Toxicon 202 (2021) 90–97

Contents lists available at ScienceDirect

Toxicon

journal homepage: www.elsevier.com/locate/toxicon

Review

Snake antivenom production in Ecuador: Poor implementation, and an unplanned cessation leads to a call for a renaissance

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ARTICLE INFO

Handling Editor: Dr. Raymond Norton

Keywords:
Snakebite
Public health
Antivenom
Serum
Snake antivenom
Epidemiology
Ecuador

ABSTRACT

Snakebite envenomation is a global health problem. This health problem asymmetrically affects rural populations in developing countries to such an extent that it recently has been listed as a priority neglected tropical disease (NTD). It is estimated that 5.4 million individuals are bitten by snakes each year, causing at least 2.7 million envenomations and more than 100,000 deaths each year. Ecuador has one of the highest snakebite envenomation incidence rates in Latin America, mostly in the coastal and Amazonian provinces. Envenomations in these regions are the result of bites primarily by species of snakes belonging to the Viperidae family. Ecuador was able to locally produce antivenoms, however serious flaws were revealed in the antivenom production process, leading to the decommissioning of the existing facility. In the interest of public health, we have summarized the political and social setbacks experienced by the antivenom serum production plant in Ecuador, while encouraging resuming local production of snake antivenom to improve the responsiveness of the already overburdened health system.

1. Introduction

Snake bites are annually estimated to occur to 5.4 million people, with envenomations totaling around 2.7 million, resulting in 81,410–137,880 deaths (WHO, 2019). While snakebite envenomations (SBE) are widespread, instances are focused in Africa, Asia, and Latin America, making it a public health problem requiring immediate attention of health authorities from both regional and global levels (WHO, 2019; Williams et al., 2019). Snakebite related-injuries are prominent in rural tropical areas affecting farmers or their families, mainly in developing countries throughout Latin America, Africa, Asia, and Oceania (Dehghani et al., 2014; Gutiérrez et al., 2010; Sharma, 2005). World Health Organization (WHO) lists SBE as a neglected disease, as little innovation has occurred in its treatment, with the burden of this health problem continuing to increase globally (Gutiérrez et al., 2010; Williams et al., 2019).

The only effective treatment for a snake envenomation is the rapid application of anti snake venom (ASV), also called snake venom antiserum (SVAS), anti-venom, or antivenom, serum (Murphy, 2010). Early medical treatment and prompt SVAS administration after a bite, increases the likelihood the patient will have a favorable outcome (Murphy, 2010; Teixeira-Araújo et al., 2017). The use of SVAS demonstrably reduces mortality, yet unfortunately there are serious deficits in availability for many several regions of the world, particularly in rural areas from developing countries, such as Ecuador. Scarcity can arise for a variety of reasons-among them problematic manufacturing, inefficient distribution, distribution of ineffective antivenoms (which lack adequate preclinical evaluations), and lax quality control which fail to follow recommendations outlined by the appropriate production guidelines of the WHO (Guimaraes et al., 2014). Historically, Ecuador was an important SVAS producer able to fully satisfy national demands (E. Ortiz-Prado, 2018). However, with the reform of the National Institute of Hygiene formerly known as “Instituto de Higiene y Medicina tropical, Leopoldo Izquieta Perez”, the former producer of antivenom

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https://doi.org/10.1016/j.toxicon.2021.09.014
Received 17 June 2021; Received in revised form 21 September 2021; Accepted 23 September 2021
Available online 25 September 2021

serum in Ecuador, and its subsequent separation into the current Public Health Institute of Ecuador (INSPI) and the National Agency for Drug and Food Regulation (ARCSA); antivenom serum production was left adrift (Mena et al., 2015). In 2012, after a presidential decree was signed, the antivenom production plant was closed indefinitely.

Although the former production plant had several shortcomings, the decision to close it without a functional replacement was unplanned. ENFARMA EP, the public pharmaceutical company that was to take over the production of the antivenom serum and vaccines, never produced anything and the authorities at the time closed it for good years later, leaving an entire country in a precaruious position due to the lack of antivenom serum (Esteban Ortiz-Prado, 2018; Ortiz-Prado et al., 2021). The sudden closure of the local production facility has further placed Ecuador in a difficult situation, depending on imported SVAS products, a situation which could be linked to the increasing number of deaths and disabilities associated with SBE especially among vulnerable populations (González-Andrade and Chippaux, 2010; Ochoa-Avilés et al., 2020).

Therefore prior to restarting antivenom production, we afford a historical review of antivenom serums production in Ecuador, including a brief description of the history behind the local experience, a detailed narrative of the production methods, and describe the current epidemiological situation of SBE.

2. Methods

We used a mixed method design to complete the current analysis. First, we described the epidemiology of snakebite related-injuries in Ecuador from 2001 to 2018 using a secondary data, observational, ecological analysis of all the hospital discharges attributed to snakebite related-injuries as well as all deaths. Data was obtained from the National Hospital Discharges Database and the national registry of deaths from the Ecuadorian National Institute of Statistics and census (INEC) from 2001 to 2018 (INEC, 2019). Information from the database was retrieved using the diagnosis CIE-10 codes for "toxic effect due to contact with venomous animals (T63)" and "traumatic contact with venomous snakes and lizards (X20)" from 2001 to 2018.

For the second part of the analysis, a comprehensive review of the literature was carried out following the PRISMA Statement for Reporting Literature Searches in Systematic Reviews (Rethlefsen et al., 2020).

2.1. Search strategy

A systematic bibliographic search for scientific literature published until December 31, 2020, was implemented both in the indexation bases in English, i.e., ClinicalKey, PubMed/Medline, Cochrane library, Google Scholar, and Scopus; and in Spanish: i.e., Lilacs, Scielo, Imbiomed. The search strategy was designed from the combination of indexed terms and keywords: *"antivenom, serum", "anti-venom ", "Snake Bites", "Snake Venoms", "Immune Sera", "Ecuador", "Epidemiology",* in English, or *"Mordeduras de Serpientes", "Venenos de Serpiente", "Sueros Inmunes", "Ecuador", "Epidemiologia",* in Spanish; along with Boolean operators: "AND" and "OR".

2.2. Study selection

Two authors reviewed the title and summary of all the 2962 bibliographies used and selected a total of 26 manuscripts. Another couple of authors reviewed each entire manuscript and found 12 were repeated, then eliminated. Manuscripts in English and Spanish languages comprised of research observations, experimental and opinion, were included, describing the epidemiology and problem of snakebite disease in Ecuador; production, efficacy, effectiveness, safety, and status of antivenom, serums in Ecuador.

2.3. Distribution analysis

The National Institute of Statistics and Censuses (INEC) database was sourced to quantify the number of cases of snake bites in Ecuador for each province in the period from 2001 to 2018. INEC is the governing body for national statistics, which is simultaneously responsible for generating the official statistics for use by decision-making agencies and informing public policies.

2.4. Descriptive statistics

Incidence and mortality rates were age-and sex-standardized using the national population census from 2001 to 2018. The number of cases and deaths were summarized as absolute numbers and relative frequencies (%). The mortality rate was calculated using the annual population at risk by sex, age group, and geographic location of incidence for every year of the analisys.

Calculations were completed using IBM SPSS version 24.0 statistics. Citation and reference retrieval were performed using Zotero Open Source software version 4.0.11. All graphs and maps were produced by the authors.

3. Results

3.1. Antivenom needs

3.1.1. Snake bites envenoming epidemiology

SBEs treatment is now considered a public health problem priority worldwide, due to annual mortalities ranging from 81,000 to 138,000. There are an additional approximately 400,000 survivors who reported physical or psychological sequelae, where the nature of these disabilities is often permanent (Williams et al., 2019). In places where access to healthcare is poor and there is a shortage of antivenom, the severity of the lesions and their complications increase. Poverty, neglect of regional health authorities, and lack of investment in the management of snake bites are some of the factors affecting the outcomes of a bite (Gutiérrez, 2011). The highest incidence of snakebite accidents are found in rural areas, composed of populations characterized by farmers, workers, miners, and native communities. Those people are especially affected by snake bites due to their working conditions, and the severity of the incident is related to the physical and psychological health of the victim (Chippaux, 2005; Harrison and Gutiérrez, 2016). Another factor that complicates the management of snake bites are barriers related to the victims ability to receive immediate health care attention, as in rural areas it has been reported that the majority of patients arrive more than 6 h after a snake bite (Habib and Warrell, 2013; Warrell, 2010).

In South America, those countries with greater expanses of forest are the most affected by snake envenomations (Table 1). The most medically

Table 1
Snake Bite Envenomations in South America during the 21st century, the incidence and mortality rates per 100,000 inhabitants. [Reproduced from (Chippaux, 2017; Gutiérrez, 2011)].

Country	Annual cases of snake bites	Incidence	Mortality
Argentina	700	1.64	0.012
Bolivia	900 - 1000	8.98–9.6	0.399
Brazil	26,000–29,000	13.39–14.0	0.05–0.06
Colombia	3000–4150	6.4–8.69	0.073
Ecuador	1400–1600	9.48–10.0	0.05–0.073
Guyana	200	25.48	0.382
French Guyana	50–100	21.05–40.0	0.631
Paraguay	250–500	3.69	0.074
Peru	1400–2150	5.0–6.98	0.032
Surinam	NA	NA	NA
Uruguay	50–80	1.8–2.43	0.061
Venezuela	5700	18.87	0.037

*NA: Not available data.

relevant species within the region are the *jergon* (*Bothrops atrox*), causing an important burden of snakebite related injuries in countries such as Brazil, Venezuela, Peru and Colombia. In other countries such as Argentina, Bolivia or Uruguay, the tropical rattlesnake and the *machaco parrot* (*Bothrops bilineatus*) are also resposible for a large portion of incidents (Gutiérrez, 2011; Katie, 2018).

3.1.2. Snake bites epidemiology in Ecuador

Ecuador has an incidence of 1400–1600 cases of bite per year, one of the highest in South America (Table 1) (Chippaux, 2017; Gutiérrez, 2011). More recent data suggest that national incidences of snake bites was 7.7–11.0 cases per 100.000 inhabitants per year from 2014 to 2019, while snake bite related mortality was reported to be 0.03 to 0.10 deaths per 100.000 inhabitants per year (Ochoa-Avilés et al., 2020). The country is divided into 3 regions, the coastal region (Western region) and Amazon region (Eastern region) with altitudes from 0 to 1200 m above sea level and <750 masl, respectively, and the Andean highlands region between 1200 and 6400 masl. The presence of Andean mountains creates a high diversity of environmental niches, which results in high levels of biodiversity, almost 70% of Ecuadorian terrain is characterized as tropical and subtropical climates where 238 species of snakes are found, of those, 55 snakes are endemic and 37 snakes are venomous (Torres-Carvajal et al., 2018). In Ecuador ophidic accidents are reported more frequently during the rainy season, they are represented mainly by the *Elapidae* and *Viperidae* families (Table 2), several species of *Bothrops* are responsible for the major number of accidents (70–80%) nationwide, followed *by Bothrocophias microphthalmus, Bothrops bilineatus, Bothrops taeniata, Lachesis muta* and unusual cases caused by the family *Elapidae* as *Micrurus lemniscatus (less than 1%)* (Manock et al., 2008; Ministerio de salud pública de Ecuador, 2017; Praba-Egge et al., 2003) (Table 2).

Table 2
Venomous snakes and their general distribution in Ecuador [Reproduced from (Torres-Carvajal et al., 2018)].

Region	Family	Snake	Type of venom
West of Ecuador	*Viperidae*	*Bothrocophias campbelli*	Hemotoxic and myotoxic
	Viperidae	*Bothrops osbornei*	Proteolytic with low action in coagulation
	Viperidae	*Bothrops punctatus*	Hemotoxic
	Viperidae	*Porthidium arcosae*	Hemotoxic
	Viperidae	*Bothriechis schlegelii*	Hemotoxic and myotoxic
	Viperidae	*Bothrops asper*	Hemotoxic
	Viperidae	*Lachesis acrochorda*	Hemotoxic
	Viperidae	*Porthidium nasutum*	Hemotoxic
	Elapidae	*Micrurus mipartitus decussatus*	Neurotoxic
	Elapidae	*Hydrophis platurus*	Neurotoxic
	Elapidae	*Micrurus ancoralis*	Neurotoxic
	Elapidae	*Micrurus bocourti*	Neurotoxic
	Elapidae	*Micrurus dumerilii*	Neurotoxic
	Elapidae	*Micrurus mertensi*	Neurotoxic
	Elapidae	*Micrurus multiscutatus*	Neurotoxic
	Elapidae	*Micrurus tschudii*	Hemotoxic
East of Ecuador	*Viperidae*	*Bothrops bilineatus*	Hemotoxic
	Viperidae	*Bothrops taeniata*	Hemotoxic and proteolytic
	Viperidae	*Bothrocophias hyoprora*	Hemotoxic
	Viperidae	*Bothrocophias microphthalmus*	Hemotoxic
	Viperidae	*Bothrops atrox*	Hemotoxic
	Viperidae	*Lachesis muta*	Hemotoxic, proteolytic, myotoxic and neurotoxic
	Viperidae	*Bothrops pulchra*	Hemotoxic
	Viperidae	*Bothrops lojanus*	Hemotoxic
	Viperidae	*Bothrops brazili*	Hemotoxic
	Elapidae	*Micrurus hemprichii*	Neurotoxic
	Elapidae	*Micrurus langsdorffi*	Neurotoxic
	Elapidae	*Micrurus lemniscatus*	Neurotoxic and myotoxic
	Elapidae	*Micrurus narducci*	Neurotoxic
	Elapidae	*Micrurus ornatissimus*	Neurotoxic
	Elapidae	*Micrurus peruvianus*	Neurotoxic
	Elapidae	*Micrurus petersi*	Neurotoxic
	Elapidae	*Micrurus scutiventris*	Neurotoxic
	Elapidae	*Micrurus spixii*	Neurotoxic
	Elapidae	*Micrurus steindachneri*	Neurotoxic
	Elapidae	*Micrurus surinamensis*	Neurotoxic

In Ecuador, during the last decade there has been a stable trend of 13.21 cases of bites per 100,000 inhabitants. However, in 2019, a total of 1489 cases were reported, which has been an increase from 2017 which had 1450 cases, the highest incidence in recent years (Ministerio de Salud Pública de Ecuador, n.d.). Based on the analyses from 1994 to 2010 Yañes et al. reported that three species have the highest probability to cause a human envenomation, which are *Bothrops asper, Bothrops atrox,* and *Bothrops bilineatus* (Yañez-Arenas et al., 2018). The highest incidence of snakebites in the country is the Amazon region, followed by the Coast (Fig. 1).

3.1.3. Geographic distribution

Snake bite incidence rates vary geographically from 524 cases per 100,000 individuals in Morona Santiago to 398 cases per 100,000 individuals in Pastaza. When analyzed by canton, there was a higher incidence in Amazonian areas, both in men and women. In men, the canton with the highest incidence rates was Morona Santiago with 258 cases per 100,000 people, in women it was Taisha with 234 cases per 100,000 people, while the lowest incidence in men and women with 0 cases per 100. 000 people was Chordeleg, El pan, Sevilla de oro, Guachapala, Deleg, Suscal, San pedro de Huaca, Penipe, Isidro Ayora, Pimampiro, San Miguel de Urcuqui, Quilanga, Olmedo, Jama, Pedro Vicente Maldonado, Puerto Quito and Ambato (Table 3).

3.2. Snake antivenoms production in Ecuador

On October 23, 1941, and by executive decree number 348, Ecuador created the National Institute of Hygiene, the first center for tropical disease control for the country and one of the very first for Latin America (Barragán et al., 2009). At that time, six laboratories were opened, however, years later it was expanded to a total of 37 laboratories countrywide.

The production of antivenoms at SBE began in 1981 using antiquated techniques, such as those harvesting serum from immunized animals, which were further developed into human antivenom to treat snake envenomations (Fig. 2).

On August 30, 2012, through Executive Decree 1290, the National Institute of Hygiene and Tropical Medicine Dr. Leopoldo Izquieta Pérez was split or divided into the National Institute of Health and Public Research (INSPI) and the National Agency for Regulation, Control and Health Surveillance (Arcsa). Due to this separation, antivenom production was jeopardized. Even though national production continued, the lack of government oversight, the ongoing institutional instability and a lack of long-term vision combined resulted in diminishing the production of antivenom serum in Ecuador (E. Ortiz-Prado, 2018).

Before INSPI took over the production of antivenom temporarily, local production-capacity reached an average of 7000 vials of antivenom serum per year (between the years of 2007 and 2012) (E. Ortiz-Prado, 2018). However, in 2012 when the Ministry of Public Health decided to abandon national production (attributed to inconsistencies related to best manufacturing practices) Ecuador was forced to enter into an era of comercial dependency in terms of importing this biological product.

3.3. Poor regulation during antivenom production in Ecuador

In a country with poor regulation in terms of good manufacturing practices (GMP), the production of antiophidic serum went from being under-regulated to hyper-regulated in less than 6 months. The production of antiophidic serum was unnoticed by the authorities for several years, however when they became aware of the shortcomings in its production, they erroneously requested GMP from one day to the next,

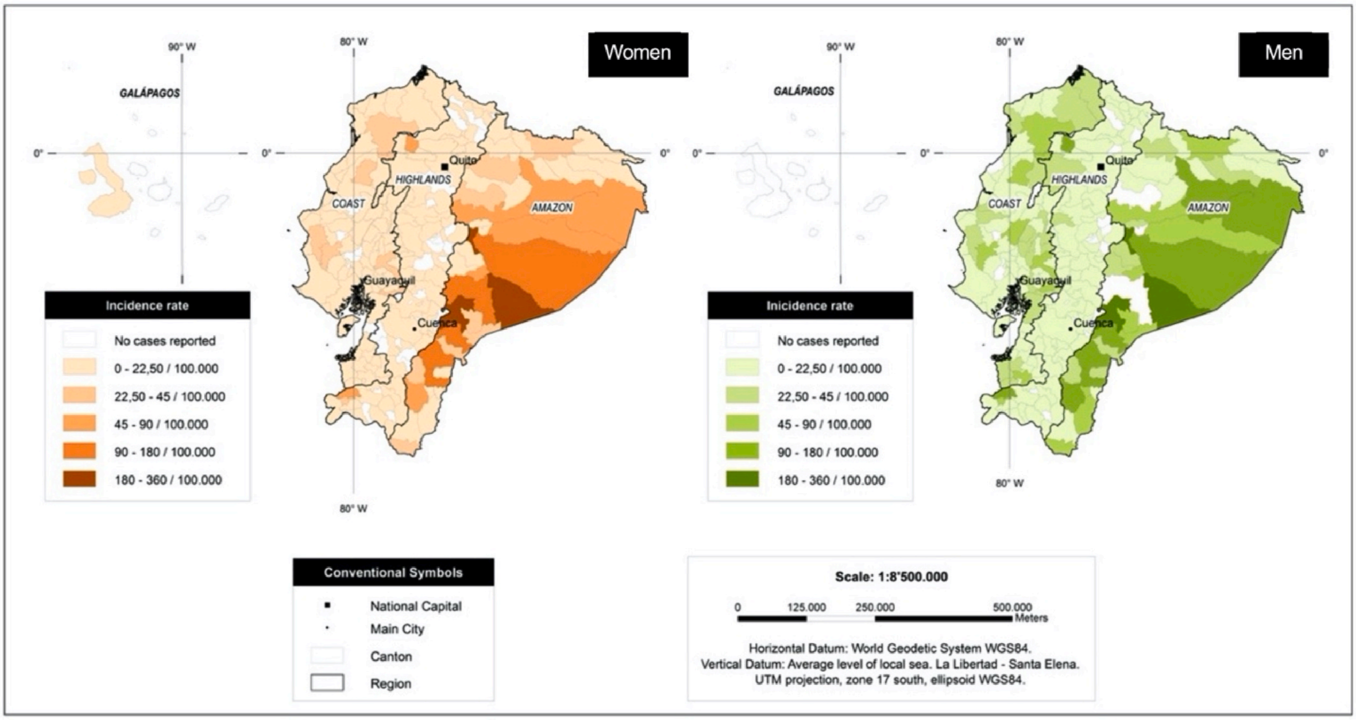

Fig. 1. Incidences per 100,000 population of snakebites by province in Ecuador from 2001 to 2018.

Table 3
Cases of snake bites by provinces in Ecuador from 2001 to 2018 [Developed from (Instituto Nacional de Estadística y Censos, n.d.)].

Provincias	Women				Men			
	# Cases	Rate*	95% CI <	%95 CI>	# Cases	Rate	95% CI <	%95 CI>
Azuay	57	6.51	3.01	10.01	92	90.79	−82.91	264.49
Bolívar	40	9.39	4.76	14.01	76	20.54	3.11	37.96
Cañar	44	4.67	2.64	6.70	114	13.47	5.59	21.35
Carchi	16	7.10	−0.42	14.64	25	10.81	1.97	19.64
Cotopaxi	89	12.85	7.69	18.00	162	25.50	13.78	37.21
Chimborazo	23	4.69	1.49	7.89	38	6.22	1.98	10.46
El Oro	317	12.15	9.25	15.05	964	46.21	18.56	73.87
Esmeraldas	889	22.98	15.99	29.97	1644	51.16	26.52	75.81
Guayas	1178	13.12	10.52	15.73	2811	36.19	19.68	52.70
Imbabura	2	1.24	0.72	1.75	1	3.09	1.93	4.25
Loja	243	37.31	13.99	60.62	460	58.23	22.29	94.16
Los Ríos	1150	22.71	13.21	32.22	2528	52.93	23.68	82.19
Manabí	1223	30.22	4.68	56.75	2512	65.57	2.955	128.20
Morona Santiago	1904	249.07	85.06	413.08	2221	274.93	114.01	435.85
Napo	442	65.45	53.47	77.42	583	73.82	57.37	90.27
Pastaza	988	189.80	133.84	245.74	1266	208.78	147.84	269.72
Pichincha	229	25.86	15.04	36.66	419	52.46	37.59	67.22
Tungurahua	25	3.17	0.52	5.82	39	2.58	0.99	4.05
Zamora Chinchipe	476	120.50	53.60	187.38	744	168.64	101.04	236.24
Galápagos	3	12.15	−13.48	37.77	0	0	0	0
Sucumbíos	440	38.90	29.42	48.37	674	73.44	50.06	96.82
Orellana	614	98.50	79.05	117.94	788	123.45	97.69	149.21
Santo Domingo de los Tsáchilas	461	14.31	10.74	17.88	844	25.49	18.58	32.39
Santa Elena	70	2.04	1.45	4.23	129	7.02	4.55	9.49

which resulted in the rapid cessation of production (E. Ortiz-Prado, 2018).

The problems related to GMP were not the only ones, other aspects related to production were also inadequate. For example they noted a high cost of animal maintenance, probably related to the inexistent system of production of snake food, and a misuse of equipment. The extraction of the hyperimmune plasma was also conducted in uncontrolled areas, and the filtration process and supply of the hematic components also placed animals in unnecessary risk (Ortiz-Prado, 2018).

3.4. Antivenom quality reported in Ecuador

In 2004 a test compared the effectiveness of polyspecific antivenom developed in Brazil, Ecuador, and Colombia against the venoms of *Bothrops atrox*, *Bothrops bilineatus*, *Bothrops s taeniatus*, *Bothrops brazili*, *Lachesis muta*. While all three antivenoms were effective, the antivenom produced in Ecuador showed a lower percentage of reactogenicity (Smalligan et al., 2004). Nonetheless, upon closing manufacturing facilities the Ecuadorian government was eventually forced to buy antiserum from other countries, to date the antiserum used is from the “

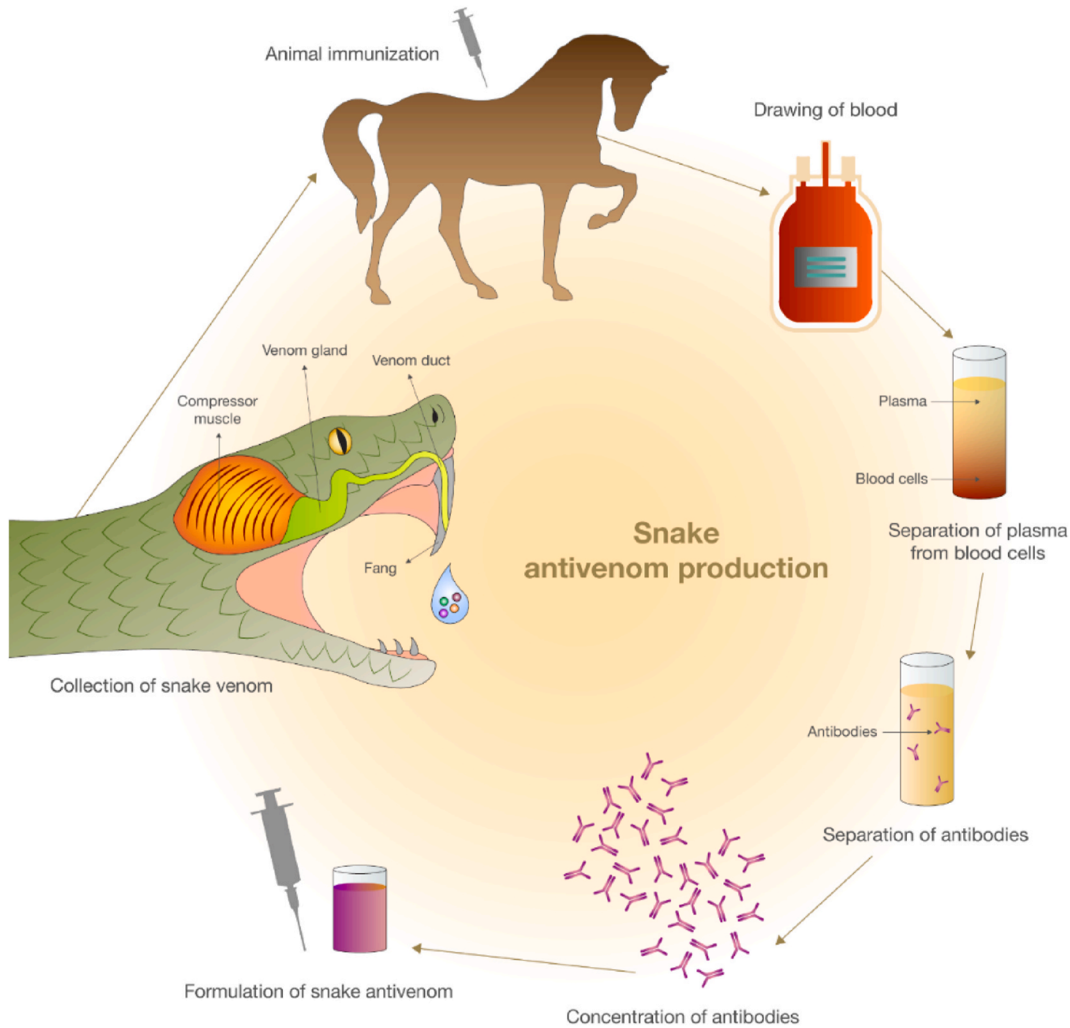

Fig. 2. Snake antivenom production scheme.

Instituto Clodomiro Picado (ICP)", Costa Rica.

3.5. Local availability of antivenom in Ecuador

For a brief time, the recently created and former National Pharmaceutical Company called "ENFARMA EP" tried to resume production to meet national needs by improving and strengthening that laboratory by enforcing production guidelines, however it was ultimately unsuccessful due to the lack of governmental oversight as well as due to the lack of long-term vision and plan from the former authorities.

Since ending the national production of antivenoms, Ecuador has relied on purchasing antivenom, serum sourced from the Clodomiro Picado Institute in Costa Rica, purchased through a local distributor named Cedimed Cía. Ltda (El Comercio, 2018). The available antivenoms are distributed in two different forms, freeze-dried powder and lyophilized liquid. The serum offered is made from the venoms of *Bothrops asper, Crotalus durissis* and *Lachesis muta* (ARCSA, 2021). From 2015 to 2017, at least 42,883 antivenom vials have been administered, representing an average annual consumption of 14,278 units.

3.6. Risks related to the lack of local production

In the 1990s it was noted that snakebite envenomations from the same snake species, but from geographically distinct localities, resulted in clinical differences in treatment (Chippaux et al., 1991). Differences were attributed to a variety of factors, such as the snake's diet, ecosystem microbiology and ambient temperature, all of which can influence the composition of the venom and its subsequent effect on humans (Daltry et al., 1996). The antivenom, serum provided by ICP uses *Bothrops asper venom*, a species that has an 80% chance of causing an SBE; however the other venom components represent species which rarely bite humans (*Lachesis muta* 5% of SBE) or are nonnative to Ecuador (*Crotalus durissis*) (ARCSA suero antiofídico, n.d.; Torres-Carvajal et al., 2018; Yañez-Arenas et al., 2018). The polyspecific bothropic serum ICP was shown to be effective in neutralizing LD_{50} hemorrhagic, coagulant, and defibrinogenic effects of Ecuadorian *Bothrops atrox* and *Bothrops asper* (Laines et al., 2014). However, Núñez et al., 2009 found phenotypic differences in *Bothrops atrox* from Colombia, Brazil, Ecuador, and Peru, this possibly due to the expansion of *Bothrops atrox* from the Caribbean to the Amazon region through the Andean corridor. It was also shown that the antivenom from Costa Rica was more efficient for *Bothrops atrox* from Brazil, Ecuador, and Peru, than from Colombian individuals (Núñez et al., 2009) indicating regional variance in efficacy. Importantly, efficacy differences have been shown among various serums against *Bothrops* snakebites of Ecuadorian origin; the Brazilian serum is most effective, followed by Ecuadorian and Colombian (Theakston et al., 1995). This further reinforces the importance of national production of native species-specific antivenom serums.

Despite the high incidence of snakebite in rural areas of sub-Saharan Africa, Asia, and some regions of Latin America, there is often limited availability of antivenom serums (Theakston, 2000), and many bite victims face long or difficult journeys to access healthcare facilities, often more than 6 h after the bite (El hattimy et al., 2018; Habib and Warrell, 2013; Warrell, 2010). It has been shown that receiving antivenom greater than 2 h after a snake bite can increase the risk of developing serious complications (RR = 2.5) (Smalligan et al., 2004). This is compounded by some rural health centers which do not have sufficient resources to adequately treat snakebite victims since the treatment requires specific and prolonged treatments and surveillance (minimum of 24 h) and testing (Harrison and Gutiérrez, 2016; Ministerio de salud pública de Ecuador, 2017). In many communities delayed treatment is also due to logistic issues such as remoteness, lack of road infrastructures, and poor ambulance services. However it may also come about due to cultural norms. In many cases the patients prefer to first visit traditional healers, whose treatments are not effective, even harmful. However these healers are perhaps especially attractive due to the lack of attention and effective antivenom in health centers, therefore traditional healers are still considered viable alternatives (Harrison and Gutiérrez, 2016). In fact, it has been estimated that approximately half of snakebites in Latin America are treated with traditional methods such as plants or hands-on healing (Smalligan et al., 2004). In Ecuador, of people who suffered snakebites in the Amazon region, 42% have reported having receiving some traditional treatment or remedy before prior arrival at hospitals (Praba-Egge et al., 2003). Proper implementation of health education regarding snakebites has shown positive results, reducing the incidence and mortality of rural community events in Asia. However, in addition to community involvement, these measures additionally require the active participation of health authorities (Sharma et al., 2013). In Costa Rica education programs exist to aid in the prevention and emergency treatment of snake bites which benefits groups such as residents of high-risk communities. Despite still possessing high frequencies of snake bites, the mortality rate is only 0.02 (Gutiérrez, 2011).

The WHO placed a high importance on antivenom, serums listing them as an essential medicine, meaning that in Ecuador it is placed as part of a list of basic medicines which should be accessible to all levels of medical care throughout the health care system (World Health Organization, 2019). Despite the importance placed on their production and distribution, antivenoms remain costly. For example the polyspecific antivenom of Africa sub-Saharan often costs around USD $400–700, making it one of the most expensive tropical disease treatments (Brown, 2012). However, in Ecuador in 2019 the National Council for the Fixation and Prices of Medicines (part of the Ministry of Public Health) determined that the antivenom, serum should have a maximum value of USD $71.57 (Secretaria Técnica de fijacion de precios de Medicamentos de Uso y Consumo Humano, 2019).

Combined, these financial, clinical, and logistical difficulties in application of antivenom, serum treatments may have contributed to the limited governmental investment in the production of the serum, which in turn resulted in the lack of control over SBE. The national database has reported a higher prevalence in coastal and Amazon areas of ophidic accidents in Ecuador from 2001 to 2018 (Instituto Nacional de Estadística y Censos, n.d.), where these localities correlate highly with victim vulnerability (Table 3). Specifically there are three provinces (Morona Santiago, Zamora Chinchipe, and Pastaza, all Amazonian) where the rate of envenomations approximate 1 case per 1000 inhabitants; among the highest worldwide (González-Andrade and Chippaux, 2010; Ochoa-Avilés et al., 2020).

3.7. Future directions for antivenom production in Ecuador

Similar scenarios of scarcity have been described in other parts of the world. For instance, in 2015 Africa faced a possible antivenom shortage due to the Sanofi-Pasteur's decision to cease production of its FAV-Afrique antivenom, which resulted in calls for urgent action. In 2017 the WHO listed SBE as a priority neglected tropical disease (NTD) after intense stakeholder advocacy including Doctors Without Borders, the World Snake Bite Initiative, Health Action International, and a detailed presentation from more than 20 countries (Scheske et al., 2015; Williams et al., 2019).

The production of anti-venom serum in Ecuador should be recovered to increase our chances to overcome a well known health problem. Local production not only secure antivenom efficacy due to our own biological diversity of native venomous species but also will increase our chances to develop our biotech industry (Ortiz-Prado et al., 2021).

For a developing country like Ecuador, producing antivenom serum will be a relatively costly process with little profit margin. Therefore instead of replying on investments from private agencies, the government should take the initiative. Therefore this will depend on a political mandate enacted by various governmental authorities. However, this initiative would also benefit from direct collaboration with non-governmental organizations, such as those dedicated to the conservation of animal species, natural science museums, and academic institutions.

The current context of the COVID-19 pandemic has revealed worldwide the critical importance of having national productive capacities (Reilly, 2020). The decision for investment in antivenom development would necessitate building significant infrastructure to produce on a large scale to supply national, and international demand from other countries in the region that lack that capacity.

Although the production of antivenom serum still maintains the same basic guidelines as more than 80 years ago, technology can now begin to explore the search for antigens found in snake venom and reproduce them in laboratories and produce vaccine, monoclonal antibodies, biologicals with much greater specificity and much lower risk of adverse events.

We firmly believe that it is fundamental that a country like Ecuador, where a large portion of its population lives in rural areas, has the productive capacity to produce antivenoms to meet local and regional needs. Resuming antivenom production would serve to strengthen and enhance the research in the field, thereby facilitating the transfer of techniques and enhance capabilities of a country that has been poised to make the great leap towards becoming developed nation.

4. Conclusions

As much as the development of the first antivenom, was a milestone in the treatment of snakebite envenomations providing hope for treatment, contemporary access limitations have resulted in unnecessarily high mortality. Dr. Calmette showed that it is possible to immunize an animal against the venom of a snake and then obtain their serum to treat another victim of envenomation by the same snake species. This was the first biological therapeutic alternative for snakebites. Subsequently, Dr. Vital Brazil demonstrated the specificity of antivenom, treatments, suggesting the subsequent development of polyspecific sera specific to species of diverse geographic regions. This should be further supported from a clinical point of view, affording information related to each antivenom, to optimize treatment.

Serum production needs to correspond to the diversity of venomous snakes in Ecuador. Specific attention should be invested by biologists to analyze venom diversity to quantify potentially important intraspecific and interspecific venom variability. This information will be critical to strategically chose the selection of venoms for serum production. Because Ecuador has a large number of ecosystems and different regions which results in high snake diversity, it is essential the country resumes domestic production of serums which treat local venom types, where production is safeguarded by high national standards ensuring quality control.

Credit author's statement

EOP was fully responsible for the conceptualization (with input from JY), data collection, and elaboration of the study. FA, CSG, PAF, and ET contributed to the data collection and the construction of figures and tables. LGB, KSR, and JSIC contributed with the descriptive statistical analysis EVG, JY and ET and contributed with introduction and discussion sections of the manuscript. EOP, JY and ET critically reviewed the entire manuscript before the submission.

Funding

This work: design of the study and collection, analysis, interpretation of data, and writing, did not receive direct financial support of any kind except for the publication fee paid in full by Universidad de las Americas, Quito, Ecuador. JY acknowledges financial support from Universidad de las Americas grant FGE.JY.20.13.

Ethical statement

This work has contemplated a review of the most relevant data on the production of anti-venom serum in Ecuador and the clinical data is anonymous and unidentifiable. Being a study of this type, the Bioethics Committee of the University of the Americas granted us an exception for not requiring any approval.

Declaration of competing interest

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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