PLoS Neglected Trop. Dis. 13 (2), e0007059.