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History and perspectives on how to ensure antivenom accessibility in the most remote areas in Brazil

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ABSTRACT

A plan to achieve self-sufficiency in manufacturing biologicals for public health has been structured for the last 40 years in Brazil, in the context of a reform in the health system. Industrial plants of the national public laboratories have been modernized, and a program for reducing morbidity and mortality of venomous snakebite has been created, as part of the National Epidemiological Surveillance System. The epidemiological data are essential to plan for the antivenom production of 400,000 vials of snake antivenoms per year, and the acquisition by the Ministry of Health, which is the exclusive purchaser in the country. Distribution is decentralized to reach hospitals in almost 3000 municipalities, and to provide free of charge antivenom treatment. The National Sanitary Surveillance Agency organized the regulatory environment to implement rules and supervise compliance of GMP procedures, elevating the quality of the biologicals that are produced, as well as reducing the costs in production. Despite all the advances in the health system, antivenom availability and accessibility is not uniform in regards to the most vulnerable parts of the populations, which inhabit remote areas in the Brazilian Amazon region. Better logistics and transportation of liquid form antivenoms is an issue to be addressed and realistic and comprehensive health programs for indigenous groups should be effectively structured, in order to reduce the high morbidity and mortality rates associated with snakebite envenoming.

1. Introduction: snakebites – a worldwide problem

Recognized as a serious health problem in tropical regions, snakebite envenoming has been included by the World Health Organization (WHO) in its list of neglected tropical diseases. However, morbidity and mortality still remain unacceptably high, in part because of the limited access to effective and safe antivenoms. Though there is a lack of robust statistical data on snakebites, an estimated 5.4 million people are bitten each year causing up to 2.7 million envenomings. Moreover, around 81,000 to 138,000 people die each year as a result of snakebites, with around three times as many amputations and other permanent disabilities caused by snakebites annually (World Health Organization, 2018). In the Latin American region, snakebites are an important health problem in Central and South America (Gutierrez et al., 2010; Gutiérrez, 2014), with a substantial number of incidences in the Amazonian regions of South American countries, where indigenous groups living in rural areas are particularly vulnerable (Chippaux, 2017).

Benefits of animal-derived immunoglobulins are well known. Snake antivenoms are the only specific treatment for snakebite envenoming; however, other polyclonal antibodies have been successfully used in the treatment and post-exposure prophylaxis of various infections and toxins (Dixit et al., 2015). Animal plasma, obtained by immunization with selective snake venoms, are fractionated and purified, resulting in mono- or polyspecific products that may be preparations of immunoglobulins or immunoglobulin fragments $F(ab')_2$ or Fab. The methods of antivenom manufacture and quality control protocols are widely described (Leon et al., 2014; Kalil and Fan, 2017; World Health Organization, 2017), but this does not necessarily mean a guarantee of availability of effective and safe antivenoms (Gutiérrez, 2012). The 46 antivenom-producing laboratories listed by the WHO are unable to provide the 10 million vials needed to supply global demand (World Health Organization, 2007). Furthermore, in the last few decades several laboratories interrupted or reduced manufacture in Africa, the Middle East, Asia and Latin America, justifying their actions by the argument of high expenses, complexity, and lack of a lucrative market. Another central obstacle for the effective treatment of snakebite envenoming is related to antivenom accessibility and failure in providing adequate medical assistance. The reduced production of specific

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antivenoms, difficulties in maintaining an adequate cold chain for distribution, and a lack of qualified health personal to administer antivenoms are common challenges. In addition, costly products result in unaffordable treatment for the patients, unless a solid national policy ensures access to antivenoms.

In Brazil, from 2000 to 2016, a total of 443,912 snakebites were reported to the official Brazilian health surveillance system, with a mean of 26,000 cases per year; the incidence is highest in the Amazon, with a rate of 48.8 cases per 100,000 inhabitants in 2016 (Ministério da Saúde, 2018). The Brazilian Amazon basin occupies roughly 40% of the South American continent and is mostly covered by dense tropical forest, although the deforestation of areas has been increasing rapidly due to soya bean plantations and ranching. The region is sparsely populated and, although the majority of people live in cities, there are still many indigenous groups and rural communities living in the jungle, which are especially vulnerable to transmissible diseases and snakebite envenoming. While a total of 1815 deaths and a lethality rate of 0.4% (Ministério da Saúde, 2018) from snakebites were recorded in Brazil between 2000 and 2016, in the Brazilian Amazon, lethality was estimated at 0.6% and was associated with factors such as lack of antivenom administration or incomplete treatments and late medical assistance, indigenous status, old age, and distance from the capitals (Feitosa et al., 2015; Souza et al., 2018). Snakebites from *Bothrops* spp. are the most commonly recorded in the Amazon, accounting for more than 80% of all cases (Fan et al., 2015). Snakes of this genus are responsible for most fatal cases in consequence of systemic bleeding, circulatory shock, sepsis and acute respiratory failure (Souza et al., 2018).

In this work, we present the Brazilian experience in the organization of a program for snakebite envenoming control. We discuss the policy for strengthening antivenom manufacture and distribution and the improvement of the victims' accessibility to medical assistance and opportunities for interventions in the Amazon River Basin of Brazil.

2. Historical and current aspects of antivenom distribution policy in Brazil

In Brazil, antivenom manufacture started in the early 20th century. Vital Brazil, with the founding of *Instituto Butantan* in 1901, started a long lasting tradition of studies on venomous animals, venoms, and envenoming in Brazil (De Franco and Kalil, 2014). His pioneering work included dissemination of the advantages of antivenom therapy, supplying rural landowners and physicians with vials of snake antivenom in exchange for snakes and data of envenoming outcomes of snake envenomings. His success motivated other scientists and institutions to focus attention on the problem of snake envenoming and antivenom preparation. Two other Brazilian laboratories were founded shortly after: *Fundação Ezequiel Dias*, in 1908, and *Instituto Vital Brazil*, in 1927. These three laboratories continue to supply the national demand for animal-derived immunoglobulins.

2.1. Health systems

National health policies for providing effective and safe products were only established in the 1970's and 1980's. Indeed, the last 4 decades were particularly important for the construction of the Unified Health System, a contemporary health reform in Brazil, driven by civil society. The advent of the Unified Health System increased access to healthcare for a substantial proportion of the population, and permitted other significant advances, including investments in human resources, science and technology, prioritization in primary care, decentralisation process of health actions, widespread social participation, and growing public awareness of a right to healthcare (Paim et al., 2011). This constitutes a favourable scenario for the implementation of a public apparatus of programs to cover the need for biological products, including vaccines and animal-derived immunoglobulins. Created in 1973, the Brazilian National Immunization Program was a milestone for the control of transmissible diseases (Domingues et al., 2012), and it brought vaccination campaigns, the implementation of strategies for snakebite envenoming control and, especially, the strengthening of the role of the national public laboratories involved in the manufacture of vaccines and antivenoms. At that time, the Ministry of Health established the basis for the program based on the following principles: 1. A national coordinating authority, with partnerships at regional and local levels, thus leading to decentralised decisions and actions; 2. Provision of sufficient financial resources to supply the population with immunobiologicals; 3. Rationalization of nationwide distribution logistics; 4. Creation of a national referral laboratory for the quality control of products, the *Instituto Nacional de Controle de Qualidade em Saúde* (INCQS), and the National Sanitary Surveillance System; 5. Training of health professionals in epidemiological surveillance, diagnosis and treatment, and 6. Health education of the population.

2.2. Antivenom shortage

At the start of the program, a major obstacle to its full functioning was the lack of mechanisms to assess the quality and effectiveness of the biological products in use. In the early 1980's, contamination in vaccines and unacceptable quality deviations in antivenom revealed the technological underdevelopment in antivenom manufacture. This scenario endangered the effective implementation of the program and exposed the population to health risks. A survey performed with the collaboration of Pan American Health Organization (PAHO) revealed the fragility of the national manufacturing laboratories and the dependence from the multinational industries to supply biological products, specifically routine vaccines (Ponte, 2003). One emblematic episode resulted in a severe crisis in the supply of snake antivenom throughout the country: in 1983, due to quality issues, the Ministry of Health ordered a halt in commercialization and distribution of vaccines manufactured by a multinational company, which was, at that time, an extensive supplier of antivenoms. Instead of refurbishing the industrial plants, the company opted to shutdown the manufacturing of immunobiologicals. By that time, a small percentage of the antivenoms came from national laboratories, which were in precarious conditions as a consequence of the lack of investments and, therefore, were not able to attend national needs. The health situation became extremely serious in 1985, when antivenoms were unavailable at medical health centers, leaving thousands of patients without antivenom therapy.

2.3. National self-sufficiency program

The response of the Ministry of Health resulted in large federal investment to provide the country with an industrial park that could become self-sufficient in antivenom manufacture and independent from the importation of vaccines. In 1985, a plan for physical, structural and technological modernization of the national laboratories was implemented and, in the early 1990's, about US$ 100 million had been allocated to six public laboratories, three of them were antivenom-producing facilities (Ponte, 2003). Such an ambitious program was based on the argument in defense of Brazil's national autonomy in the manufacture of immunobiologicals, by considering: 1. It was a matter of national security to be not too dependent on the political or economic fluctuations in the importation of vaccines; 2. The nationalization of immunobiological manufacture could provide, in the future, a surplus amount of products for exportation; 3. Government should finance public laboratories to manufacture and supply the country of some vaccines and the animal-derived immunoglobulins, and 4. The opportunity to develop and increase scientific and technological skills in these areas.

Almost 40 years later, self-sufficiency in antivenom manufacture was achieved by the 300,000 vials supplied per year of five types of snake antivenoms (AVs): *Bothrops* AV (the main one), *Crotalus* AV,

Bothrops-Crotalus AV, *Bothrops-Lachesis* AV, and *Micrurus* AV (Fan et al., 2015). Antivenoms for arthropods envenomings are also produced in Brazil, including *Loxoceles* and *Phonetria* spiders and *Tityus* scorpion AVs, *Lonomia* caterpillar AV, which account for 200,000 vials per year. All batches of antivenom manufactured by the official laboratories are released after quality control analysis performed by INCQ (Araújo et al., 2008). Since 1999, the National Sanitary Surveillance Agency (ANVISA, abbreviated from Portuguese) is responsible for executing sanitary control of the production, marketing and use of products subject to health regulation, besides other regulatory actions (De Seta et al., 2017).

2.4. Surveillance system

A program for the surveillance of injuries caused by venomous animals was established in 1986, as part of the national epidemiological surveillance system. Since then, antivenom manufacture has been standardized and the total quantity produced from the three national laboratories (Instituto Butantan, Fundação Ezequiel Dias, and Instituto Vital Brazil) is acquired by the Ministry of Health for distribution to patients free of charge (Fan et al., 2015). An electronic databank has been created to supply local, regional and central levels of the National Health Surveillance System with relevant information to implement co-shared control and prevention actions (Laguardia et al., 2004). The policy of antivenom distribution is currently a responsibility of the National Program for Immunization, based on data generated by the epidemiological surveillance system. An electronic information system provides a large amount of epidemiological data concerning envenoming caused by animals. A historical trend of snakebite envenoming cases and deaths are shown in Fig. 1.

Snakebite envenoming is a disease of compulsory report in Brazil. Data collected from the hospitals are transferred electronically to reach the central level at the Ministry of Health. In the period of 2000–2016, a historical trend of snakebites indicated the occurrence of an average of 26,000 cases (incidence rate = 15 cases per 100,000 population) per year. The number of deaths did not decrease significantly, with more than 100 lethal cases reported yearly, although antivenom availability was considered satisfactory. Quality of medical assistance is a constrain to reduce case-fatality rates, that remained over than 0.4% in the last years.

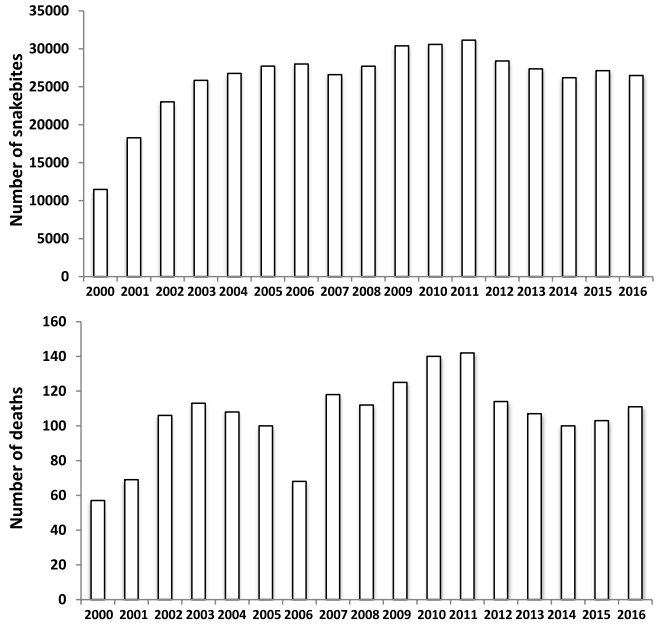

Fig. 1. Snakebite envenoming cases and deaths, per year in Brazil, from 2000 to 2016, according to the National Health Surveillance System.

3. Availability of snake antivenoms in Brazil: economical approach and gaps

3.1. Good manufacture practice standards

The process of antivenom manufacture is time-consuming and costly, especially the preparation of appropriate venom mixtures and antigens. Another critical step is the production of hyperimmune plasma, which depends on the response of horses or other animals to immunization schedules (World Health Organization, 2017). The purification of immunoglobulins fragments from the starting plasma pool demands a highly cost industrial infrastructure and utilities, as antivenoms must meet requirements of purity, safety, and efficacy. Quality control tests, validation of processes and stability studies to assure the quality of the antivenoms are also expensive steps, requiring large financial expenses mostly for consumable materials and services. Specialized personnel demand compatible salaries, social security contributions and benefits, which represent a significant proportion in the production costs. Over time, the technological and quality requirements from regulatory agencies have increased the cost of antivenom manufacture, quality control tests, and validation studies. In Brazil, under the coordination of ANVISA, the country has made significant advances in relation to the regulation of the pharmaceutical sector, which has culminated in the publication of Good Manufacturing Practice (GMP) standards now in force (Agência Nacional de Vigilância Sanitária, 2018). Naturally, both public and private laboratories have been adjusting their industrial plants to the higher standards. Instituto Butantan was the first to obtain the GMP certificate for antivenom production in Brazil, and it is expected in the next few years that all products distributed to the public health system will be acquired only from certified manufacturers. Centralized acquisition by the government of hundreds of thousands of vials of antivenoms assures a captive, but exclusive market, as all antivenom-producing laboratories are supposed only to attend to the national demand.

3.2. Financial support for antivenom manufacture

Financial support for scientific and technological development has been obtained mainly through public foundations, that have been conducting national and international technological innovation programs; therefore, facilitating cooperation with academic groups Gutiérrez et al., 2007, 2009). Otherwise, investments to modernize and renovate the industrial complex to accomplish to GMP rules depend mostly on the own sources of the laboratories, leading to a gap between private and public ones, the latter usually with little or no capital reserve. Often, investments in infrastructure and equipment are necessary, but increasing the qualification of technical and professional personnel is also a priority. This heterogeneity of the situation of antivenom-producing laboratories involves different scenarios and situations that have to be faced individually (Gutiérrez, 2012; Scheske et al., 2015). Inevitably, the result is a highly expensive product. How to assure funding sources to have high-quality and free-of-charge antivenoms available in the public health system, is a problem to be solved, even more considering the complexity of the Brazilian Unified Health System (Cornall and Shankland, 2008) and, particularly, the manufacturing processes of the biological products. Budget for acquisition of biologicals exceeded US$ 300 million in 2010 (Domingues et al., 2012). Although antivenoms represent a minor proportion of about 5%, a significant sum of resources to maintain the self-sufficiency policy for antivenoms has been spent.

3.3. Policy of antivenom distribution

The final cost of antivenom availability does not depend only on the

manufacturing process, but also involves national policies for distribution and use (Gutiérrez et al., 2009). Since 1996, the acquisition process in Brazil has been centralized by the Ministry of Health; therefore, there is no commercial sale of antivenoms for the treatment of patients bitten by snakes. The distribution process, in turn, is decentralized, from the State Secretaries of Health, then to the Regional Offices of Health, then to the Municipal Secretaries and finally to the Health Services, based on the antivenom needs of each region. The decision regarding which regions should receive antivenoms, the corresponding quantities and types of antivenoms is based on the following parameters: (a) epidemiological risk of envenoming supported by the official surveillance system; (b) conditions for adequate storage and administration of antivenoms; (c) existence of health posts and health staff; (d) access to health centers in a relatively short time interval; and (e) availability of referral hospitals. In practice, distribution is unequal through the territory (Gutiérrez et al., 2009). While in most of the Amazon region, each municipality has at least one hospital with a stock of antivenoms, and should provide medical assistance for snakebites 24 h a day, in other parts of the country only one of four municipalities are provided of antivenoms. Mostly, antivenoms are deployed to hospitals located in the cities, but not to the rural health facilities where most snakebites occur. These criteria for antivenom distribution in Brazil should be reviewed, as such policy has shown to deprive considerable part of the rural and indigenous population from antivenom treatment. As medical emergencies, snakebite envenoming demand a rapid intervention, preferentially in the first six hours after bite and frequently with antivenoms administration. However, many vulnerable groups in the Amazon region may take days to reach medical assistance, by the time antivenom cannot be able to reserve effects of envenoming.

Approximately 500,000 vials of different types of antivenoms were distributed yearly in 2010 and 2011, with a reported use of 40–50%. Since 2013, there is a tendency to reduce the quantity of antivenoms to be distributed (Reckziegel, personal communication). This reduction aims to minimize waste due to errors in estimating the necessities and thus leading to a great number of expired vials at the hospitals. However, it should be considered that these figures are based on official data generated by hospitals mostly located in urban areas. Likely, reports of snakebite envenoming in remote rural areas are unreliable, and the number of patients that remain deprived of antivenom therapy remains an unanswered question.

4. Antivenom accessibility: current status and opportunities for improving performance

4.1. Gaps in accessibility to remote areas

Immunobiological preparations are thermolabile, requiring refrigeration from the production laboratory until their administration to the patient. Therefore, a major concern is the lack of an adequate cold chain, which impairs antivenom distribution to remote areas. Also, inadequate storage and transportation may result in loss of product. Avoidable types of damage are broken vials, exposure to inadequate temperature in case of interruption in the electricity supply, mechanical failure in the refrigeration equipment, expired validity, errors in standardized technical procedures and failure of the transport process. In Brazil, the mode of transport predominantly used in the distribution of immunobiologicals is via road. In the Brazilian Amazon region, however, fluvial and air transport is also used, since access to a large part of the municipalities does not occur by means of terrestrial transport. In these areas, the level of the rivers influences the routine and routes of pharmaceutical distribution, requiring more complex logistics for inventory management tools to ensure access to antivenoms throughout the year (Medeiros, 2012). It is worth mentioning that the region also presents difficulties with regard to the structural conditions of its ports, in which the lack of signaling and marking of the passages cause insecurity and restriction to their nocturnal navigation, increasing transport duration and the possibility of failure during transport. Due to the wide territory to be covered, antivenom distribution necessarily also involves air transport from the national warehouse to the capitals of the 27 states. Usually, the antivenoms are distributed to the states, and then to the municipalities, on a monthly basis, according to estimates of necessity and use of a given number of vials in the previous month. This schedule can only be made feasible in certain parts of the Amazon by air transport, especially during the dry season, where fluvial transport may take weeks from the capital to the furthest municipality.

4.2. Antivenom loss along the cold chain

Although no systematic evaluation on the causes of antivenom losses has been carried out in Brazil, a study performed on the vaccine distribution chain showed that physical damage resulting from “power outages” and cold chain interruptions were very common in four Brazilian states, with a financial cost of approximately US$ 2.5 million (Panamerican Health Organization, 2018). Another study, performed in Southern Brazil, indicated that, from 2007 to 2010, physical damage occurred in 3.0% of vaccines doses distributed (Pereira et al., 2013). Partly, this excessive rate of avoidable losses is the result of no specific training in storage and administration of health professionals (Luna et al., 2011; Aranda and Moraes, 2006; Melo et al., 2010; Raglione et al., 2016). Unfortunately, detailed information concerning the causes of losses of antivenoms is scarce and the National Immunization Program has no reliable data. Only one local investigation indicated that losses of antivenoms were associated mostly with expired validity (79%), broken vials (4%), power outage (4%), equipment failure (4%), inappropriate procedures to prepare antivenom solution (3%), and transportation failure (1%) (Oliveira et al., 2014).

Large financial resources have been spent and a great effort has been made to improve the efficiency of the logistical management of the flow of products between antivenom-producing laboratories, the Ministry of Health, the states and the municipalities (Fig. 2). However, in the nodal points of the network, which are located closer to the health care services, the quality of the operations decreases, jeopardizing the continuity of the supply of immunobiologicals (Coelho-Netto, 2008). Management capacity for immunobiological distribution is known to be higher in the upper levels, in which there are larger financial resources for staff training, better facilities, transport, and equipment maintenance. However, the probability of antivenom loss is higher in the lower levels, especially at the municipal levels, where transport and equipment failures and procedural errors mostly occur.

4.3. Freeze dried antivenoms

In remote areas, a major concern regarding effective treatment of snakebite envenoming relates to the impossibility of liquid antivenom distribution to healthcare centers, due to the lack of an adequate cold chain system to storage the products. This invariably results in delayed patient care and, ultimately, in higher complications and case fatality rates. Despite the urgency of more stable and easy to distribute antivenoms, this issue has not been included in the agenda of the Brazilian healthcare authorities' negotiations with antivenoms manufacturers; therefore, no freeze-dried antivenoms is available in the public health system.

Freeze-drying is a very critical process, as proteins are sensitive to the stress of freezing and drying, and this may damage antibodies, causing impact on protein activity and aggregation, which can affect the efficacy and safety of the product. Some studies have been performed in Costa Rica testing alternatives to improve the physicochemical stability of the protein (Herrera et al., 2014) and characterizing physicochemical structure of commercial freeze-dried antivenoms from India, Mexico, Thailand and Costa Rica showing acceptable quality standards (Herrera et al., 2017). Freeze-dried formulations may become a good alternative for the availability of more stable products in

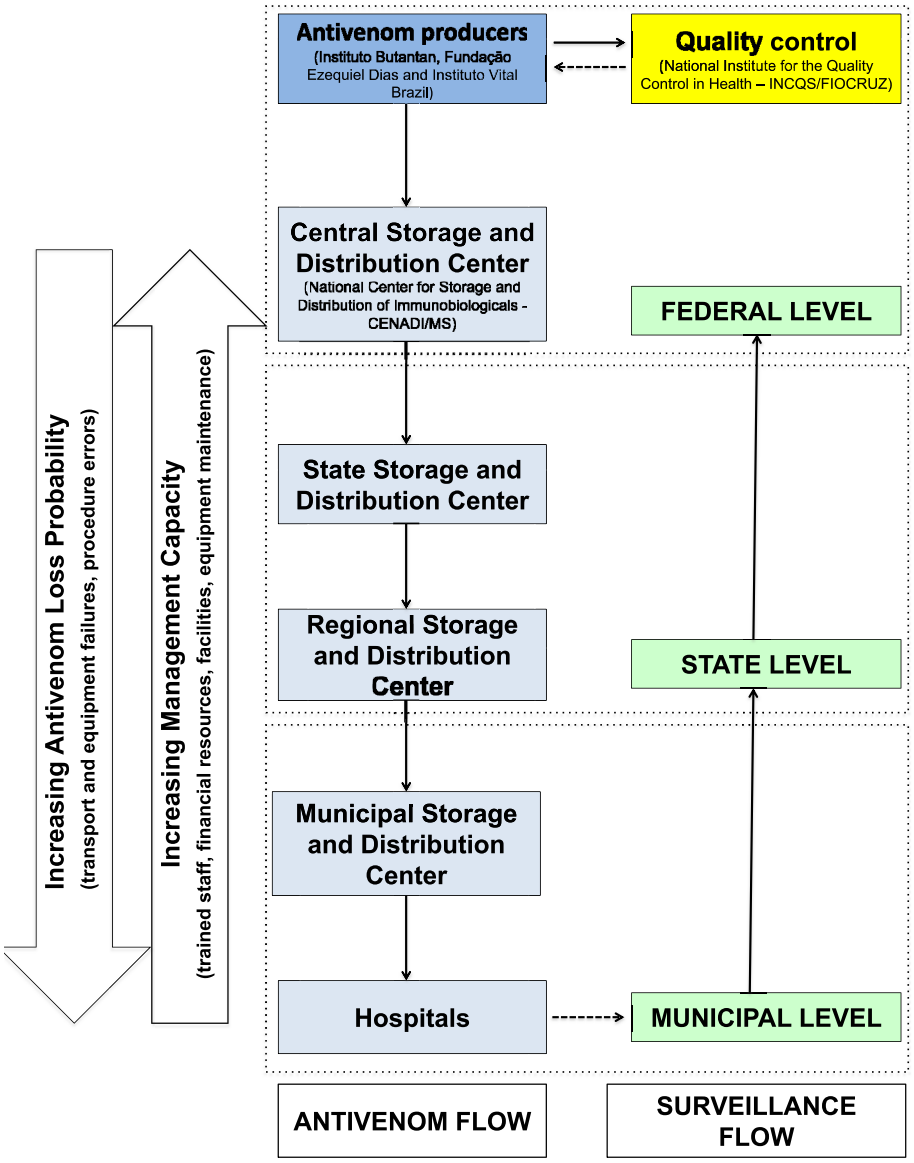

Fig. 2. Flow of antivenom distribution from the antivenom-manufacturing laboratories to the hospitals and surveillance flow in the opposite direction. Model derived from the immunobiological national distribution proposed by Coelho-Netto (2008).

regions where high temperatures are common and the cold chain is poor, such as in the Brazilian Amazon.

Nevertheless, there is a very limited literature on clinical efficacy and safety for freeze-dried antivenoms. A small trial testing a pilot trivalent *Bothrops-Lachesis-Crotalus* freeze-dried antivenom, in comparison with the standard liquid formulation provided by Instituto Butantan and the Brazilian Ministry of Health, respectively, showed promising results for efficacy, safety and thermal stability of the freeze-dried antivenom (Mendonça-da-Silva et al., 2017).

Currently, this issue represents a big challenge for the Brazilian antivenom manufacturing laboratories. However, it is time to increase the availability of stable, safe and efficient antivenoms in remote areas, preferably to be stored at room temperature.

5. Medical assistance decentralization

5.1. The rural/indigenous populations' situation

There are still regions in Brazil, namely the Amazon, where access to antivenoms is limited and where patients have to travel long distances to receive antivenom treatment (Feitosa et al., 2015; Fan et al., 2015). Currently, in this region, the capitals and a few other large cities monopolize the systems of supply, transportation, provision of services and the conduct of political life, in a setting of weak leading roles of other municipalities and rarefied interaction between them. In this case, this model establishes a type of healthcare organization in which residents of the interior of the state are obliged to resort to the metropolis regularly in search of care, without a network of health interactions that resembles what is advocated for a healthcare region (Garnelo et al., 2017). These structural inequities are associated not only with geographical and political isolation, but also with the low capacity of management and collection by the administration of lower municipalities, which also makes it impossible to incorporate technology into their services, perpetuates low performance and poor healthcare levels (Garnelo et al., 2017; Oliveira, 2008; Viana et al., 2015).

The low health system performance in the interior compared to capitals clearly reflects in clinical outcomes in snake bitten patients. Fig. 3 shows that although Manaus, capital of Amazonas state, and other municipalities in the countryside present similar antivenom use

Fig. 3. Three emblematic cases of severe Brazilian pit viper (*Bothrops* spp.) envenoming from in the Amazon region. Patients received late antivenom therapy (> 6 h) and developed severe local complications. A) Patient presented with secondary infection (culture positive for *Morganella morgani*) and tissue necrosis in the bite site; B) Patient presented with tissue necrosis and secondary infection in the bite area and compartmental syndrome affecting hand and left forearm; C) Patient presented with compartmental syndrome in the affected limb and renal failure. Surgical intervention and prolonged hospitalization in a tertiary care centre were needed in the three cases.

and underdosage rates, late medical assistance (> 6 h after snakebite) is significantly more frequently observed in the indigenous and interior populations after snakebites from *Bothrops* spp.

5.2. Long time from bite to treatment

Late medical assistance is attributed to the difficulty populations in the interior have in order to reach healthcare infrastructure in the municipal setting, for the reason that this population depends on fluvial transport by boats, and this is possibly the cause of the higher lethality and severity rates in countryside (Feitosa et al., 2015). To improve poor outcomes, it is vital that they should all be made aware of the importance of immediate immobilization of the limb and transfer to the hospital at the earliest possible moment. Simple educational messages and promotion of immediate and rapid transport of victims by motorcycle to a treatment center decreased the mortality rate and incidence of snakebite in southeastern Nepal (Sharma et al., 2013). In the Amazon, a small number of riverside communities have fluvial units from the public mobile emergency service, which are permanently based in the communities. The vehicles are ambulance service motorboats (known as '*ambulanchas*') and assist in the rapid rescue of patients in the riverside communities. Alternative strategies, implemented by non-profit organizations to increase the health status of the riverine populations in Amazon, resulted in mobile health units, based on boats, with medical staff and medicines, that work on the banks of the Amazonian rivers to provide access to primary care programs and emergency assistance, including antivenom therapy (Scannavino and Anastácio, 2007). However, this type of health program has a high cost and is usually dependent on governmental and international financial support.

Although decentralization of the fluvial emergency service certainly helps to shorten the time from bite to treatment for the victims who live in these communities (Fig. 4), these are still only available in very few locations mostly in areas surrounding the capital. In some cases, severe snakebites require aero-medical evacuation by the Brazilian Air Force or by private companies, an expensive specialized service hired by the countryside's city departments.

5.3. Lack of access to antivenom treatment

Antivenom underdosage is more common among indigenous populations, as well as an even longer time to reach medical assistance, resulting in the highest poor outcome rates (Fig. 5). In a previous study, a distance > 300 km from the place of bite and the state capital, and indigenous status were independently associated with case fatality from snakebites (Feitosa et al., 2015).

In 1999, a special model of the health system was implemented by the Brazilian Ministry of Health, for indigenous groups that, given the increased vulnerability of this population to disease, yielded benefits from products, some not yet routinely available to the general population (Domingues et al., 2012). The accessibility to some vaccines, such as the seasonal influenza vaccine for children over 6 months, indeed decreased indigenous morbidity and mortality, while other special immunobiologicals, such as human anti-rabies and anti-tetanus immunoglobulins, are still only available in hospital reference centres, far from indigenous villages. Antivenoms have never been included in the

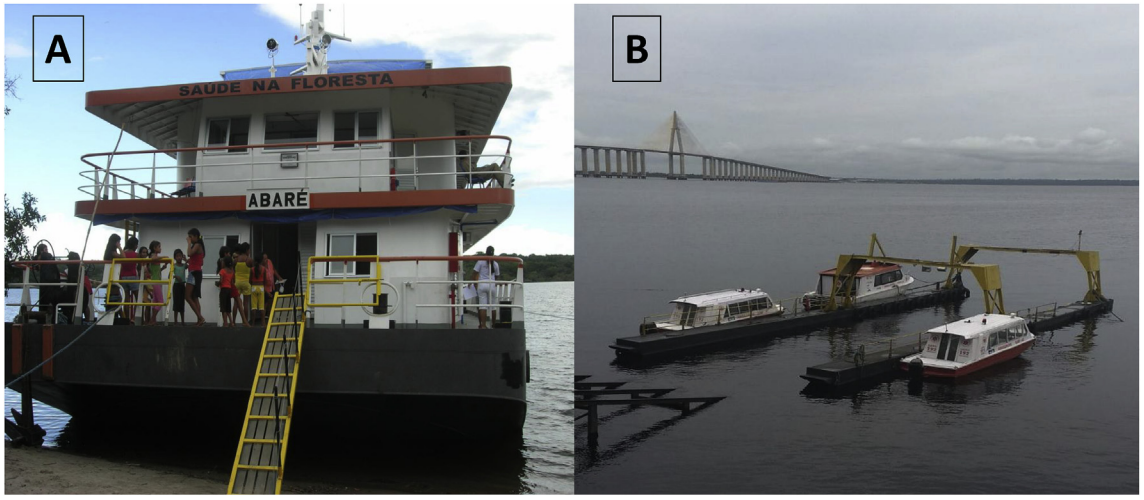

Fig. 4. Alternative models of healthcare assistance in Amazon region. A) Mobile health unit named *Abaré* ('*companheiro do homem*', in Portuguese; man's companion) on the Tapajós River, Pará state, Brazilian Amazon; B) Ambulance service motorboats (known as '*ambulanchas*', in Portuguese) for the rapid rescue of patients in the riverside communities surrounding Manaus, Amazonas State, Brazilian Amazon.

list of the products to be provided by a special program to indigenous populations, making antivenom treatment accessible through the general health system. This results in long distance trips from villages to hospitals in the cities, frequently violating traditional beliefs concerning diseases and treatments (Montenegro and Stephens, 2006), and explain the results of Fig. 4. Moreover, a parallel information system for indigenous health was created, but not integrated to the general epidemiological surveillance system. Statistics of snakebites in indigenous groups are unreliable and access to antivenoms are still far from acceptable.

5.4. Lack of health professionals

Another crucial factor for access to antivenom is the presence of a physician in the health care unit, since by federal legislation parenteral formulations require medical prescription. As opposed to being distributed to peripheral health clinics, in which more basic health problems are solved by nurses, antivenom treatment is generally available only in one hospital in Brazilian municipalities, where a medical doctor has to be present. Thus, the expansion of antivenom therapy to more health units could be an intervention to increase patients' access to treatment. However, in the countryside of the Amazon region, there is a huge shortage of health professionals, with some municipalities of the State of Amazonas having only 0.2 physicians for every 1000 inhabitants, showing a panorama of greater vulnerability (Silveira and Pinheiro, 2014). To increase health access for vulnerable populations and to contribute towards the consolidation of primary health care in Brazil, the *Mais Médicos* Program was launched in July 2013 with public calls to recruit physicians for priority areas. Although the shortage decreased and health access for vulnerable populations increased from its implementation (Lima et al., 2016; Santos et al., 2017), an overall situation of insecurity in care persists, reflecting the

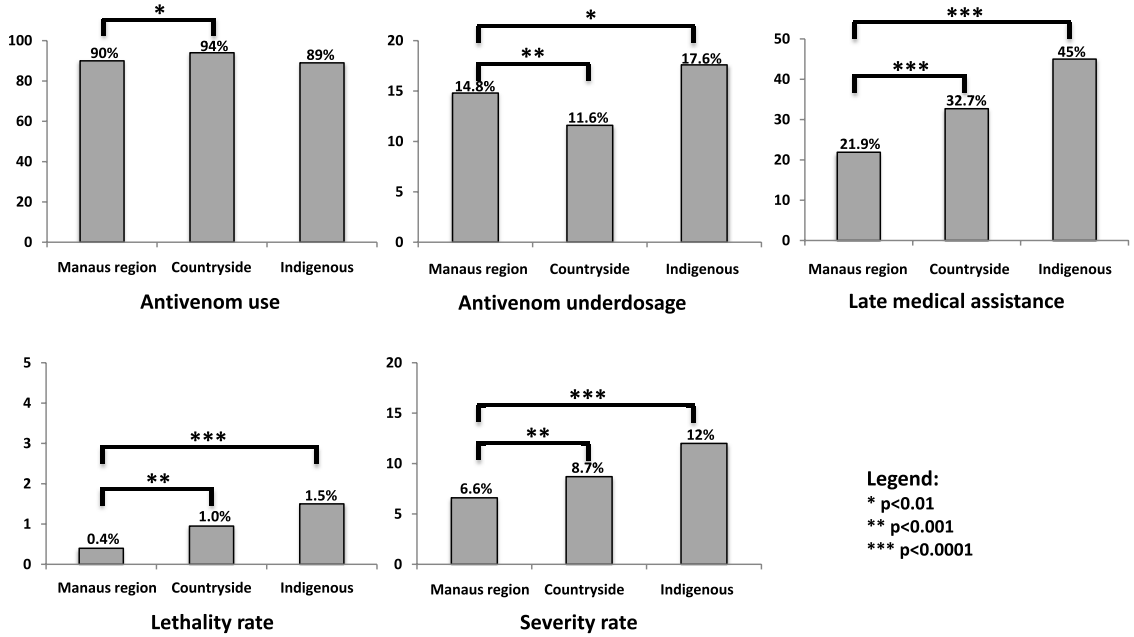

Fig. 5. Comparison between antivenom use, antivenom underdosage, late medical assistance, lethality and severity levels in Manaus region, countryside and indigenous population in the Amazonas state, for snakebites from *Bothrops* spp.

dependence of municipalities on the supply of physicians by the federal government (Girardi et al., 2016).

5.5. Training human resources

Despite the high incidence of snakebites, there is a lack of systematic, professional training, diagnosis, specific therapies, and clinical management of envenoming complications. Current training programs seek to link and integrate medical knowledge with the snake and scorpion biology and surveillance. However, this approach often does not reflect the need for professional diagnosis algorithms and coherent and responsive medical management (Fan et al., 2015). Thus, adherence to medical training and courses in this area has been a major challenge. Furthermore, there is a high turnover of health professionals in small Amazon cities. The use of electronic media for training professionals in the management of envenoming is increasing and may be an alternative to classroom courses. In the large Amazon areas, telehealth tools should be used for improving medical care performance in remote areas. In Brazil, there is a Tele-health Network Program that seeks to improve basic care and the quality of care in the Unified Health System by integrating teaching and service through information technology tools that offer conditions to promote Tele-assistance and Tele-education. In the Amazonas state, for instance, there are tele-health points connected to Manaus in almost all of the municipal seats and in some indigenous communities, making it possible to have long distance patient/clinician contact and care, advice, reminders, education, intervention, monitoring and remote admissions. However, although communication technologies that greatly facilitate knowledge dissemination have increased in the area, these are still barely harnessed (Universidade do Estado do Amazonas, 2018). Clinical management of snakebite complications has to be standardized in concepts and management protocols. The possibility of reducing local complications by means of drugs with anti-inflammatory properties, early antibiotic therapy for secondary infection, cross-neutralization of antivenoms for different types of envenoming incidents, and new complementary treatments need to be further investigated while observing good clinical practice and, preferably, in multicenter studies (Fan et al., 2015).

The burden of loss of physical functions associated to snakebite envenomings to vulnerable populations remains as a major research gap, both from the health system and society perspective. In the state of Acre, in the Western Brazilian Amazon, functional impairment of the bitten limb was recorded in 10% of the indigenous and riverine population surveyed, including permanent loss of function and sensibility, amputations, and permanent scarring (Pierini et al., 1996). In order to improve the victims' ability to function normally, their quality of life, and their life expectancy as much as possible, public policies aiming to identify incapacitated victims and provide them socio-economical support and physical rehabilitation should be part of integrated national programs for chronic pathologies.

6. Final remarks

The establishment of an antivenom-producing facility, distribution logistics, the organization of quality control and the institution of epidemiological surveillance are achievements that have led to self-sufficiency in production and which guarantee free access to the treatment of victims of venomous animals in Brazil. This advance has only been possible thanks to the presence and the work of proper technical staff to forge areas of consensus in the central positions. However, a gap remains in access to antivenom treatment of vulnerable populations in rural areas, due to the lack of investment in personnel and logistics at the local levels of the decentralization of the health system. It is of urgent importance to provide incentives and encourage implementation of specific strategies to reach these populations, by a wider, interconnected network among local, regional and central levels of health policies.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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