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A brief review on the natural history, venomics and the medical importance of bushmaster (*Lachesis)* pit viper snakes

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ABSTRACT

Snakes of the genus *Lachesis*, commonly known as bushmasters, are the largest venomous snakes in the Americas. Because these snakes have their habitats in areas of remote forests they are difficult to find, and consequently there are few studies of *Lachesis* taxa in their natural ecosystems. Bushmasters are distributed in tropical forest areas of South and Central America. In Brazil they can be found in the Amazon Rainforest and the Atlantic Forest. Despite the low incidence of cases, laquetic envenoming causes severe permanent sequelae due to the high amount of inoculated venom. These accidents are characterized by local pain, hemorrhage and myonecrosis that can be confused with bothropic envenomings. However, victims of *Lachesis* bites develop symptoms characteristic of *Lachesis* envenoming, known as vagal syndrome. An important message of this bibliographic synthesis exercise is that, despite having the proteomic profiles of all the taxa of the genus available, very few structure-function correlation studies have been carried out. Therefore the motivation for this review was to fill a gap in the literature on the genus *Lachesis*, about which there is no recent review. Here we discuss data scattered in a number of original articles published in specialized journals, spanning the evolutionary history and extant phylogeographic distribution of the bushmasters, their venom composition and diet, as well as the pathophysiology of their bites to humans and the biological activities and possible biotechnological applicability of their venom toxins.

1. Overview of genus *Lachesis*

Genus *Lachesis* (Daudin, 1803) (Viperidae: Crotalinae), commonly called in Brazil "Surucucu-pico-de-jaca" and in other countries "Bushmaster". With the largest known specimens reaching 3.05–3.36 m (Bellairs, 1969), 3.35 m (Ditmars, 1937), 3.5 m (Abalos, 1977), 4.27 m (Dunn, 1951), and 4.5 m (Hoge and Lancini, 1962), bushmasters comprises the longest snakes in the Western Hemisphere, and the longest vipers (Viperidae: Crotalidae) in the world. *Lachesis* taxa are the only oviparous species (Fig. 1B) among New World vipers (Campbell and Lamar, 2004; McDiarmid et al., 1999). They lay up to 20 eggs to which the female provides parental care curling up in the eggs to protect them (Ditmars, 1910; Mole, 1924) (Fig. 1A). It has also been reported that females remain with eggs until hatching, and that males stay close to females for some time after mating (Emsley, 1977).

The four nominal species within *Lachesis* are nocturnal terrestrial venomous pit vipers found in primary and secondary forested areas of Central and South America and on the island of Trinidad (Campbell and Lamar, 2004; McDiarmid et al., 1999; Zamudio and Greene, 1997). The Central American bushmaster, *L. stenophrys* (Cope, 1975), is endemic to the Caribbean coast of Central America; the black-headed bushmaster, *L. melanocephala* (Solorzano and Cerdas, 1986) has an extremely limited distribution restricted to the Corcovado. National Park along the Pacific coast of southwestern Costa Rica, and possibly in the extreme western

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part of Panama. The Chocoan bushmaster L. *acrochorda* (Garcia, 1896) ranges in both the Atlantic and Pacific versants of western Panama and into northwestern Colombia, on the Atlantic coast where it extends southward into the Cauca and Magdalena river Valleys, and along the Pacific versant of Colombia into northwestern Ecuador. Among the two subspecies of *L. muta* (Linnaeus, 1766), the nominal subspecies, the South American bushmaster (*L. muta muta*), can be found in South America in the equatorial forests east of the Andes and the island of Trinidad, and the Atlantic Forest bushmaster, *L. muta rhombeata* (Wied-Neuwied, 1824) inhabits Coastal forests of southeastern Brazil, from southern Rio Grande do Norte to Rio de Janeiro (Fig. 2).

The Central and South American forms diverged 18–6 Mya, perhaps due to the uplifting of the Andes, whereas the two Central American subspecies may have diverged 11–4 Mya with the uprising of the Cordillera de Talamanca that separates them today (Zamudio and Greene, 1997). The split between Central American L. *melanocephala* and *L. stenophrys* is estimated to have taken place 11–4 Mya, and differentiation among the South American lineages happened only 800,000 to 300,000 years ago (Fernandes et al., 2004; Zamudio and Greene, 1997) (Fig. 3).

Bushmaster can live long. There are records of a male of *L. m. muta* that lived for more than 16 years in captivity at the Fort Worth Zoo and a specimen of *L. stenophrys* that lasted 31 years and 7 months at the Atlanta Zoo (Slavens and Slavens, 2000). Campbell and Lamar (2004) also mention an *L. stenophrys* from Costa Rica, kept for almost 30 years in Europe. However, there are no data on longevity in its natural ecosystem.

Bushmasters prey primarily on small mammals, such as rodents and marsupials (Beebe, 1946; Cunha and Nascimento, 1993; Martins and Oliveira, 1998; Medem, 1969; Mole, 1924), but also hedgehog (Fountain, 1902), birds and amphibians (Carrillo de Espinoza, 1970). Although the specimens examined were adults, the prey was relatively small. Juvenile snakes (and some adults) maintain control when attacking prey, and an epicantic fold protects the eyes from possible damage during predation. Juvenile individuals may have the tip of the tail bright orange or yellow, but tail movements to attract prey ("tail luring") has not been reported (Ripa, 2001).

Lachesis, daughter of Erebus (Darkness) and Nyx (Night), is a goddess who in the Greek mythology assigned individual destinies to mortals at birth. This epithet given to the homonymous genus may refer to the feeling that during an encounter with these imposing snakes one's own fate is momentarily at the snake's will. However, human envenomings by *Lachesis* taxa are infrequent as these snakes do not exhibit aggressive behavior, inhabit shelters in fallen trees, burrows and excavations of rodents or in rocky caves of remote forest area (Fonseca, 1949), where contact with man is scarce (Souza, 2007). *Lachesis* have nocturnal habits, remaining throughout the day in a state of torpor. Only in the breeding season, males are on day alert and ready for combat. In addition, venom lethality is weak compared to those of some other vipers (Bolaños, 1972; da Silva et al., 2020). Brown (1973) quote the following LD50 values of *L. m. muta* venom for mice: 1.5 mg/kg (intravenous), 1.6–6.2 mg/kg (intraperitoneal) and 6.0 mg/kg (subcutaneous). Nevertheless, human envenomings can be rather severe due to the large venom yield (200–411 mg) (Brown, 1973; Málaque and França, 2003).

Venomics studies have been conducted on all species and subspecies within genus *Lachesis* (Madrigal et al., 2012; Pla et al., 2013; Sanz et al., 2008). Comparison of their venom proteomes provided an overview of the geographic and ontogenetic variation of the toxic arsenal across genus *Lachesis*. Hence, notwithstanding minor qualitative and quantitative differences, the venom arsenals of *L. melanocephala* and *L. acrochorda* are broadly similar between themselves and also closely mirror those of adult *L. stenophrys* and *L. muta* venoms. On the other hand, the toxin composition of *L. stenophrys* venom undergoes ontogenetic changes, which involve changes in the concentration of vasoactive peptides and serine proteinases, which steadily decrease from birth to adulthood, and age-dependent biosynthesis of Gal-lectin and snake venom metalloproteinases (SVMPs). The net result is a shift from a bradykinin-potentiating and C-type natriuretic peptide (BPP/C-NP)-rich and serine proteinase-rich venom in newborns and 2-years-old juveniles to a (PI > PIII) SVMP-rich venom in adults (Madrigal et al., 2012). The venom of newborn *L. stenophrys* has lower toxicity to mice than venom from older conspecific snakes (Gutiérrez et al., 1990). However, bites by a 10 to 14-day-old and a 2-month-old *L. stenophrys* specimens produced substantial toxicity to humans, which similar to an adult bite completely overwhelmed the 80 kg victim within 30 min (Ripa, 2003). The venomics analysis of neonate and juvenile *L. stenophrys* suggests that the high content of vasoactive peptides and serine proteinases may be responsible for the high toxicity of newborn venom in humans. On the other hand, the high similarity of their venom proteomes is mirrored by a high immunological conservation across the genus (Pla et al., 2013). A corollary of this fortunate circumstance is that antivenoms generated against venom mixtures containing any *Lachesis* spp. venom may exhibit paraspecific protection against (Daltry et al., 1996; Davies and Arbuckle, 2019) the toxic activities of venoms from any other congeneric species (Madrigal et al., 2017).

Adaptations result from selective pressures on both morphological and molecular phenotypic traits that maximize the organism's fitness in local environments, e.g., the snake foraging success on preferred prey. Venom is an intrinsically ecological trophic trait crucial for the foraging success of the organisms that produce it. Hence, functional evolution of venoms is intimately linked to the ecology and dietary habits of the

Fig. 1. *Lachesis* sp in different behaviors. (A) Parental care of a *L. stenophrys* female along with the eggs (Corrales et al., 2014) (B) A neonate of *L. acrochorda* that just hatched (Daniel Fuentes and Corrales, 2016). Photos kindly provided by Greivin Corrales.

Fig. 2. Geographic distribution of the genus *Lachesis* in Central and South America. *L. muta muta* (red: highest medical importance, and in orange: secondary medical importance) distributed in the following countries: Venezuela, Colombia, Trinidad and Tobago, Guyana, Suriname, French Guiana, Ecuador, Perú, Bolivia and Brazil (in the States: Goiânia, Mato-Grosso, Tocantis, Para, Amazonas, Rondônia, Acre, Amapá, Roraima and Maranhão). Photo: Paulo Sérgio Bernarde. *L. m. rhombeata* (blue), found in Coastal forest of southeastern Brazil (Ceara, Rio de Janeiro, Paraíba, Pernambuco, Bahia, Espirito Santo, Minas Gerais, Alagoas and Rio Grande do Norte). *L. acrochorda* (green) found in the countries: Panamá, Colombia e Ecuador. Photo: Jairo Maldonado. *L. stenophrys* (yellow) found in Costa Rica and Panamá. Photo: Instituto Clodomiro Picado. *L. melanocephala* (gray) found in Costa Rica. Photo: Jaime Culebras. Maps taken from (World Health Organization) (https://apps.who.int/bloodproducts/snakeantivenoms/database/).

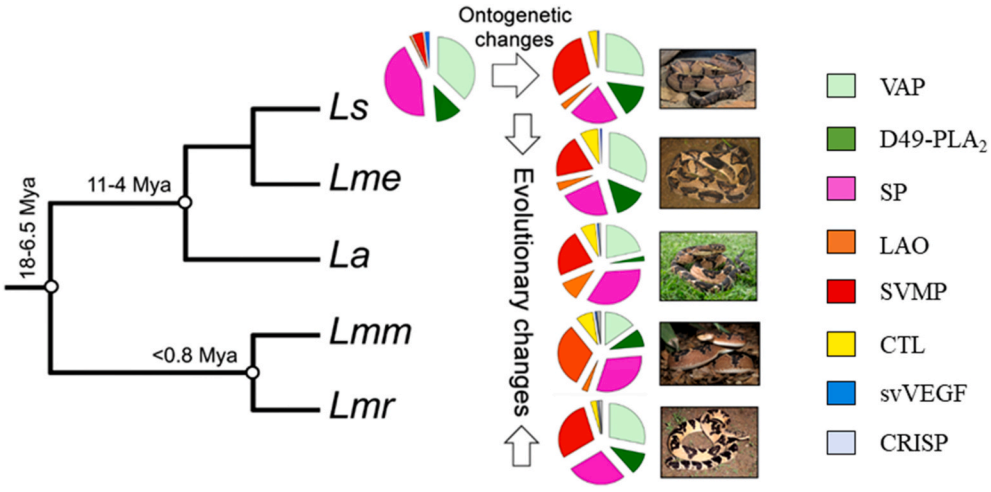

Fig. 3. Phylogenetic tree of genus *Lachesis* highlighting the estimated divergence time between the Central and South American taxa (Zamudio and Greene, 1997), the remarkably similar overall venom compositional profiles among the five species of Central and South American bushmasters (Pla et al., 2013; Sanz et al., 2008), and the ontogenetic changes in the venom composition of *L. stenophrys* (Madrigal et al., 2012). La, *L. acrochorda*; Lme, *L. melanocephala*; Lmm, *L. muta muta*; Lmr, *L. m. rhombeata*; Ls, *L. stenophrys*. Acronyms = VAP: BPP, bradykinin-potentiating peptide, and C-NP, type natriuretic peptide; D49-PLA_2, Asp49 phospholipase A_2; SP, snake venom serine proteinase; LAO, L-aminoacid oxidase; SVMP, snake venom metalloproteinase; CTL: Gal lectin, galactose-specific lectin; svVEGF, snake venom vascular endothelial growth factor; CRISP, cysteine-rich secretory protein. Phylogenetic scheme adapted from Fig. 5 (Calvete, 2017), kindly provided by Professor Juan Calvete.

venomous organisms. A still small but increasing number of studies support the idea that snake venom evolution is driven by diet-related selection pressures leading to local adaptations (Barlow et al., 2009; Barua and Mikheyev, 2019; Daltry et al., 1996; Davies and Arbuckle, 2019; Jackson et al., 2004; Smiley-Walters et al., 2019). Consequently, the changes in toxic characteristics of venom that ocurr during the development of *L. stenophrys* (Madrigal et al., 2012), should be rationalized in the context of its use by the venomous predator. Optimal foraging theory predicts that juvenile gape-limited predators should feed efficiently in order to compete with adults for food (Schoener,

1971) and to minimize their exposure to predators (Sih et al., 1985). Carrier (1996) predicted that juvenile animals should compensate for their small size by increasing their overall performance relative to adults (compensation hypothesis, e.g. decreased ingestion and/or handling times relative to body size compared with adults). In line with this view, concomitantly with age-dependent venom compositional changes, newborn *L. stenophrys* venom showed highest coagulant effect on human plasma, in line with its high serine proteinase content, whereas the venom lethal, proteolytic, hemorrhagic, edema-forming, myotoxic, and PLA_2 activities raise as snakes aged (Gutiérrez et al., 1990). The different pharmacological effects of venom from neonate and adult individuals is mirrored by clinical reports indicating that human envenomings by juvenile specimens are often associated to prominent alterations and symptoms despite the low amount of venom that a small size specimens may inject in a bite (Chaves et al., 1992; Gutiérrez et al., 1980). Neonate L. *stenophrys* specimens produce substantial toxicity to humans, which similar to an adult bite completely overwhelmed an 80 kg victim within 30 min (Ripa, 2003). The proteomic analysis of ontogenetic changes in *L. stenophrys* venom suggests that the high content of vasoactive peptides and serine proteinases may be responsible for the high toxicity of newborn *L. stenophrys* venom in humans (Madrigal et al., 2012).

Age-related changes in venom composition, as it happens in *L. stenophrys*, have been reported in a number of New World pit viper species from different genera, i.e. *Crotalus*, *Bothrops*, *Sistrurus*, and *Bothiechis* (Alape-Girón et al., 2008; Calvete et al., 2011, 2010; Gibbs et al., 2011; Gonçalves-Machado et al., 2016; Guércio et al., 2006; Mackessy, 1988; Pla et al., 2017; Saldarriaga et al., 2003; Zelanis et al., 2010, 2008, 2011). A similar pattern was noted for the Brown Treesnake (*Boiga irregularis*), with juvenile venoms more toxic than adult venoms towards geckos (Mackessy et al., 2006), suggesting that this trend has not exclusively evolved in pit vipers. A shift in the feeding habits of juvenile versus adult snakes, from cold-blooded (arthropods, frogs and lizards) to warm-blooded (mammals) prey, has been invoked to explain the ontogenetic venom change in some pitviper species (Andrade and Abe, 1999). In concordance with this view, it has been documented that venoms from neonate snakes are more toxic to lizards and inbred mice than adult venoms (Mackessy, 1988). Young *Bothrops* snakes preferentially eat amphibians, lizards, birds, and shift to mammals when they become adults (Campbell and Lamar, 2004). However, *Lachesis* taxa feed from birth on vertebrates, primarily rodents (i.e., brown mice (*Akodon*), rice rats (*Oryzomys*), spiny rats (*Proechimys*)) and marsupials of the family Didelphidae (Campbell and Lamar, 2004). Similarly, the venom composition of the Central American rattlesnake, *Crotalus simus*, a species that feeds from its birth primarily on small rodents and lizards (Calvete et al., 2010), changes dramatically during development, from a neurotoxic to a hemorrhagic phenotype, and these ontogenetic changes appears to be post-transcriptionally modulated by miRNAs (Durban et al., 2013). Predator body size is one of the most important factors shaping predator–prey interactions (Jackson et al., 2004; Persson and Hansson, 1999; Peters, 1983), and dietary decisions define the trophic niche of the organism and have significant implications on the individual's energy budget. Ontogenetic venom composition shift resulting in a different pharmacological venom profile, may fulfill the requirements to subdue prey of different sizes and initiate its digestion may change with the size of both the predator and the prey. This is particularly important when a large prey (in relation to the snake's digestive apparatus size) is ingested. Biochemical features of venom that enhance trophic functions are likely very important for snakes. It has been hypothesized that tissue-degrading enhancement of venom may facilitate efficient prey digestion at suboptimal temperatures encountered in the field, thereby reducing the risk of prey putrefying before it can be digested (Thomas and Pough, 1979). Putrefaction forces a snake to regurgitate its prey, which had been swallowed whole, head first without mastication. Regurgitation can thus be a severe, and in some instances a life-threatening problem (Flannagan and Harwell, 1983). Injection of proteolytic venom may hasten the entrance of the acidic secretions of the snake's stomach into the prey's gut, reducing or eliminating the action the putrefactive bacteria (Thomas and Pough, 1979). It is therefore not unreasonable to suggest that he high amounts of histolytic enzymes contained in the venom of newborn *L. stenophrys* snakes may serve to breakdown the bolus, contributing to reduce the chances of putrefaction of the ingested prey.

Table 1
Serotherapy and clinical manifestations of laquetic accidents.

ACTIVITY	CLASSIFICATION AND INITIAL CLINICAL EVALUATION	
Serotherapy No. of ampoules	Moderate	Severe
	10	20
Route of administration	Endovenous	
Acute inflammatory	Endothelial injury and necrosis at the bite site. Release of inflammatory mediators.	
Coagulant	Blood incoagulability	
Hemorrhagic	Bleeding in the bite region (ecchymosis) and at distance (gingival, hematuria).	
Vagal neurotoxic	Cholinergic stimulation (vomiting, abdominal pain, diarrhea, hypotension, shock).	

(Source: adapted from Brazil, 2019)

2. Lachesis envenoming: epidemiology, symptoms and treatment

Snakebites by front-fanged snakes is an occupational disease that cause envenomings to at least 1.8–2.7 million people worldwide per year, with combined upper WHO estimates of mortality ranging from 81,000 to 138,000 deaths, and maims >400,000 people every year (Chippaux et al., 2019; Chippaux, 1998; Gutiérrez et al., 2017; Williams et al., 2019). The only scientific validated treatment of snakebite envenoming is the timely administration of an effective antivenoms (Gutiérrez, 2014; Gutiérrez et al., 2011a, 2011b). One of the greatest limitations for developing effective interventions for snakebite envenomation is the paucity of reliable information on incidence and mortality (Gutiérrez and Fan, 2018). A recent report on data gathered from Ministries of Health the specialized literature identified a total of 57,500 snakebite cases in the Americas, 370 of which resulted in death (Chippaux, 2017). However, due to the limitations of the information systems in many countries where snakebite reporting is not compulsory, these figures are likely to be underestimations.

In Brazil, snakebites are mainly associated with agricultural work and, in the Amazon region, also with extractive activities (Silva et al., 2020; Feitosa et al., 2015; Pierini et al., 1996; Waldez and Vogt, 2009). Approximately 29,000 cases of snakebite accidents are reported each year by the SINAN (Reporting Disease Information System), with an average of 129 yearly deaths (0.44% lethality) (Bernarde, 2014). According to data from the Ministry of Health, 939 laquetic accidents were reported in Brazil in the period 1990–1993. This figure is equivalent to 1.4% of the total envenomings caused by venomous snakes in Brazil (Brasil, 1996). Another study carried out from 2001 to 2015 reported 13, 044 accidents (84 deaths) by the *Lachesis* taxa, i.e. approximately 869 accidents per year (Magalhães, 2017). In the Amazon region bites caused by *Lachesis* taxa in the period 2010–2015 were responsible for 5217 cases, only superated by envenomations caused by snakes of genus *Bothrops* (57,374 cases, 81.02%, including a high proportion of deaths (74.48%) and amputations (86.88%) among the victims) (Magalhães et al., 2018). In line with these data, a recent study by da Silva and coworkers (2020), conducted in the Alto Juruá, a region in the western Brazilian Amazonia, also reported low frequency of accidents caused by *Lachesis* snakebites. Despite these data, in the same study da Silva and coworkers (2020) investigated the ethnobiological perception of dangerousness of different snake species by the population of the rural areas of Alto Juruá. Interviews to 100 villagers active in the forests revealed that *L. muta muta* was considered the most dangerous

venomous snake, and *B. atrox* appeared to be the most feared snake species. The authors interpreted that the high incidence, severity, and mortality of *B. atrox* bites and the severity and mortality of *L. muta* bites represented the factors that contributed to these species being perceived as the most feared and venomous snakes, respectively. This villagers' perception reflects the fact that although encounters with human are infrequent owing to their little aggressive behavior and elusive ecological habits, envenomings by *Lachesis* taxa are characterized by the high amounts of venom inoculated, (200–411 mg) (Brown, 1973; Málaque and França, 2003), which makes bite by bushmasters serious and result in high rates of permanent sequelae and mortality (Oliveira et al., 2002; Sánchez et al., 1992; Tanus Jorge et al., 1997).

The symptoms of envenomations caused by *Lachesis* taxa can be similar to those observed in bothropic envenomings, i.e. local pain, edema, hemorrhage and myonecrosis. Distinct features of bites by *Lachesis* taxa are agonizing burning-throbbing local pain and edema, within the first few minutes after the bite, followed within the next within 15–20 min by a "vagal symptomatology" characterized by profuse sweating, abdominal colic, nausea, recurrent vomiting, watery diarrhea, diastolic and systolic hypotension, sinus bradycardia, uncoordinated march, lapses of consciousness (Silva-Haad, 1982; Warrell, 2004). The vagal syndrome, may assists in the differential diagnosis between laquetic and bothropic accidents (de Lima and Junior, 2015; Tanus Jorge et al., 1997). Laquetic accidents are classified according to their clinical manifestations as i) Mild: mild or absent edema and mild or absent hemorrhagic manifestations. Absence of vagal manifestations; ii) Moderate: with evident edema and discrete hemorrhagic manifestations at a distance (gingivorrhagia, epistaxis). Absence of vagal manifestations; and iii) Severe: presence of severe edema and systemic manifestations such as profuse hemorrhage. Presence of vagal manifestations (diarrhea, bradycardia, hypotension or shock) (Souza et al., 2020) (Table 1). In Brazil, treatment of laquetic envenoming is based on the severity of the accident, administering when necessary the Brazilian Soro Antibotrópico-Laquético (SABL) intravenously (Brasil, 2001; Pardal et al., 2007). The antivenom, manufactured at Instituto Butantan (São Paulo, Brazil), is obtained from the plasma of horses hyperimmunized with a mixture of venoms from five species of snakes of genus *Bothrops* (*B. jararaca* (50%), *B. jararacussu* (12.5%), *B. moojeni* (12.5%), *B. alternatus* (12.5%) and *B. neuwiedi* (12.5%) and from the plasma of horses hyperimmunized with venom of *L. muta*. The final formulation consists of purified $F(ab')_2$ fragments generated by digestion with pepsin of ammonium sulphate-precipitated IgG molecules. A vial of SABL (10 mL) nominally neutralizes at least 50.0 mg of *B. jararaca* venom (the reference venom for assessing the bothropic antivenom potency in Brazil) and no less than 30 mg of the *L. muta* reference venom (Brasil, 1996; Monaco, 2018; Raw et al., 1991).

Key technical issues concerning the generation of an antidote for snakebite envenoming are i) the design of the immunization mixture in such a way that the resulting antivenoms results effective against most venoms of the medically-relevant snake species within the geographical range where these antivenoms is intended to be used, and ii) a reliable taxonomy. This purpose is not trivial given the well-documented occurrence of venom variability at all the taxonomic levels (genus, species, subspecies, population and individual) (Calvete et al., 2013) and the instability of the phylogeny of certain snake clades (Carrasco et al., 2016). In addition, the rational generation of polyvalent antivenoms of broad clinical spectrum require a deep understanding of the toxicovenomics profile of the target venoms (Gutiérrez et al., 2014). Toxicovenomics refers to the screening of individual venom fractions of a toxin-resolved chromatographic profile for specific toxic activities (Lauridsen et al., 2016; Lomonte and Calvete, 2017). Genus *Lachesis* meets these criteria for what we can consider it a prospective model system to define knowledge-based omics strategies (Calvete et al., 2018, 2014) for the production of next-generation pan-generic antivenoms.

3. Bioactive components of *Lachesis* venom

Lachesis m. muta venom gland transcriptomic analysis (Junqueira-de-Azevedo et al., 2006) and proteomic analyses of the venoms of all the nominal species and subspecies within genus *Lachesis: L. m. muta*, (Sanz et al., 2008); *L. m. rhombeata* (Pla et al., 2013); *L. stenophrys*, *L. acrochorda*, and *L. melanocephala* (Madrigal et al., 2012), have provided a genus-wide insight into the overall complexity of their toxic arsenals. Bushmaster venoms comprise a relatively conserved set of proteins and peptides, belonging to just a few major (i.e. relative abundances between 10 and 30% of the total venom proteome:

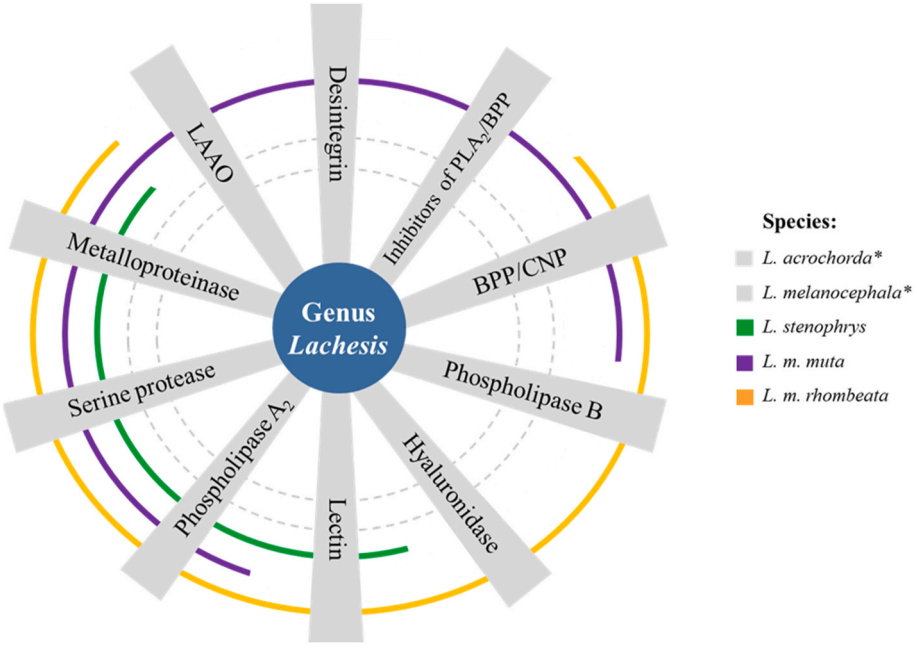

Fig. 4. Distribution of *Lachesis* venom toxin families from which individual toxins have been isolated and charaterized (Table 2). Toxin families are represented as gray bars and the different color lines refer to the species/subspecies. Discontinuous gray lines indicate absence of data on isolated toxins from the *Lachesis* taxa labeled with an asterisk.

bradykinin-potentiating peptides; snake venom serine proteinases; PIII- and PI-snake venom metalloproteinases; and PLA_2) and minor (L-aminoacid oxidase; galactose-specific lectin; vascular endothelial growth factor; cysteine-rich secretory protein; phospholipase B; and hyaluronidase) toxin families (Fig. 2 and Fig. 4). Pairwise comparisons showed overall similarities of 33–51% across the different conspecific venom proteomes (Pla et al., 2013), with PLA_2 showing the greatest interspecific variability (Sanz et al., 2008). Despite the wealth of low-resolution proteomics and biochemical information available (Table 2) (Bregge--Silva et al., 2012; Damico et al., 2005), the timing and relevance of individual venom proteins and overall venom proteome divergence in the mechanisms of adaptation to local ecosystems and speciation of the Bushmasters remains elusive.

Table 2 lists molecules characterized in *Lachesis* venoms. Most of these proteins are myotoxins, neurotoxins, anticoagulant and antithrombotic PLA_2s, thrombin-like, gyroxin and kallikrein serine proteinases, and hemorrhagic PIII-metalloproteinases, including *L. m. muta* LHF-I and II and a new P-1 class metalloproteinase (Lmr-MP) isolated from the venom of *L. m. rhombeata* venom (Cordeiro et al., 2018). Other toxins, include serine proteinase (LmrSP-4), type C lectin (LmrLEC-1) (Wiezel et al., 2019) and bradykinin-potentiating peptides (Pinheiro-Júnior et al., 2018). However, little is known about the biological roles of these proteins and peptides in the mechanisms underlying *Lachesis* envenoming. Furthermore, there are few superficial investigations on the biotechnological potential of *Lachesis* venom components, with biological activities mainly restricted to hypotensive effect (Diniz et al., 1992; Pinheiro-Júnior et al., 2018), thrombolytic activity (Agero et al., 2007; Rucavado et al., 1999; Sánchez et al., 1991), antimicrobial activity against methicillin-resistant strains of *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* (Diniz-Sousa et al., 2018), and antiparasitic activity against *Leishmania braziliensis* (Bregge-Silva et al., 2012).

4. Concluding remarks and perspectives

Bushmaster are important components of tropical ecosystems. However, our understanding of the details of their natural history, ecology and dietary habits of *Lachesis* taxa in the wild is scarce and limited to only some species of the genus (Campbell and Lamar, 2004; Ripa, 2001; Savage, 2002; Solórzano, 2004; Zamudio and Greene, 1997), and a good number of reports are derived from observations of specimens in captivity (Boyer et al., 2007; Chacón and Valverde, 2004; Corrales et al., 2014; Ripa, 1994; Souza, 2007). This is, in part, due to the challenge of observing these snakes in their natural habitats in remote tropical moist forested areas where, except during breeding activities, bushmasters are solitary crepuscular or nocturnal predators (Campbell and Lamar, 2004). The limited work conducted on bushmaster species suggests these snakes are dependent on several specific resources and are thus particularly susceptible to disturbance. Hence, due to habitat destruction, the population density of *Lachesis* taxa has decreased worryingly to the point that *L. muta. ssp. rhombeata*, which exhibits the broadest range in the Amazon region of Brazil and surrounding countries, is listed as vulnerable according to the IUCN Red List of Threatened Species criteria and considered endangered throughout its range (IUCN, 2000). Habitat loss, pollution and poaching are the main reasons for its decline. At the other extreme, the Atlantic bushmaster L. *m. rhombeata*, a species endemic to Brazil, has a very restricted distribution that is becoming increasingly fragmented through deforestation for using the cleared areas for agriculture and human settlements (Martins and Marques, 2000). Another species, the black-headed bushmaster *L. melanocephala*, inhabits also a very small geographic range, including tropical, premontane and montane humid, very humid, and pluvial forests. The limited work that has been conducted on this bushmaster species suggests that it is particularly susceptible to disturbance (Solórzano, 2004). Due to its restricted geographic range and habitat specificity, the severe and continued loss of lowland and mid-elevation forests throughout its range pose serious threats to the persistence of the endemic black-headed bushmaster in Costa Rica and Panamá (González-Maya et al., 2014). The paucity of information on *L. melanocephala*, which is due in large part to its cryptic nature spending much time underground and its occurrence at low densities, prevents any effective conservation actions for this species.

Omic technologies, including comparative genomics across the reptile phylogeny along with paleogeographic niche reconstruction, can provide important insights into the ecological factor and evolutionary pressures that shaped the explosive diversification of many species-rich clades, including caenophidian snakes, in the wake of the Cretaceous-Paleogene (K-Pg) Mass Extinction 66 Mya, when a massive asteroid struck the Earth, brought a calamitous end to the reign of dinosaurs, and account for the loss of 75 percent of known species (Alvarez et al., 1980; Gulick et al., 2019). The K-Pg global mass extinction event left numerous ecological niches vacant creating new ecological opportunities (Feng et al., 2017; Hsiang et al., 2015; Martill et al., 2015; Pyron and Burbrink, 2012; Skipwith et al., 2019). Although some aspects of the phylogeny of some clades within the medically important snake families Viperidae, Elapidae, and Colubridae are still under dispute, in general, their phylogenetic relationships and time of divergence between lineages are well supported from fossil and molecular (nuclear and mitochondrial gene) information (Alencar et al., 2016; Pyron et al., 2013; Reeder et al., 2015; Zaher et al., 2019). Venom emerged as a key evolutionary innovation that underpinned the explosive radiation of caenophidian snakes. A reliable phylogeny is key to establishing the evolutionary trends that have shaped the patterns of venom across the speciation of a clade of snakes.

An increasing trend in venom analysis is the identification of evolutionary trends across whole genera, taxonomic clades, and phylogenetic families. The overall picture, rather than the individual venom proteomes, provides hints for reconstructing the origin of evolutionary trends (Calvete, 2017, 2013). *Lachesis* represents one of the few snake genus for which the venom proteomes of all its species have been unveiled. Mapping the pattern of present-day venom variability into a phylogenetic and biogeographic framework may lay the foundation for understanding the evolutionary trends that have shaped the venomic landscape across the clade. In addition, the genome also encodes traces from both functionally-failed recombinations and those that passed the natural selection filter and contributed to the functional genome of the species (Kvon et al., 2016; Li et al., 2018; Lind et al., 2019; Pasquesi et al., 2018; Peng et al., 2020; Perry et al., 2018; Reyes-Velasco et al., 2020; Schield et al., 2019). The development of comparative genomics in the last 20 years has taught us that no lineage can be studied genomically in isolation from related lineages. However, despite the genomes of birds and nonavian reptiles will not only uncover a treasure trove of biological information to reconstruct the evolution of venomous reptiles and their venom genes, but are also critical for understanding genome evolution in mammals and amniotes generally (Janes et al., 2010; Tollis et al., 2018, 2014), snake genome sequencing is in its infancy. Squamates exhibit some of the most extreme and fascinating biological adaptations among vertebrates (Shaney et al., 2014). However, genomic resources are currently only available for a handful of squamous reptiles (Alföldi et al., 2011; Castoe et al., 2013; Giorgianni et al., 2020; Green et al., 2014; Kerkkamp et al., 2016; Li et al., 2018; Lind et al., 2019; Peng et al., 2020; Schield et al., 2019; Shibata et al., 2018; Suryamohan et al., 2020; Tollis et al., 2014; Ullate-Agote et al., 2014; Vonk et al., 2013; Yin et al., 2016). Comparative Squamata omics (genomics, transcriptomics, and proteomics) will play a fundamental role in filling this gap and addressing the connection between genome evolution and the present-day adaptive phenotype for fitness related traits (Cenik et al., 2015; Drukewitz and von Reumont, 2019; Eckalbar et al., 2013; Hajirasouliha and Tilgner, 2019).

The wide spectrum of pathological and pathophysiological manifestations of snake envenomings, due to the concerted actions of the unpredictable venom variability across the phylogeny and distribution

Table 2
Main components characterized in venoms of the genus *Lachesis*.

NAME	SPECIE	PROTEIN/PEPTIDE	MOLECULAR MASS (kDa)	BIOLOGICAL PROPERTIES	THERAPEUTIC POTENTIAL	REFERENCES
LmrBPP9	*L. m. rhombeata*	Bradykinin-potentiating peptides (BPP)	1.08	Inhibit ACE activity *in vitro*	Hypotensive effect	Pinheiro-Júnior et al. (2018)
Lmr-MP	*L. m. rhombeata*	Metalloproteinase	22.85	Proteolytic activity on synthetic substrate of human kallikrein	–	Cordeiro et al. (2018)
LmrSP-4	*L. m. rhombeata*	Serine proteinase	28.19	Aα- fibrinogenolytic; Proteolytic activity on synthetic substrate of human kallikrein	–	Wiezel et al. (2019)
LmrLEC-1	*L. m. rhombeata*	C-type lectin	~14	–	–	Wiezel et al. (2019)
LmuTX	*L. m. muta*	PLA_2 Lys-49	13.8	Cytotoxicity on C2C12 cells differentiated in myotubes	Antibacterial activity against strains of MRSA and *Pseudomonas aeruginosa*	Diniz-Sousa et al. (2018)
LmLAAO	*L. muta*	L-amino acid oxidase (LAAO)	60	Without myotoxic activities, hemorrhagic and edematogenic	Cytotoxic activity on AGS and MCF-7 cells; *L. braziliensis* activity	Bregge-Silva et al. (2012)
Stenoxobin	*L. stenophyrs*	Serine proteinase (thrombin-like)	37	α and β- fibrinogenolytic	–	Aragon-Ortiz and Gubensek (1993)
LsPA-1	*L. stenophyrs*	PLA_2 Asp49	13.87	–	–	De Assis et al. (2008)
LmTX-I	*L. m. muta*	Basic PLA_2 Asp49	14.24	Phospholipase activity on synthetic substrates; edema; myotoxicity; neurotoxicity	–	(Damico et al., 2008, 2006, 2005)
LmTX-II	*L. m. muta*	Basic PLA_2 Asp49	14.18	Phospholipase activity on synthetic substrates	–	Damico et al. (2005)
LmrTX	*L. m. rhombeata*	Basic PLA_2 Asp49	14.27	Anticoagulant and antithrombotic activities	–	Damico et al. (2012)
Lmr-PLA_2	*L. m. rhombeata*	Acidic PLA_2 Asp49	13.97	Inhibition of platelet aggregation	–	Cordeiro et al. (2015)
LV-Ka	*L. m. muta*	Serine proteinase (calicreína-símile)	33	Plasminogen activation	–	Felicori et al. (2003)
LM-PLA_2-I	*L. muta*	Acidic PLA_2 Asp49	–	Myotoxicity	–	Fuly et al. (2000)
LM-PLA_2-II	*L. muta*	Acidic PLA_2 Asp49	18	Myotoxicity; inhibition of platelet aggregation; edematogenic activity.	–	(Fuly et al., 2003, 2002)
TLE-B	*L. m. muta*	Serine proteinase	44	α and β- fibrinogenolytic.	–	Magalhaes et al. (2003)
TLB-P	*L. m. muta*	Serine proteinase	43	α and β- fibrinogenolytic.	–	Magalhaes et al. (2003)
Mutalisin I (LHF-I)	*L. m. muta*	Metalloproteinase	100	α and β-fibrinogenolytic; high hemorrhagic activity; caseinolytic activity.	–	(Sanchez et al., 1995, 1987)
Mutalisin II (LHF-II)	*L. m. muta*	Metalloproteinase	22	Degradation of laminin, fibronectin and type IV collagen; edematogenic; low hemorrhagic activity.	Thrombolytic effect	(Agero et al., 2007; Rucavado et al., 1999; Sánchez et al., 1991)
Mut IIa	*L. m. muta*	Mutalisin isoform II	≈23	α and β- fibrinogenolytic; proteolytic activity on dimethylcasein.	–	Sánchez et al. (2003)
Mut IIb	*L. m. muta*	Mutalisin isoform II	≈23	α e β-fibrinogenolítica; proteolytic activity on dimethylcasein.	–	Sánchez et al. (2003)
Hyaluronidase	*L. m. rhombeata*	Hyaluronidase	60	–	–	Wiezel et al. (2015)
PLB	*L. m. rhombeata*	Phospholipase B	–	–	–	Wiezel et al. (2015)
LMR-47	*L. m. rhombeata*	Serine proteinase (gyroxin)	47	α - fibrinogenolytic	–	Aguiar et al. (1996)
Protein similar to lectin	*L. stenophyrs*	Lectin	16.2	Hemagglutination	–	(Aragón-Ortiz et al., 1996; Aragón-Ortíz et al., 1989)
Lachesin	*L. muta*	Disintegrin	–	Inhibition of platelet aggregation; binding to integrin αIIbβ3	–	Scarborough et al. (1993)
LSF	*L. stenophyrs*	Metalloproteinase	24	–	–	Leonardi et al. (1999)
Serine proteinase	*L. m. muta*	Serine proteinase	45	–	–	Magalhães et al. (1997)
Kininogenin	*L. muta*	Serine proteinase	29.7		Hypotensive effect	Diniz et al. (1992)
Gyroxin	*L. m. muta*	Serine proteinase	≈60	High lethality	–	da Silva et al. (1989)
Thrombin-like	*L. m. muta*	Serine proteinase	≈41-47	Fibrinogenolytic	–	Silveira et al. (1989)
Serine proteinase	*L. m. muta*	Serine proteinase	40	α and β- fibrinogenolytic	–	Yarleque et al. (1989)
Arginine esterase	*L. muta*	–	≈30	Arginyl esterase activity	–	Silva et al. (1985)
BIP	*L. muta*	Bradykinin inhibitor	1.06	Inhibitory activity on bradykinin via B2 receptors	–	Graham et al. (2005)
βPLIs	*L. muta*	Beta-type inhibitors PLA_2s	36.5	–	–	Lima et al. (2011)
LNF1 and LNF2	*L. m. muta*	Gamma-type inhibitors PLA_2s	≈20	–	–	Fortes-Dias et al. (2003)
	L. m. muta	Serine proteinase	25.6	–	–	Magalhaes et al. (1993)

(*continued on next page*)

Table 2 (*continued*)

NAME	SPECIE	PROTEIN/PEPTIDE	MOLECULAR MASS (kDa)	BIOLOGICAL PROPERTIES	THERAPEUTIC POTENTIAL	REFERENCES
Thrombin-like/ analogous to gyroxin						
LV-PA	*L. m. muta*	Serine proteinase	33	Plasminogen activation	–	(Sanchez et al., 2006, 2000)
Lm-BPP 1 to 5 and Lm-CNP	*L. muta*	BPPs and C-type natriuretic peptides	1 a 2.2	–	–	Soares et al. (2005)

range of extant snakes, represents a great challenge for the development, and preclinical evaluation of the efficacy of antivenoms. From a biotechnological stand point, this goal requires knowing the phylogeographical patterns of present-day snake venoms, identifying their most medically-important molecules in the context of a human envenoming, and assessing the specific and para-specific efficacy of current antivenoms against the different medically relevant snake venoms. For the case of genus *Lachesis,* the high conservation of the overall composition of Central and South American bushmaster venoms provides the ground for rationalizing the "*Lachesis syndrome*" documented in envenomings by different species of this wide-ranging genus. From an evolutionary ecology perspective legitimate human snake envenomings result from defensive bites inflicted by sympatric venomous snakes when snake and human have a fortuitous encounter in their shared natural environment that blows the snake's alarms. In this context, knowledge gained on the natural history and organismal physiology of medically important snakes, particularly those that prey on mammals, have conceptually applicability in clinical toxinology as in the ecological context, highlighting the mutually enlightening relationship between evolutionary and translational venomics (Calvete, 2019).

Clearly, we believe that it is not an exaggeration to conclude that our field, molecular toxinology, has a very exciting future ahead. We trust this short review on the bushmasters may help to put this genus of medically and ecologically relevant snakes in the spotlight of near future basic and applied developments.

Credit author statement

Rafaela Diniz-Sousa: Conceptualization, Writing, Data curation and Formal analysis, Editing, Jeane do N. Moraes: Writing, Data curation and Formal analysis, Tainara M. Rodrigues-da-Silva: Writing, Data curation and Formal analysis, Cláudia S. Oliveira: Writing, Cleópatra A. da S. Caldeira: Conceptualization, Writing, Data curation and Formal analysis, Editing.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Abalos, J.W., 1977. Que sabe usted de viboras?, Losada. Buenos Aires.
Agero, U., Arantes, R.M.E., Lacerda-Queiroz, N., Mesquita, O.N., Magalhães, A., Sanchez, E.F., Carvalho-Tavares, J., 2007. Effect of mutalysin II on vascular recanalization after thrombosis induction in the ear of the hairless mice model. Toxicon 50, 698–706. https://doi.org/10.1016/j.toxicon.2007.06.003.
Aguiar, A.S., Alves, C.R., Melgarejo, A., Giovanni-De-Simone, S., 1996. Purification and partial characterization of a thrombin-like/gyroxin enzyme from bushmaster *Lachesis muta rhombeata* venom. Toxicon 34, 555–565. https://doi.org/10.1016/0041-0101(95)00159-X.
Alape-Girón, A., Sanz, L., Escolano, J., Flores-Díaz, M., Madrigal, M., Sasa, M., Calvete, J. J., 2008. Snake venomics of the lancehead pitviper bothrops asper. Geographic, individual, and ontogenetic variations. J. Proteome Res. 7, 3556–3571. https://doi.org/10.1021/pr800332p.
Alencar, L.R.V., Quental, T.B., Grazziotin, F.G., Alfaro, M.L., Martins, M., Venzon, M., Zaher, H., 2016. Diversification in vipers: phylogenetic relationships, time of divergence and shifts in speciation rates. Mol. Phylogenet. Evol. 105, 50–62. https://doi.org/10.1016/j.ympev.2016.07.029.
Alföldi, J., Di Palma, F., Grabherr, M., Williams, C., Kong, L., Mauceli, E., Russell, P., Lowe, C.B., Glor, R.E., Jaffe, J.D., Ray, D.A., Boissinot, S., Shedlock, A.M., Botka, C., Castoe, T.A., Colbourne, J.K., Fujita, M.K., Moreno, R.G., Ten Hallers, B.F., Haussler, D., Heger, A., Heiman, D., Janes, D.E., Johnson, J., De Jong, P.J., Koriabine, M.Y., Lara, M., Novick, P.A., Organ, C.L., Peach, S.E., Poe, S., Pollock, D. D., De Queiroz, K., Sanger, T., Searle, S., Smith, J.D., Smith, Z., Swofford, R., Turner-Maier, J., Wade, J., Young, S., Zadissa, A., Edwards, S.V., Glenn, T.C., Schneider, C. J., Losos, J.B., Lander, E.S., Breen, M., Ponting, C.P., Lindblad-Toh, K., 2011. The genome of the green anole lizard and a comparative analysis with birds and mammals. Nature 477, 1–5. https://doi.org/10.1038/nature10390.
Alvarez, L.W., Alvarez, W., Asaro, F., Michel, H.V., 1980. Extraterrestrial cause for the Cretaceous-Tertiary extinction. Science 208, 1095–1108. https://doi.org/10.1126/science.208.4448.1095.
Andrade, D.V., Abe, A.S., 1999. Relationship of venom ontogeny and diet in. Bothrops. Herpetologica.
Aragón-Ortíz, F., Brenes-Brenes, J.R., Gubensek, F., 1989. Characterization of a lectin-like protein isolated from *Lachesis muta* snake venom. Rev. Biol. Trop. 37, 79–83.
Aragon-Ortiz, F., Gubensek, F., 1993. A thrombin-like enzyme from bushmaster (*Lachesis muta stenophyrs*) venom. Toxicon 31, 1435–1443. https://doi.org/10.1016/0041-0101(93)90209-2.
Aragón-Ortiz, F., Mentele, R., Auerswald, E.A., 1996. Amino acid sequence of a lectin-like protein from *Lachesis muta stenophyrs* venom. Toxicon 34, 763–769. https://doi.org/10.1016/0041-0101(96)00011-6.
Barlow, A., Pook, C.E., Harrison, R.A., Wüster, W., 2009. Coevolution of diet and prey-specific venom activity supports the role of selection in snake venom evolution. Proc. Biol. Sci. 276, 2443–2449. https://doi.org/10.1098/rspb.2009.0048.
Barua, A., Mikheyev, A.S., 2019. Many Options, Few Solutions: Over 60 My Snakes Converged on a Few Optimal Venom Formulations. Mol. Biol. Evol. 36, 1964–1974. https://doi.org/10.1093/molbev/msz125.
Beebe, C.W., 1946. Field notes on the snakes of kartabo, British Guiana, and caripito, Venezuela. Zoologica (N. Y.) 31, 11–52.
Bellairs, A., 1969. The life of reptiles. London.
Bernarde, P.S., 2014. Serpentes Peçonhentas e Acidentes Ofídicos no Brasil. Anolis Books, São Paulo.
Bolaños, R., 1972. Toxicity of Costa Rican snake venoms for the white mouse. Am. J. Trop. Med. Hyg. 21, 360–363. https://doi.org/10.4269/ajtmh.1972.21.360.

Boyer, D.M., Mitchell, L.A., Murphy, J.B., 2007. Reproduction and husbandry of the bushmaster *Lachesis m. muta* at the dallas Zoo. Int. Zoo Yearbk. 28, 190–194. https://doi.org/10.1111/j.1748-1090.1989.tb03279.x.

Brasil, 1996. Ministério da Saúde. Normas de Produção e controle de Qualidade de Soros Antiofídicos. Diário Oficial da União 23491–23512.

Brasil, M. da S., 2001. Manual de diagnóstico e tratamento de acidentes ofídicos. Brasília: fundação Nacional de Saúde, Coordenação de Controle de Zoonoses e Animais Peçonhentos [WWW Document]. URL. https://bvsms.saude.gov.br/bvs/publicacoes/funasa/manu_peconhentos.pdf.

Bregge-Silva, C., Nonato, M.C., de Albuquerque, S., Ho, P.L., Junqueira de Azevedo, I.L. M., Vasconcelos Diniz, M.R., Lomonte, B., Rucavado, A., Díaz, C., Gutiérrez, J.M., Arantes, E.C., 2012. Isolation and biochemical, functional and structural characterization of a novel l-amino acid oxidase from *Lachesis muta* snake venom. Toxicon 60, 1263–1276. https://doi.org/10.1016/j.toxicon.2012.08.008.

Brown, J.H., 1973. Toxicology and Pharmacology of Venoms from Poisonous Snakes. Thomas, Springfield.

Calvete, J.J., 2017. Venomics: integrative venom proteomics and beyond. Biochem. J. https://doi.org/10.1042/BCJ20160577.

Calvete, J.J., 2013. Snake venomics: from the inventory of toxins to biology. Toxicon 75, 44–62. https://doi.org/10.1016/j.toxicon.2013.03.020.

Calvete, Juan J., 2019. Snake venomics at the crossroads between ecological and clinical toxinology. Biochemist 41 (6), 28–33. https://doi.org/10.1042/BIO04106028.

Calvete, J.J., Gutiérrez, J.M., Sanz, L., Pla, D., Lomonte, B., 2013. Antivenomics: a proteomics tool for studying the immunoreactivity of antivenoms, in: analyzing biomolecular interactions by mass spectrometry. https://doi.org/10.1002/9783527673391.ch7.

Calvete, J.J., Rodríguez, Y., Quesada-Bernat, S., Pla, D., 2018. Toxin-resolved antivenomics-guided assessment of the immunorecognition landscape of antivenoms. Toxicon 148, 107–122. https://doi.org/10.1016/j.toxicon.2018.04.015.

Calvete, J.J., Sanz, L., Cid, P., De La Torre, P., Flores-Díaz, M., Dos Santos, M.C., Borges, A., Bremo, A., Angulo, Y., Lomonte, B., Alape-Girón, A., Gutiérrez, J.M., 2010. Snake venomics of the Central American Rattlesnake *Crotalus simus* and the South American *Crotalus durissus* complex points to neurotoxicity as an adaptive paedomorphic trend along Crotalus dispersal in South America. J. Proteome Res. 9, 528–544. https://doi.org/10.1021/pr9008749.

Calvete, J.J., Sanz, L., Pérez, A., Borges, A., Vargas, A.M., Lomonte, B., Angulo, Y., Gutiérrez, J.M., Chalkidis, H.M., Mourão, R.H.V., Furtado, M.F.D., Moura-Da-Silva, A.M., 2011. Snake population venomics and antivenomics of *Bothrops atrox*: paedomorphism along its transamazonian dispersal and implications of geographic venom variability on snakebite management. Journal of proteomics 74, 510–527. https://doi.org/10.1016/j.jprot.2011.01.003.

Calvete, J.J., Sanz, L., Pla, D., Lomonte, B., Gutiérrez, J., Calvete, J.J., Sanz, L., Pla, D., Lomonte, B., Gutiérrez, J.M., 2014. Omics meets biology: application to the design and preclinical assessment of antivenoms. Toxins 6, 3388–3405. https://doi.org/10.3390/toxins6123388.

Campbell, J.A., Lamar, W.W., 2004. The venomous reptiles of the western Hemisphere. Comstock publishing associates, ithaca and london. https://doi.org/10.1016/j.trstmh.2004.12.002.

Carrasco, P.A., Venegas, P.J., Chaparro, J.C., Scrocchi, G.J., 2016. Nomenclatural instability in the venomous snakes of the *Bothrops* complex: implications in toxinology and public health. Toxicon 119, 122–128. https://doi.org/10.1016/j.toxicon.2016.05.014.

Carrier, D.R., 1996. Ontogenetic limits on locomotor performance. Physiol. Zool. 69, 467–488. https://doi.org/10.1086/physzool.69.3.30164211.

Carrillo de Espinoza, N., 1970. Contribución al conocimiento de los reptiles del Perú (Squamata, Crocodylia, Testudinata: reptilia). Publicaciones del Museo de Historia Natural 'Javier Prado", Serie A. Zool. 22, 1–64.

Castoe, T. a, de Koning, a P.J., Hall, K.T., Card, D.C., Schield, D.R., Fujita, M.K., Ruggiero, R.P., Degner, J.F., Daza, J.M., Gu, W., Reyes-Velasco, J., Shaney, K.J., Castoe, J.M., Fox, S.E., Poole, A.W., Polanco, D., Dobry, J., Vandewege, M.W., Li, Q., Schott, R.K., Kapusta, A., Minx, P., Feschotte, C., Uetz, P., Ray, D. a, Hoffmann, F.G., Bogden, R., Smith, E.N., Chang, B.S.W., Vonk, F.J., Casewell, N.R., Henkel, C.V., Richardson, M.K., Mackessy, S.P., Bronikowski, A.M., Bronikowsi, A.M., Yandell, M., Warren, W.C., Secor, S.M., Pollock, D.D., 2013. The Burmese python genome reveals the molecular basis for extreme adaptation in snakes. In: Proceedings of the National Academy of Sciences of the United States of America, vol. 110, pp. 20645–20650. https://doi.org/10.1073/pnas.1314475110.

Cenik, C., Cenik, E.S., Byeon, G.W., Grubert, F., Candille, S.I., Spacek, D., Alsallakh, B., Tilgner, H., Araya, C.L., Tang, H., Ricci, E., Snyder, M.P., 2015. Integrative analysis of RNA, translation, and protein levels reveals distinct regulatory variation across humans. Genome Res. 25, 1610–1621. https://doi.org/10.1101/gr.193342.115.

Chacón, D., Valverde, R., 2004. *Lachesis stenophrys* (bushmaster) reproduction. Herpetol. Rev. 35–68.

Chaves, F., Gutiérrez, J., Brenes, F., 1992. Pathological and biochemical changes induced in mice after intramuscular injection of venom from newborn specimens of the snake *Bothrops asper* (Terciopelo). Toxicon 30, 1099–1109. https://doi.org/10.1016/0041-0101(92)90055-A.

Chippaux, J.-P., Massougbodji, A., Habib, A.G., 2019. The WHO strategy for prevention and control of snakebite envenoming: a sub-Saharan Africa plan. J. Venom. Anim. Toxins Incl. Trop. Dis. 25 https://doi.org/10.1590/1678-9199-jvatitd-2019-0083.

Chippaux, J., 1998. Snake-bites: Appraisal of the Global Situation.

Chippaux, J.P., 2017. Snakebite envenomation turns again into a neglected tropical disease! J. Venom. Anim. Toxins Incl. Trop. Dis. 23, 1–2. https://doi.org/10.1186/s40409-017-0127-6.

Cope, E.D., 1975. On the Batrachia and Reptilia of Costa Rica: with Notes on the Herpetology and Ichthyology of Nicaragua and Peru. Palala Press.

Cordeiro, F.A., Marques Coutinho, B., Wiezel, G.A., De Castro, K., Bordon, F., Bregge-Silva, C., Gonsales Rosa-Garzon, N., Cabral, H., Ueberheide, B., Arantes, E.C., 2018. Purification and enzymatic characterization of a novel metalloprotease from *Lachesis muta rhombeata* snake venom. J. Venom. Anim. Toxins Incl. Trop. Dis. 24, 1–11. https://doi.org/10.1186/s40409-018-0171-x.

Cordeiro, F.A., Perini, T.G.K., Bregge-Silva, C., Cremonez, C.M., Rodrigues, R.S., Boldrini-França, J., Bordon, K., Souza, de C.F., Ache, D.L.N., Rodrigues, D.C., Santos, V. de M., dos, W.F., Rosa, J.C., Arantesa, E.C., 2015. A new phospholipase A_2 from *Lachesis muta rhombeata*: purification, biochemical and comparative characterization with crotoxin B. Protein Pept. Lett. 22, 816–827. https://doi.org/10.2174/0929866522666150706112431.

Corrales, G., Meidinger, R., Rodríguez, S., Chacón, D., Gómez, A., 2014. Reproduction in captivity of the central American bushmaster (*Lachesis stenophrys*, serpentes: Viperidae), in Costa Rica. Cuad. Herpetol. 28, 137–139. https://doi.org/10.31017/2408.

Cunha, O.R., Nascimento, F.P., 1993. Ofídios da Amazônia. As cobras da região leste do Pará. Papéis Avulsos Museu Paraense Emílio Goeldi. Zool. 9, 1–191.

da Silva, A.M., Colombini, M., Moura-Da-Silva, A.M., de SOUZA, R.M., Monteiro, W.M., Bernarde, P.S., 2020. Epidemiological and clinical aspects of snakebites in the upper juruá river region, western Brazilian Amazonia. Acta Amazonica 50, 90–99. https://doi.org/10.1590/1809-4392201901561.

da Silva, N.J., Aird, S.D., Seebart, C., Kaiser, I.I., 1989. A gyroxin analog from the venom of the bushmaster (*Lachesis muta muta*). Toxicon 27, 763–771. https://doi.org/10.1016/0041-0101(89)90043-3.

Daltry, J.C., Wüster, W., Thorpe, R.S., 1996. Diet and snake venom variation. Nature.

Damico, D.C.S., Bueno, L.G.F., Rodrigues-Simioni, L., Marangoni, S., da Cruz-Höfling, M. A., Novello, J.C., 2006. Functional characterization of a basic D49 phospholipase A_2 (LmTX-I) from the venom of the snake *Lachesis muta muta* (Bushmaster). Toxicon 47, 759–765. https://doi.org/10.1016/j.toxicon.2006.02.007.

Damico, D.C.S., Da Cruz Höfling, M.A., Cintra, M., Leonardo, M.B., Calgarotto, A.K., Da Silva, S.L., Marangoni, S., 2008. Pharmacological study of edema and myonecrosis in mice induced by venom of the bushmaster snake (*Lachesis muta muta*) and its basic Asp49 phospholipase A2 (LmTX-I). Protein J. 27, 384–391. https://doi.org/10.1007/s10930-008-9148-x.

Damico, D.C.S., Lilla, S., De Nucci, G., Ponce-Soto, L.A., Winck, F.V., Novello, J.C., Marangoni, S., 2005. Biochemical and enzymatic characterization of two basic Asp49 phospholipase A_2 isoforms from *Lachesis muta muta* (Surucucu) venom. Biochim. Biophys. Acta Gen. Subj. 1726, 75–86. https://doi.org/10.1016/j.bbagen.2005.05.022.

Damico, D.C.S., Vassequi-Silva, T., Torres-Huaco, F.D., Nery-Diez, A.C.C., de Souza, R.C. G., Da Silva, S.L., Vicente, C.P., Mendes, C.B., Antunes, E., Werneck, C.C., Marangoni, S., 2012. LmrTX, a basic PLA_2 (D49) purified from *Lachesis muta rhombeata* snake venom with enzymatic-related antithrombotic and anticoagulant activity. Toxicon 60, 773–781. https://doi.org/10.1016/j.toxicon.2012.06.010.

Daniel Fuentes, R., Corrales, G., 2016. New distribution record and reproductive data for the chocoan bushmaster, *Lachesis acrochorda* (serpentes: Viperidae), in Panama. Mesoamerican Herpetology 115, 114–127.

Daudin, F.M., 1803. Histoire naturelle générale et particulière des reptiles. In: Dufart, F. (Ed.), De l'Imprimerie de F. Dufart. https://doi.org/10.5962/bhl.title.60678. Paris.

Davies, E.L., Arbuckle, K., 2019. Coevolution of snake venom toxic activities and diet: evidence that ecological generalism favours toxicological diversity. Toxins 11, 1–14. https://doi.org/10.3390/toxins11120711.

De Assis, E.B., Estevão-Costa, M.I., Do Carmo Valentim, A., Silva-Neto, A., Agostini Cotta, G., Alvarenga Mudado, M., Richardson, M., Fortes-Dias, C.L., 2008. Purification and complete primary structure of the first PLA2 from *Lachesis stenophrys* (the Central American Bushmaster) snake venom. Protein J. 27, 327–333. https://doi.org/10.1007/s10930-008-9141-4.

de Lima, P.H.S., Junior, V.H., 2015. A snakebite caused by a bushmaster *(Lachesis muta)*: report of a confirmed case in state of Pernambuco, Brazil. Rev. Soc. Bras. Med. Trop. 48, 636–637. https://doi.org/10.1590/0037-8682-0143-2015.

Diniz-Sousa, R., Caldeira, C.A.S., Kayano, A.M., Paloschi, M.V., Pimenta, D.C., Simões-Silva, R., Ferreira, A.S., Zanchi, F.B., Matos, N.B., Grabner, F.P., Calderon, L.A., Zuliani, J.P., Soares, A.M., 2018. Identification of the molecular determinants of the antibacterial activity of LmutTX, a Lys49 phospholipase A_2 homologue isolated from Lachesis muta muta snake venom (linnaeus, 1766). Basic Clin. Pharmacol. Toxicol. 122, 413–423. https://doi.org/10.1111/bcpt.12921.

Diniz, M.R.V., Oliveira, E.B., 1992. Purification and properties of a kininogenin from the venom of *Lachesis muta* (bushmaster), 30, 247–258.

Ditmars, R.L., 1937. Snakes of the World. Macmillan, New York.

Ditmars, R.L., 1910. Reptiles of the World tortoises and turtles, crocodilians, lizards, and snakes of the eastern and western hemispheres. Sturgis and walton, 373.

Drukewitz, S.H., von Reumont, B.M., 2019. The significance of comparative genomics in modern evolutionary venomics. Frontiers in Ecology and Evolution 7 (163). https://doi.org/10.3389/fevo.2019.00163.

Dunn, E.R., 1951. Venomous reptiles of the tropics. In: Shattuck. Diseases of the Tropics. Appleton-Century-Crofts, pp. 741–754.

Durban, J., Pérez, A., Sanz, L., Gómez, A., Bonilla, F., Rodríguez, S., Chacón, D., Sasa, M., Angulo, Y., Gutiérrez, J.M., Calvete, J.J., 2013. Integrated "omics" profiling indicates that miRNAs are modulators of the ontogenetic venom composition shift in the Central American rattlesnake, Crotalus simus simus. BMC Genomics 14. https://doi.org/10.1186/1471-2164-14-234.

Eckalbar, W.L., Hutchins, E.D., Markov, G.J., Allen, A.N., Corneveaux, J.J., Lindblad-Toh, K., Di Palma, F., Alföldi, J., Huentelman, M.J., Kusumi, K., 2013. Genome

reannotation of the lizard Anolis carolinensis based on 14 adult and embryonic deep transcriptomes. BMC Genom. 14 (49) https://doi.org/10.1186/1471-2164-14-49.
Emsley, M., 1977. Snakes, and Trinidad and Tobago. Marylad Herpetol. Soc. 13, 201–304.
Feitosa, E.S., Sampaio, V., Sachett, J., De Castro, D.B., Noronha, M., das, D.N., Lozano, J. L.L., Muniz, E., De Ferreira, L.C.L., De Lacerda, M.V.G., Monteiro, W.M., 2015. Snakebites as a largely neglected problem in the brazilian Amazon: highlights of the epidemiological trends in the state of Amazonas. Rev. Soc. Bras. Med. Trop. 48, 34–41. https://doi.org/10.1590/0037-8682-0105-2013.
Felicori, L.F., Souza, C.T., Velarde, D.T., Magalhaes, A., Almeida, A.P., Figueiredo, S., Richardson, M., Diniz, C.R., Sanchez, E.F., 2003. Kallikrein-like proteinase from bushmaster snake venom. Protein Expr. Purif. 30, 32–42. https://doi.org/10.1016/S1046-5928(03)00053-6.
Feng, Y.J., Blackburn, D.C., Liang, D., Hillis, D.M., Wake, D.B., Cannatella, D.C., Zhang, P., 2017. Phylogenomics reveals rapid, simultaneous diversification of three major clades of Gondwanan frogs at the Cretaceous–Paleogene boundary. Proc. Nat. Acad. Sci. U. S. A 114, E5864–E5870. https://doi.org/10.1073/pnas.1704632114.
Fernandes, D.S., Franco, F.L., Fernandes, R., 2004. Systematic revision of the genus *Lachesis* daudin, 1803 (serpentes, Viperidae). Herpetologica 60, 245–260. https://doi.org/10.1655/02-85.
Flannagan, J.P., Harwell, G.M., 1983. Pathobiology and Management of Chronic Regurgitation in Snakes. In: Fowler, M.E. (Ed.). Proc. Am. Assoc. Zoo Vet. Am. Assoc. Zoo Vet., Tampa, FL, p. 208.
Fonseca, F., 1949. Empresa Gráfica da Revista dos Tribunais, São Paulo. In: Animais peçonhentos, Paulo, São (Eds.).
Fortes-Dias, C.L., Barcellos, C.J., Estevão-Costa, M.I., 2003. Molecular cloning of a γ-phospholipase A_2 inhibitor from *Lachesis muta muta* (the bushmaster snake). Toxicon 41, 909–917. https://doi.org/10.1016/S0041-0101(03)00073-4.
Fountain, P., 1902. The Great Mountains and Forest of South America. Longmans, Green, London, p. 360.
Fuly, A.L., Calil-Elias, S., Martinez, A.M.B., Melo, P.A., Guimarães, J.A., 2003. Myotoxicity induced by an acidic Asp-49 phospholipase A_2 isolated from *Lachesis muta* snake venom: comparison with lysophosphatidylcholine. Int. J. Biochem. Cell Biol. 35, 1470–1481. https://doi.org/10.1016/S1357-2725(03)00129-8.
Fuly, A.L., Calil-Elias, S., Zingali, R.B., Guimarães, J.A., Melo, P.A., 2000. Myotoxic activity of an acidic phospholipase A_2 isolated from *Lachesis muta* (Bushmaster) snake venom. Toxicon 38, 961–972. https://doi.org/10.1016/S0041-0101(99)00208-1.
Fuly, A.L., De Miranda, A.L.P., Zingali, R.B., Guimarães, J.A., 2002. Purification and characterization of a phospholipase A_2 isoenzyme isolated from *Lachesis muta snake* venom. Biochem. Pharmacol. 63, 1589–1597. https://doi.org/10.1016/S0006-2952(02)00873-0.
Garcia, E., 1896. Los ofidios venenosos del Cauca: métodos empíricos y racionales empleados contra los accidentes producidos por la mordedura de esos reptiles. Cali.
Gibbs, H.L., Sanz, L., Chiucchi, J.E., Farrell, T.M., Calvete, J.J., 2011. Proteomic analysis of ontogenetic and diet-related changes in venom composition of juvenile and adult Dusky Pigmy rattlesnakes (Sistrurus miliarius barbouri). Journal of Proteomics 74, 2169–2179. https://doi.org/10.1016/j.jprot.2011.06.013.
Giorgianni, M.W., Dowell, N.L., Griffin, S., Kassner, V.A., Selegue, J.E., Carroll, S.B., 2020. The origin and diversification of a novel protein family in venomous snakes. Proc. Natl. Acad. Sci. Unit. States Am. 201920011 https://doi.org/10.1073/pnas.1920011117.
Gonçalves-Machado, L., Pla, D., Sanz, L., Jorge, R.J.B., Leitão-De-Araújo, M., Alves, M.L. M., Alvares, D.J., De Miranda, J., Nowatzki, J., de Morais-Zani, K., Fernandes, W., Tanaka-Azevedo, A.M., Fernández, J., Zingali, R.B., Gutiérrez, J.M., Corrêa-Netto, C., Calvete, J.J., 2016. Combined venomics, venom gland transcriptomics, bioactivities, and antivenomics of two *Bothrops jararaca* populations from geographic isolated regions within the Brazilian Atlantic rainforest. Journal of Proteomics 135, 73–89. https://doi.org/10.1016/j.jprot.2015.04.029.
González-Maya, J.F., Castañeda, F., González, R., Pacheco, J., Ceballos, G., 2014. Distribution, range extension, and conservation of the endemic black-headed bushmaster (*Lachesis melanocephala*) in Costa Rica and Panama. Herpetol. Conserv. Biol. 9, 369–377.
Graham, R.L.J., Graham, C., McClean, S., Chen, T., O'Rourke, M., Hirst, D., Theakston, D., Shaw, C., 2005. Identification and functional analysis of a novel bradykinin inhibitory peptide in the venoms of New World Crotalinae pit vipers. Biochem. Biophys. Res. Commun. 338, 1587–1592. https://doi.org/10.1016/j.bbrc.2005.10.130.
Green, R.E., Braun, E.L., Armstrong, J., Earl, D., Nguyen, N., Hickey, G., Vandewege, M. W., St John, J.A., Capella-Gutiérrez, S., Castoe, T.A., Kern, C., Fujita, M.K., Opazo, J. C., Jurka, J., Kojima, K.K., Caballero, J., Hubley, R.M., Smit, A.F., Platt, R.N., Lavoie, C.A., Ramakodi, M.P., Finger, J.W., Suh, A., Isberg, S.R., Miles, L., Chong, A. Y., Jaratlerdsiri, W., Gongora, J., Moran, C., Iriarte, A., McCormack, J., Burgess, S.C., Edwards, S.V., Lyons, E., Williams, C., Breen, M., Howard, J.T., Gresham, C.R., Peterson, D.G., Schmitz, J., Pollock, D.D., Haussler, D., Triplett, E.W., Zhang, G., Irie, N., Jarvis, E.D., Brochu, C.A., Schmidt, C.J., McCarthy, F.M., Faircloth, B.C., Hoffmann, F.G., Glenn, T.C., Gabaldón, T., Paten, B., Ray, D.A., 2014. Three crocodilian genomes reveal ancestral patterns of evolution among archosaurs. Science 346. https://doi.org/10.1126/science.1254449.
Guércio, R. a P., Shevchenko, A.A., Shevchenko, A.A., López-Lozano, J.L., Paba, J., Sousa, M.V., Ricart, C. a O., 2006. Ontogenetic variations in the venom proteome of the Amazonian snake *Bothrops atrox*. Proteome Sci. 4 (11) https://doi.org/10.1186/1477-5956-4-11.
Gulick, S.P.S., Bralower, T.J., Ormö, J., Hall, B., Grice, K., Schaefer, B., Lyons, S., Freeman, K.H., Morgan, J.V., Artemieva, N., Kaskes, P., De Graaff, S.J., Whalen, M. T., Collins, G.S., Tikoo, S.M., Verhagen, C., Christeson, G.L., Claeys, P., Coolen, M.J. L., Goderis, S., Goto, K., Grieve, R.A.F., McCall, N., Osinski, G.R., Rae, A.S.P., Riller, U., Smit, J., Vajda, V., Wittmann, A., 2019. The first day of the Cenozoic. Proc. Nat. Acad. Sci. U. S. A 116, 19342–19351. https://doi.org/10.1073/pnas.1909479116.
Gutiérrez, Burnouf, T., Harrison, R.A., Calvete, J.J., Kuch, U., Warrell, D.A., David, Williams, J., 2014. A multicomponent strategy to improve the availability of antivenom for treating snakebite envenoming. Bull. World Health Organ. https://doi.org/10.2471/BLT.13.132431.
Gutiérrez, J., Avila, C., Camacho, Z., Lomonte, B., 1990. Ontogenetic changes in the venom of the snake *Lachesis muta stenophrys* (Bushmaster) from Costa Rica. Toxicon 28, 419–426. https://doi.org/10.1016/0041-0101(90)90080-Q.
Gutiérrez, J.M., 2014. Reducing the impact of snakebite envenoming in Latin America and the Caribbean: achievements and challenges ahead. Trans. R. Soc. Trop. Med. Hyg. 108, 530–537. https://doi.org/10.1093/trstmh/tru102.
Gutiérrez, J.M., Calvete, J.J., Habib, A.G., Harrison, R.A., Williams, D.J., Warrell, D.A., 2017. Snakebite envenoming. Nature Reviews Disease Primers 3 (17063). https://doi.org/10.1038/nrdp.2017.63.
Gutiérrez, J.M., Chaves, F., Bolaños, R., 1980. Estudio comparativo de venenos de ejemplares recien nacidos y adultos de *Bothrops asper*. Rev. Biol. Trop. 28, 341–351.
Gutiérrez, J.M., Fan, H.W., 2018. Improving the control of snakebite envenomation in Latin America and the Caribbean: a discussion on pending issues. Trans. R. Soc. Trop. Med. Hyg. 112, 523–526. https://doi.org/10.1093/TRSTMH/TRY104.
Gutiérrez, J.M., León, G., Burnouf, T., 2011a. Antivenoms for the treatment of snakebite envenomings: the road ahead. Biologicals. https://doi.org/10.1016/j.biologicals.2011.02.005.
Gutiérrez, J.M., León, G., Lomonte, B., Angulo, Y., 2011b. Antivenoms for snakebite envenomings. Inflamm. Allergy - Drug Targets 10, 369–380.
Hajirasouliha, I., Tilgner, H.U., 2019. The tech for the next decade: promises and challenges in genome biology, in: genome Biology. BioMed Central Ltd., p. 86. https://doi.org/10.1186/s13059-019-1695-2.
Hoge, A.R., Lancini, A.R., 1962. Sinopsis de las serpientes venenosas de Venezuela. Publicaciones Ocasionales del Museo de Ciencias Naturales. Caracas (Zool.) 1, 1–24.
Hsiang, A.Y., Field, D.J., Webster, T.H., Behlke, A.D.B., Davis, M.B., Racicot, R.A., Gauthier, J.A., 2015. The origin of snakes: revealing the ecology, behavior, and evolutionary history of early snakes using genomics, phenomics, and the fossil record. BMC Evol. Biol. 15 (87) https://doi.org/10.1186/s12862-015-0358-5.
Iucn, 2000. Red list: Lachesis muta ssp. rhombeata [WWW document]. IUCN red list. URLaccessed 6.24.2020. https://www.iucnredlist.org/species/39903/10281034.
Jackson, A.C., Rundle, S.D., Attrill, M.J., Cotton, P.A., 2004. Ontogenetic changes in metabolism may determine diet shifts for a sit-and-wait predator. J. Anim. Ecol. 73, 536–545. https://doi.org/10.1111/j.0021-8790.2004.00831.x.
Janes, D.E., Organ, C.L., Fujita, M.K., Shedlock, A.M., Edwards, S.V., 2010. Genome evolution in reptilia, the sister group of mammals. Annu. Rev. Genomics hum. For. Genet. 11, 239–264. https://doi.org/10.1146/annurev-genom-082509-141646.
Junqueira-de-Azevedo, I.L.M., Ching, A.T.C., Carvalho, E., Faria, F., Nishiyama, M.Y., Ho, P.L., Diniz, M.R.V., 2006. *Lachesis muta* (Viperidae) cDNAs reveal diverging pit viper molecules and scaffolds typical of cobra (Elapidae) venoms: implications for snake toxin repertoire evolution. Genetics 173, 877–889. https://doi.org/10.1534/genetics.106.056515.
Kerkkamp, H., Kini, R., Pospelov, A., Vonk, F., Henkel, C., Richardson, M., 2016. Snake genome sequencing: results and future prospects. Toxins 8 (360). https://doi.org/10.3390/toxins8120360.
Kvon, E.Z., Kamneva, O.K., Melo, U.S., Barozzi, I., Osterwalder, M., Mannion, B.J., Tissières, V., Pickle, C.S., Plajzer-Frick, I., Lee, E.A., Kato, M., Garvin, T.H., Akiyama, J.A., Afzal, V., Lopez-Rios, J., Rubin, E.M., Dickel, D.E., Pennacchio, L.A., Visel, A., 2016. Progressive loss of function in a limb enhancer during snake evolution. Cell 167, 633–642. https://doi.org/10.1016/j.cell.2016.09.028 e11.
Lauridsen, L.P., Laustsen, A.H., Lomonte, B., Gutiérrez, J.M., 2016. Toxicovenomics and antivenom profiling of the Eastern green mamba snake (*Dendroaspis angusticeps*). Journal of Proteomics 136, 248–261. https://doi.org/10.1016/J.JPROT.2016.02.003.
Leonardi, A., Aragon-Ortiz, F., Gubenšek, F., Križaj, I., 1999. Partial primary structure of a fibrinogenase from the venom of the snake *Lachesis stenophrys*. J. Chromatogr. A 852, 237–243. https://doi.org/10.1016/S0021-9673(99)00260-5.
Li, J.T., Gao, Y.D., Xie, L., Deng, C., Shi, P., Guan, M.L., Huang, S., Ren, J.L., Wu, D.D., Ding, L., Huang, Z.Y., Nie, H., Humphreys, D.P., Hillis, D.M., Wang, W.Z., Zhang, Y. P., 2018. Comparative genomic investigation of high-elevation adaptation in ectothermic snakes. Proc. Nat. Acad. Sci. U. S. A 115, 8406–8411. https://doi.org/10.1073/pnas.1805348115.
Lima, R.M., Estevão-Costa, M.I., Junqueira-de-Azevedo, I.L.M., Lee Ho, P., Vasconcelos Diniz, M.R., Fortes-Dias, C.L., 2011. Phospholipase A_2 inhibitors (BPLIs) are encoded in the venom glands of *Lachesis muta* (Crotalinae, Viperidae) snakes. Toxicon 57, 172–175. https://doi.org/10.1016/j.toxicon.2010.10.005.
Lind, A.L., Lai, Y.Y.Y., Mostovoy, Y., Holloway, A.K., Iannucci, A., Mak, A.C.Y., Fondi, M., Orlandini, V., Eckalbar, W.L., Milan, M., Rovatsos, M., Kichigin, I.G., Makunin, A.I., Johnson Pokorná, M., Altmanová, M., Trifonov, V.A., Schijlen, E., Kratochvíl, L., Fani, R., Velenský, P., Rehák, I., Patarnello, T., Jessop, T.S., Hicks, J. W., Ryder, O.A., Mendelson, J.R., Ciofi, C., Kwok, P.Y., Pollard, K.S., Bruneau, B.G., 2019. Genome of the Komodo dragon reveals adaptations in the cardiovascular and chemosensory systems of monitor lizards. Nat. Ecol. Evol. 3, 1241–1252. https://doi.org/10.1038/s41559-019-0945-8.
Linnaeus, C., 1766. Systema Naturae, Per Regna Tria Naturae :secundum Classes, Ordines, Genera, Species Cum Characteribus, Differentiis, Synonymis, Locis. In: Editio duo (Ed.), Laurentii Salvii. Holmiae, Stockholm. https://doi.org/10.5962/bhl.title.559.

Lomonte, B., Calvete, J.J., 2017. Strategies in "snake venomics" aiming at an integrative view of compositional, functional, and immunological characteristics of venoms. J. Venom. Anim. Toxins Incl. Trop. Dis. 23 https://doi.org/10.1186/s40409-017-0117-8.

Mackessy, S.P., 1988. Venom ontogeny in the pacific rattlesnakes *Crotalus viridis helleri* and *C. v. Oreganus*. Copeia 1988 (92). https://doi.org/10.2307/1445927.

Mackessy, S.P., Sixberry, N.M., Heyborne, W.H., Fritts, T., 2006. Venom of the Brown Treesnake, Boiga irregularis: ontogenetic shifts and taxa-specific toxicity. Toxicon 47, 537–548. https://doi.org/10.1016/j.toxicon.2006.01.007.

Madrigal, M., Pla, D., Sanz, L., Barboza, E., Arroyo-Portilla, C., Corrêa-Netto, C., Gutiérrez, J.M., Alape-Girón, A., Flores-Díaz, M., Calvete, J.J., 2017. Cross-reactivity, antivenomics, and neutralization of toxic activities of *Lachesis* venoms by polyspecific and monospecific antivenoms. PLoS Neglected Tropical Diseases 11, e0005793. https://doi.org/10.1371/journal.pntd.0005793.

Madrigal, M., Sanz, L., Flores-Díaz, M., Sasa, M., Núñez, V., Alape-Girón, A., Calvete, J.J., 2012. Snake venomics across *genus Lachesis. Ontogenetic changes in the venom composition of Lachesis stenophrys and comparative proteomics of the venoms of adult Lachesis melanocephala and Lachesis acrochorda.* Journal of Proteomics. https://doi.org/10.1016/j.jprot.2012.09.003.

Magalhaes, A., Da Fonseca, B.C.B., Diniz, C.R., Gilroy, J., Richardson, M., 1993. The complete amino acid sequence of a thrombin-like enzyme/gyroxin analogue from venom of the bushmaster snake *(Lachesis muta muta)*. FEBS (Fed. Eur. Biochem. Soc.) Lett. 329, 116–120. https://doi.org/10.1016/0014-5793(93)80205-9.

Magalhaes, A., Ferreira, R.N., Richardson, M., Gontijo, S., Yarleque, A., Magalhaes, H.P. B., Bloch, C., Sanchez, E.F., 2003. Coagulant thrombin-like enzymes from the venoms of Brazilian and Peruvian bushmaster (*Lachesis muta muta*) snakes. Comparative Biochemistry and Physiology - B Biochemistry and Molecular Biology 136, 255–266. https://doi.org/10.1016/S1096-4959(03)00202-1.

Magalhães, S.F.V., Maia Peixoto, H., Moura, N., Marcelo Monteiro, W., Regina Fernandes de Oliveira, M., 2018. Snakebite envenomation in the Brazilian Amazon: a descriptive study. Trans. R. Soc. Trop. Med. Hyg. 113, 143–151. https://doi.org/10.1093/trstmh/try121.

Magalhães, A., Monteiro, M.R., Magalhães, H.P.B., Mares-Guia, M., Rogana, E., 1997. Thrombin-like enzyme from *Lachesis muta muta* venom: isolation and topographical analysis of its active site structure by means of the binding of amidines and guanidines as competitive inhibitors. Toxicon 35, 1549–1559. https://doi.org/10.1016/S0041-0101(97)00003-2.

Magalhães, A.E.L., 2017. Panorama Atual dos Acidentes Crotálicos e Laquéticos no Brasil: perfil epidemiológico e padrão de distribuição espacial. Universidade Federal do Estado do Rio de Janeiro.

Málaque, C.M.S., França, F.O. de S., 2003. Animais Peçonhentos no Brasil. Biologia, Clínica e Terapêutica dos Acidentes. In: Cardoso, J., Franca, F., Wen, F., Málaque, C., Hadad, V. (Eds.), São Paulo 87–90. Acidente Laquético. Sarvier.

Martill, D.M., Tischlinger, H., Longrich, N.R., 2015. A four-legged snake from the early cretaceous of gondwana. Science 349, 416–419. https://doi.org/10.1126/science.aaa9208.

Martins, M., Marques, O.A.V., 2000. *Lachesis muta ssp. rhombeata.* e.T39903A10281034.

Martins, M., Oliveira, M.E., 1998. Natural history of snakes in forests of the Manaus region, Central Amazonia, Brazil. Herpetol. Nat. Hist. 6, 78–150.

McDiarmid, R.W., Campbell, J.A., Touré, T.A., 1999. Snake Species of the World ;: a Taxonomic and Geographic Reference. Herpetologists' League. D. C, Washington.

Medem, F., 1969. El desarrollo de la herpetología en Colombia. Revista de la Academia Colombiana de Ciencias Exactas. Físicas y Naturales 13, 144–199.

Mole, R.R., 1924. Trinidad snakes. Proceedings of the Agricultura Society of Trinidad and Tobago 14, 363–369.

Monaco, L.M., 2018. Soros e vacinas do Butantan.

Oliveira, J.C.R., Montes De Oca, H., Duarte, M.M., Diniz, C.R., Fortes-Dias, C.L., 2002. Toxicity of South American snake venoms measured by an in vitro cell culture assay. Toxicon 40, 321–325. https://doi.org/10.1016/S0041-0101(01)00229-X.

Pardal, P.P., de, O., Bezerra, I.S., Rodrigues, L. da S., Pardal, J.S. de O., Farias, P.H.S. de, 2007. Acidente por surucucu (*Lachesis muta muta*) em Belém-Pará: relato de caso. Rev. Para. Med. 37–42.

Pasquesi, G.I.M., Adams, R.H., Card, D.C., Schield, D.R., Corbin, A.B., Perry, B.W., Reyes-Velasco, J., Ruggiero, R.P., Vandewege, M.W., Shortt, J.A., Castoe, T.A., 2018. Squamate reptiles challenge paradigms of genomic repeat element evolution set by birds and mammals. Nat. Commun. 9, 1–11. https://doi.org/10.1038/s41467-018-05279-1.

Peng, C., Ren, J.-L., Deng, C., Jiang, D., Wang, J., Qu, J., Chang, J., Yan, C., Jiang, K., Murphy, R.W., Wu, D.-D., Li, J.-T., 2020. The genome of shaw's sea snake (hydrophis curtus) reveals secondary adaptation to its marine environment. Mol. Biol. Evol. 37, 1744–1760, v5, 10.6084/m9.figshare.11391606.

Perry, B.W., Card, D.C., Mcglothlin, J.W., Pasquesi, G.I.M., Adams, R.H., Schield, D.R., Hales, N.R., Corbin, A.B., Demuth, J.P., Hoffmann, F.G., Vandewege, M.W., Schott, R.K., Bhattacharyya, N., Chang, B.S.W., Casewell, N.R., Whiteley, G., Reyes-Velasco, J., Mackessy, S.P., Gamble, T., Storey, K.B., Biggar, K.K., Passow, C.N., Kuo, C.-H., Mcgaugh, S.E., Bronikowski, A.M., Jason De Koning, A.P., Edwards, S.V., Pfrender, M.E., Minx, P., Brodie, E.D., Warren, W.C., Castoe, T.A., Reid, A., 2018. Molecular adaptations for sensing and securing prey and insight into amniote genome diversity from the garter snake genome GBE. Genome Biol. Evol 10, 2110–2129. https://doi.org/10.1093/gbe/evy157.

Persson, A., Hansson, L.-A., 1999. Diet shift in fish following competitive release. Can. J. Fish. Aquat. Sci. 56, 70–78. https://doi.org/10.1139/f98-141.

Peters, R.H., 1983. The Ecological Implications of Body Size, the Ecological Implications of Body Size. Cambridge University Press. https://doi.org/10.1017/cbo9780511608551.

Pierini, S.V., Warrell, D.A., De Paulo, A., Theakston, R.D.G., 1996. High incidence of bites and stings by snakes and other animals among rubber tappers and Amazonian Indians of the Jurua valley, acre state. Brazil. Toxicon 34, 225–236. https://doi.org/10.1016/0041-0101(95)00125-5.

Pinheiro-Júnior, E.L., Boldrini-França, J., de Campos Araújo, L.M.P., Santos-Filho, N.A., Bendhack, L.M., Cilli, E.M., Arantes, E.C., 2018. LmrBPP9: a synthetic bradykinin-potentiating peptide from *Lachesis muta rhombeata* venom that inhibits the angiotensin-converting enzyme activity in vitro and reduces the blood pressure of hypertensive rats. Peptides 102, 1–7. https://doi.org/10.1016/j.peptides.2018.01.015.

Pla, D., Sanz, L., Molina-Sánchez, P., Zorita, V., Madrigal, M., Flores-Díaz, M., Alape-Girón, A., Núñez, V., Andrés, V., Gutiérrez, J.M., Calvete, J.J., 2013. Snake venomics of *Lachesis muta rhombeata* and genus-wide antivenomics assessment of the paraspecific immunoreactivity of two antivenoms evidence the high compositional and immunological conservation across *Lachesis.* Journal of Proteomics. https://doi.org/10.1016/j.jprot.2013.05.028.

Pla, D., Sanz, L., Sasa, M., Acevedo, M.E., Dwyer, Q., Durban, J., Pérez, A., Rodriguez, Y., Lomonte, B., Calvete, J.J., 2017. Proteomic analysis of venom variability and ontogeny across the arboreal palm-pitvipers (genus Bothriechis). Journal of Proteomics 152, 1–12. https://doi.org/10.1016/j.jprot.2016.10.006.

Pyron, R.A., Burbrink, F.T., 2012. Extinction, ecological opportunity, and the origins of global snake diversity. Evolution 66, 163–178. https://doi.org/10.1111/j.1558-5646.2011.01437.x.

Pyron, R.A., Burbrink, F.T., Wiens, J.J., 2013. A phylogeny and revised classification of Squamata, including 4161 species of lizards and snakes. BMC Evol. Biol. 13, 1–54. https://doi.org/10.1186/1471-2148-13-93.

Raw, I., Guidolin, R., Higashi, H., Kelen, E., 1991. Antivenins in Brazil: preparation. In: Handbook of Natural Toxins: Reptile Venoms and Toxins. Marcel Dekker, pp. 557–581. New York.

Reeder, T.W., Townsend, T.M., Mulcahy, D.G., Noonan, B.P., Wood, P.L., Sites, J.W., Wiens, J.J., 2015. Integrated analyses resolve conflicts over squamate reptile phylogeny and reveal unexpected placements for fossil taxa. PLoS ONE 10, e0118199. https://doi.org/10.1371/journal.pone.0118199.

Reyes-Velasco, J., Adams, R.H., Boissinot, S., Parkinson, C.L., Campbell, J.A., Castoe, T. A., Smith, E.N., 2020. Genome-wide SNPs clarify lineage diversity confused by coloration in coralsnakes of the *Micrurus diastema* species complex (Serpentes: Elapidae). Mol. Phylogenet. Evol. 147 (106770) https://doi.org/10.1016/j.ympev.2020.106770.

Ripa, D., 2003. Six New Cases of Bushmaster Envenoming. The Bushmasters (Genus Lachesis Daudin, 1803): Morphology in Evolution and Behavior. Electronic book, Wilmington, NC. Cape Fear Serpentarium.

Ripa, D., 2001. The bushmasters (genus *Lachesis* daudin, 1803). In: Morphology in Evolution and Behavior. North Carolina, USA, Wilmington.

Ripa, D., 1994. The reproduction of the Central American bushmaster (*Lachesis muta stenophrys*) and the blackheaded bushmasters (*Lachesis muta melanocephala*) for the first time in captivity. Bull. Chic. Herpetol. Soc. 29, 165–183.

Rucavado, A., Flores-Sánchez, E., Franceschi, A., Magalhaes, A., Gutiérrez, J.M., 1999. Characterization of the local tissue damage induced by LHF-II, a metalloproteinase with weak hemorrhagic activity isolated from *Lachesis muta muta* snake venom. Toxicon 37, 1297–1312. https://doi.org/10.1016/S0041-0101(98)00268-2.

Saldarriaga, M.M., Otero, R., Núñez, V., Toro, M.F., Díaz, A., Gutiérrez, J.M., 2003. Ontogenetic variability of *Bothrops atrox* and *Bothrops asper* snake venoms from Colombia. Toxicon 42, 405–411. https://doi.org/10.1016/S0041-0101(03)00171-5.

Sanchez, E.F., Costa, M.I.E., Assakura, M.T., 1995. Characterization of a hemorrhagic factor, LHF-I, isolated from Bushmaster snake (*Lachesis muta muta*) venom, 33, 1653–1667.

Sanchez, E.F., Felicori, L.F., Chavez-Olortegui, C., Magalhaes, H.B.P., Hermogenes, A.L., Diniz, M.V., Junqueira-de-Azevedo, I., de, L.M., Magalhaes, A., Richardson, M., 2006. Biochemical characterization and molecular cloning of a plasminogen activator proteinase (LV-PA) from Bushmaster snake venom. Biochim. Biophys. Acta Gen. Subj. 1760, 1762–1771. https://doi.org/10.1016/j.bbagen.2006.08.023.

Sánchez, E.F., Freitas, T.V., Ferreira-Alves, D.L., Velarde, D.T., Diniz, M.R., Cordeiro, M. N., Agostini-Cotta, G., Diniz, C.R., 1992. Biological activities of venoms from south american snakes. Toxicon 30, 95–103.

Sanchez, E.F., Magalhaes, A., Diniz, C.R., 1987. Purification of hemorrhagic factor (LHF-I) from the venom of the Bushmaster snake, *Lachesis muta muta.* Toxicon 25, 611–619.

Sánchez, E.F., Magalhës, A., Mandelbaum, F.R., Diniz, C.R., 1991. Purification and characterization of the hemorrhagic factor II from the venom of the Bushmaster snake (*Lachesis muta muta*). Biochim. Biophys. Acta 1074, 347–356.

Sanchez, E.F., Santos, C.I., Magalhaes, a, Diniz, C.R., Figueiredo, S., Gilroy, J., Richardson, M., 2000. Isolation of a proteinase with plasminogen-activating activity from *Lachesis muta muta* (Bushmaster) snake venom. Arch. Biochem. Biophys. 378, 131–141. https://doi.org/10.1006/abbi.2000.1781.

Sánchez, E.F., Souza, C.T., Bello, C.A., Richardson, M., Oliveira, E.B., Magalhaes, A., 2003. Resolution of isoforms of mutalysin II, the metalloproteinase from Bushmaster snake venom. Toxicon 41, 1021–1031. https://doi.org/10.1016/S0041-0101(03)00076-X.

Sanz, L., Escolano, J., Ferretti, M., Biscoglio, M.J., Rivera, E., Crescenti, E.J., Angulo, Y., Lomonte, B., Gutiérrez, J.M., Calvete, J.J., 2008. Snake venomics of the South and Central American Bushmasters. Comparison of the toxin composition of *Lachesis muta* gathered from proteomic versus transcriptomic analysis. Journal of proteomics 71, 46–60. https://doi.org/10.1016/j.jprot.2007.10.004.

Savage, J.M., 2002. The Amphibians and reptiles of Costa Rica: a herpetofauna between two continents. In: Between Two Seas, first ed. The University of Chicago Press, Chicago.

Scarborough, R.M., Rose, J.W., Naughton, M.A., Phillips, D.R., Nannizzi, L., Arfsten, A., Campbell, A.M., Charo, I.F., 1993. Characterization of the integrin specificities of disintegrins isolated from American pit viper venoms. J. Biol. Chem. 268, 1058–1065.

Schield, D.R., Card, D.C., Hales, N.R., Perry, B.W., Pasquesi, G.M., Blackmon, H., Adams, R.H., Corbin, A.B., Smith, C.F., Ramesh, B., Demuth, J.P., Betrán, E., Tollis, M., Meik, J.M., Mackessy, S.P., Castoe, T.A., 2019. The origins and evolution of chromosomes, dosage compensation, and mechanisms underlying venom regulation in snakes. Genome Res. 29, 590–601. https://doi.org/10.1101/gr.240952.118.

Schoener, T.W., 1971. Theory of feeding strategies. Annu. Rev. Ecol. Systemat. 2, 369–404. https://doi.org/10.1146/annurev.es.02.110171.002101.

Shaney, K.J., Card, D.C., Schield, D.R., Ruggiero, R.P., Pollock, D.D., Mackessy, S.P., Castoe, T.A., 2014. Squamate reptile genomics and evolution. Springer Science 1–18. https://doi.org/10.1007/978-94-007-6649-5_34-2.

Shibata, H., Chijiwa, T., Oda-Ueda, N., Nakamura, H., Yamaguchi, K., Hattori, S., Matsubara, K., Matsuda, Y., Yamashita, A., Isomoto, A., Mori, K., Tashiro, K., Kuhara, S., Yamasaki, S., Fujie, M., Goto, H., Koyanagi, R., Takeuchi, T., Fukumaki, Y., Ohno, M., Shoguchi, E., Hisata, K., Satoh, N., Ogawa, T., 2018. The habu genome reveals accelerated evolution of venom protein genes. Sci. Rep. 8, 1–11. https://doi.org/10.1038/s41598-018-28749-4.

Sih, A., Crowley, P., McPeek, M., Petranka, J., Strohmeier, K., 1985. Predation, competition, and prey communities: a review of field experiments. Annu. Rev. Ecol. Systemat. 16, 269–311. https://doi.org/10.1146/annurev.es.16.110185.001413.

Silva-Haad, J., 1982. Accidentes humanos por las serpientes de los gêneros *Bothrops* y *Lachesis*. Mem. Inst. Butantan (Sao Paulo) 44, 403–423. https://doi.org/10.1016/0041-0101(85)90122-9.

Silva, Jessyca Lima da, da Siva, Ageane Mota, Amaral, Gardênia Lima Gurgel do, Ortega, Givanildo Pereira, Monteiro, Wuelton Marcelo, Bernarde, Paulo Sérgio, 2020. The deadliest snake according to ethnobiological perception of the population of the Alto Juruá region, western Brazilian Amazonia. Rev. Soc. Bras. Med. Trop. 53 https://doi.org/10.1590/0037-8682-0305-2019.

Silva, L.M., Diniz, C.R., Magalhães, A., 1985. Purification and partial characterization of an arginine ester hydrolase from the venom of the bushmaster snake, *Lachesis muta noctivaga*. Toxicon 23, 707–718. https://doi.org/10.1016/0041-0101(85)90375-7.

Silveira, A.M.V., Magalhães, A., Diniz, C.R., De Oliveira, E.B., 1989. Purification and properties of the thrombin-like enzyme from the venom of *Lachesis muta muta*. Int. J. Biochem. 21, 863–871. https://doi.org/10.1016/0020-711X(89)90285-1.

Skipwith, P.L., Bi, K., Oliver, P.M., 2019. Relicts and radiations: phylogenomics of an australasian lizard clade with east gondwanan origins (gekkota: diplodactyloidea). Mol. Phylogenet. Evol. 140 (106589) https://doi.org/10.1016/j.ympev.2019.106589.

Slavens, F.L., Slavens, K., 2000. Reptiles and amphibians in captivity: breeding, longevity and inventory. Slaveware. Seattle 1–400.

Smiley-Walters, S.A., Farrell, T.M., Gibbs, H.L., 2019. High levels of functional divergence in toxicity towards prey among the venoms of individual pigmy rattlesnakes. Biol. Lett. 15 (20180876) https://doi.org/10.1098/rsbl.2018.0876.

Soares, M.R., Oliveira-Carvalho, A.L., Wermelinger, L.S., Zingali, R.B., Ho, P.L., Junqueira-de-Azevedo, I.D.L.M., Diniz, M.R.V., 2005. Identification of novel bradykinin-potentiating peptides and C-type natriuretic peptide from *Lachesis muta* venom. Toxicon: official journal of the International Society on Toxinology 46, 31–38. https://doi.org/10.1016/j.toxicon.2005.03.006.

Solorzano, A., Cerdas, L., 1986. A new subspecies of the bushmaster, *Lachesis muta*, from southeastern Costa Rica. J. Herpetol. 20 (463) https://doi.org/10.2307/1564518.

Solórzano, L.A., 2004. Serpientes de Costa Rica;: distribución, taxonomía e historia natural = Snakes of Costa Rica : distribution, taxonomy, and natural history/, 1. INBio, [Santo Domingo de Heredia] Costa Rica.

Souza, A.R.B., de Tavares, A.M., Buhrnheim, P.F., 2020. Acidentes por animais peçonhentos 1–5.

Souza, R.C.G. De, 2007. Aspectos clínicos do acidente laquético.

Suryamohan, K., Krishnankutty, S.P., Guillory, J., Jevit, M., Schröder, M.S., Wu, M., Kuriakose, B., Mathew, O.K., Perumal, R.C., Koludarov, I., Goldstein, L.D., Senger, K., Dixon, M.D., Velayutham, D., Vargas, D., Chaudhuri, S., Muraleedharan, M., Goel, R., Chen, Y.-J.J., Ratan, A., Liu, P., Faherty, B., de la Rosa, G., Shibata, H., Baca, M., Sagolla, M., Ziai, J., Wright, G.A., Vucic, D., Mohan, S., Antony, A., Stinson, J., Kirkpatrick, D.S., Hannoush, R.N., Durinck, S., Modrusan, Z., Stawiski, E.W., Wiley, K., Raudsepp, T., Kini, R.M., Zachariah, A., Seshagiri, S., 2020. The Indian cobra reference genome and transcriptome enables comprehensive identification of venom toxins. Nat. Genet. https://doi.org/10.1038/s41588-019-0559-8.

Tanus Jorge, M., Sano-Martins, I.S., Tomy, S.C., Castro, S.C.B., Ferrari, R.A., Adriano Ribeiro, L., Warrell, D.A., 1997. Snakebite by the Bushmaster (*Lachesis muta*) in Brazil: case report and review of the literature. Toxicon 35, 545–554. https://doi.org/10.1016/S0041-0101(96)00142-0.

Thomas, R.G., Pough, F.H., 1979. The effect of rattlesnake venom on digestion of prey. Toxicon 17, 221–228. https://doi.org/10.1016/0041-0101(79)90211-3.

Tollis, M., Hutchins, E.D., Kusumi, K., 2014. Reptile genomes open the frontier for comparative analysis of amniote development and regeneration. Int. J. Dev. Biol. 58, 863–871. https://doi.org/10.1387/ijdb.140316kk.

Tollis, M., Hutchins, E.D., Stapley, J., Rupp, S.M., Eckalbar, W.L., Maayan, I., Lasku, E., Infante, C.R., Dennis, S.R., Robertson, J.A., May, C.M., Crusoe, M.R., Bermingham, E., Denardo, D.F., Hsieh, S.T.T., Kulathinal, R.J., McMillan, W.O., Menke, D.B., Pratt, S.C., Rawls, J.A., Sanjur, O., Wilson-Rawls, J., Wilson Sayres, M. A., Fisher, R.E., Kusumi, K., 2018. Comparative genomics reveals accelerated evolution in conserved pathways during the diversification of anole lizards. Genome Biology and Evolution 10, 489–506. https://doi.org/10.1093/gbe/evy013.

Ullate-Agote, A., Milinkovitch, M.C., Tzika, A.C., 2014. The genome sequence of the corn snake (*Pantherophis guttatus*), a valuable resource for EvoDevo studies in squamates. Int. J. Dev. Biol. 58, 881–888. https://doi.org/10.1387/ijdb.150060at.

Vonk, F.J., Casewell, N.R., Henkel, C.V., Heimberg, A.M., Jansen, H.J., McCleary, R.J.R., Kerkkamp, H.M.E., Vos, R. a, Guerreiro, I., Calvete, J.J., Wüster, W., Woods, A.E., Logan, J.M., Harrison, R. a, Castoe, T. a, de Koning, a P.J., Pollock, D.D., Yandell, M., Calderon, D., Renjifo, C., Currier, R.B., Salgado, D., Pla, D., Sanz, L., Hyder, A.S., Ribeiro, J.M.C., Arntzen, J.W., van den Thillart, G.E.E.J.M., Boetzer, M., Pirovano, W., Dirks, R.P., Spaink, H.P., Duboule, D., McGlinn, E., Kini, R.M., Richardson, M.K., 2013. The king cobra genome reveals dynamic gene evolution and adaptation in the snake venom system. In: Proceedings of the National Academy of Sciences of the United States of America, vol. 110, pp. 20651–20656. https://doi.org/10.1073/pnas.1314702110.

Waldez, F., Vogt, R.C., 2009. Aspectos ecológicos e epidemiológicos de acidentes ofídicos em comunidades ribeirinhas do baixo rio Purus, Amazonas, Brasil. Acta Amazonica 39, 681–692. https://doi.org/10.1590/s0044-59672009000300025.

Warrell, D., 2004. Snakebites in Central and South America:epidemiology, clinical features, and clinical management. In: Campbell, J., Lamar, W. (Eds.), The Venomous Reptiles of the Western Hemisphere. Comstock Publishing, Ithaca and London, pp. 709–761.

Wied-Neuwied, M.P. zu, 1824. Abbildungen zur Naturgeschichte Brasilien, Abbildungen zur Naturgeschichte Brasiliens/. im Verlage des Grossherzogl. Sächs. priv. Landes-Industrie-Comptoirs, Weimar. https://doi.org/10.5962/bhl.title.51486.

Wiezel, G.A., Bordon, K.C.F., Silva, R.R., Gomes, M.S.R., Cabral, H., Rodrigues, V.M., Ueberheide, B., Arantes, E.C., 2019. Subproteome of *Lachesis muta rhombeata* venom and preliminary studies on LmrSP-4, a novel snake venom serine proteinase. Journal of Venomous Animals and Toxins Including Tropical Diseases 25. https://doi.org/10.1590/1678-9199-jvatitd-1470-18.

Wiezel, G.A., dos Santos, P.K., Cordeiro, F.A., Bordon, K.C.F., Selistre-de-Araújo, H.S., Ueberheide, B., Arantes, E.C., 2015. Identification of hyaluronidase and phospholipase B in *Lachesis muta rhombeata* venom. Toxicon. https://doi.org/10.1016/j.toxicon.2015.08.029.

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 Tropical Diseases 13, e0007059. https://doi.org/10.1371/journal.pntd.0007059.

Yarleque, A., Campos, S., Escobar, E., Lazo, F., Sanchez, N., Hyslop, S., 1989. Isolation and characterization of a fibrinogen- clotting enzyme from venom of the snake, *Lachesis muta muta* (Peruvian bushmaster). Toxicon 27, 1189–1197.

Yin, W., Wang, Z.J., Li, Q.Y., Lian, J.M., Zhou, Y., Lu, B.Z., Jin, L.J., Qiu, P.X., Zhang, P., Zhu, W.B., Wen, B., Huang, Y.J., Lin, Z.L., Qiu, B.T., Su, X.W., Yang, H.M., Zhang, G. J., Yan, G.M., Zhou, Q., 2016. Evolutionary trajectories of snake genes and genomes revealed by comparative analyses of five-pacer viper. Nat. Commun. 7, 1–11. https://doi.org/10.1038/ncomms13107.

Zaher, H., Murphy, R.W., Arredondo, J.C., Graboski, R., Machado-Filho, P.R., Mahlow, K., Montingelli, G.G., Quadros, A.B., Orlov, N.L., Wilkinson, M., Zhang, Y.-P., Grazziotin, F.G., 2019. Large-scale molecular phylogeny, morphology, divergence-time estimation, and the fossil record of advanced caenophidian snakes (Squamata: serpentes). PLOS ONE 14, e0216148. https://doi.org/10.1371/journal.pone.0216148.

Zamudio, K.R., Greene, H.W., 1997. Phylogeography of the bushmaster (*Lachesis muta*: Viperidae): implications for neotropical biogeography, systematics, and conservation. Biol. J. Linn. Soc. 62, 421–442. https://doi.org/10.1111/j.1095-8312.1997.tb01634.x.

Zelanis, A., Tashima, A.K., Pinto, A.F.M., Paes Leme, A.F., Stuginski, D.R., Furtado, M.F., Sherman, N.E., Ho, P.L., Fox, J.W., Serrano, S.M.T., 2011. *Bothrops jararaca* venom proteome rearrangement upon neonate to adult transition. Proteomics 11, 4218–4228. https://doi.org/10.1002/pmic.201100287.

Zelanis, A., Tashima, A.K., Rocha, M.M.T., Furtado, M.F., Camargo, A.C.M., Ho, P.L., Serrano, S.M.T., 2010. Analysis of the ontogenetic variation in the venom proteome/peptidome of *Bothrops jararaca* reveals different strategies to deal with prey. J. Proteome Res. 9, 2278–2291. https://doi.org/10.1021/pr901027r.

Zelanis, A., Travaglia-Cardoso, S.R., De Fátima Domingues Furtado, M., 2008. Ontogenetic changes in the venom of *Bothrops insularis* (Serpentes: Viperidae)and its biological implication. South American Journal of Herpetology 3, 43–50. https://doi.org/10.2994/1808-9798(2008)3[43:ocitvo]2.0.co;2.