

Mapping of clinical management resources for snakebites and other animal envenomings in the Brazilian Amazon

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ABSTRACT

Snakebite envenomings (SBEs) and other envenomings triggered by venomous animals (VAEs) represent a significant disease burden in Brazil, with 29,152 SBEs reported in 2021 alone with nearly half of those occurring in the remote Brazilian Amazon. In 2021, Brazil recorded 240,294 envenomings from snakes, scorpions, spiders, and caterpillars. Therefore, there is an unequal distribution of SBEs with high morbidity and mortality in the Brazilian Amazon. The severity of SBEs increases when patients require more than 6 h to access antivenom treatment, a common issue for the rural and indigenous populations. Understanding currently available resources and practices in Amazon remote areas of Brazil can serve to inform future interventions and guide health care policies. This study aims to develop a resource map of existing healthcare resources for the Brazilian Amazon's clinical management of VAEs with emphasis in SBEs, which will aid future strategic interventions. Data collection included a literature review, secondary data collected by government departments and organizational records, GIS mapping activities, and expert input. Our framework was guided by the three levels of healthcare service ecosystem analysis (macro, meso, and micro). Our resource map lays out a comprehensive overview of antivenom access, the distribution landscape, differences in patient transportation, and barriers to access healthcare that face populations in the Brazilian Amazon.

1. Introduction

In 2021, Brazil recorded 240,294 envenomings by snakes, scorpions,

spiders, and caterpillars (Ministério da Saúde, 2022a). Moreover, there is an unequal distribution of venomous animals' envenomings (VAEs) with high morbidity and mortality in the Brazilian Amazon (Queiroz

Abbreviations: VAE, Venomous animals' envenoming; SBE, Snakebite envenoming; AV, Antivenom; MoH, Brazilian Ministry of Health.

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et al., 2015; Feitosa et al., 2015; Sampaio et al., 2016). For instance, Brazil recorded 29,152 snakebite envenomings (SBEs) in 2021, with 12,701 occurring in the Brazilian Amazonia (Ministério da Saúde, 2022a). Notably, the Brazilian Amazon accounts for less than 9% of the total population of the country, yet is responsible for 44% of SBEs (Ministério da Saúde, 2022a). In this region, lethality rate from SBEs is significantly higher in indigenous and riverine populations (1.4%) compared to populations living closer to urban areas (0.5%) (Monteiro et al., 2020). The true number of SBEs in Brazil is expected to be substantially higher due to underreporting (Salazar et al., 2021).

For more than a century, public national laboratories have been responsible for antivenom (AV) manufacture in Brazil. Since the 1980's distribution to referral centers is federal-funded and free of charge for VAE victims. Nevertheless, financial, cultural, and logistical barriers impact AV access in the Amazon with consequent increased rates of complications, disabilities, and mortality (Wen et al., 2015; Wen and Monteiro, 2018). Indeed, there are few hospitals with AV treatment available in this region, combined with river transport challenges, low acceptance of medical healthcare by indigenous victims, and the use of ineffective or deleterious self-care practices (Wen et al., 2015; Wen and Monteiro, 2018; da Silva Souza et al., 2018). Understanding currently available resources, their logistics, and clinical practices in these areas can be useful to improve interventions and guide healthcare policy. This

study aims to develop a resource map for the management of VAEs highlighting SBEs in the Brazilian Amazon.

This paper is a result of the collaboration between researchers and clinician experts from Brazil (*Fundação de Medicina Tropical Dr. Heitor Vieira Dourado* and *Instituto Butantan*) and the United States (Duke University), in close cooperation with the Technical Group of Animal Envenomings Surveillance of the Brazilian Ministry of Health (MoH) and the Zoonoses Department of the *Fundação de Vigilância em Saúde do Amazonas*. The data presented describes the three levels for healthcare service ecosystem analysis (macro, meso, and micro) (Beirão et al., 2017) (Figs. 1 and 2).

2. Macro (national) level of resources

In 1986, the National Program for the Control of Snakebites (*Programa Nacional de Controle do Ofidismo - PNCO*) was launched, aiming to reduce SBE mortality. In 1989, it was renamed as National Program for the Control of Venomous Animal Envenomings (*Programa Nacional de Controle dos Acidentes por Animais Peçonhentos - PNCAAP*) with expanded scope to include scorpions, spiders and other venomous animals. The MoH coordinates actions within the context of a national program for self-sufficiency in immunobiologicals (vaccines and immunoglobulins).

The Brazilian MoH supported the modernization of the industrial

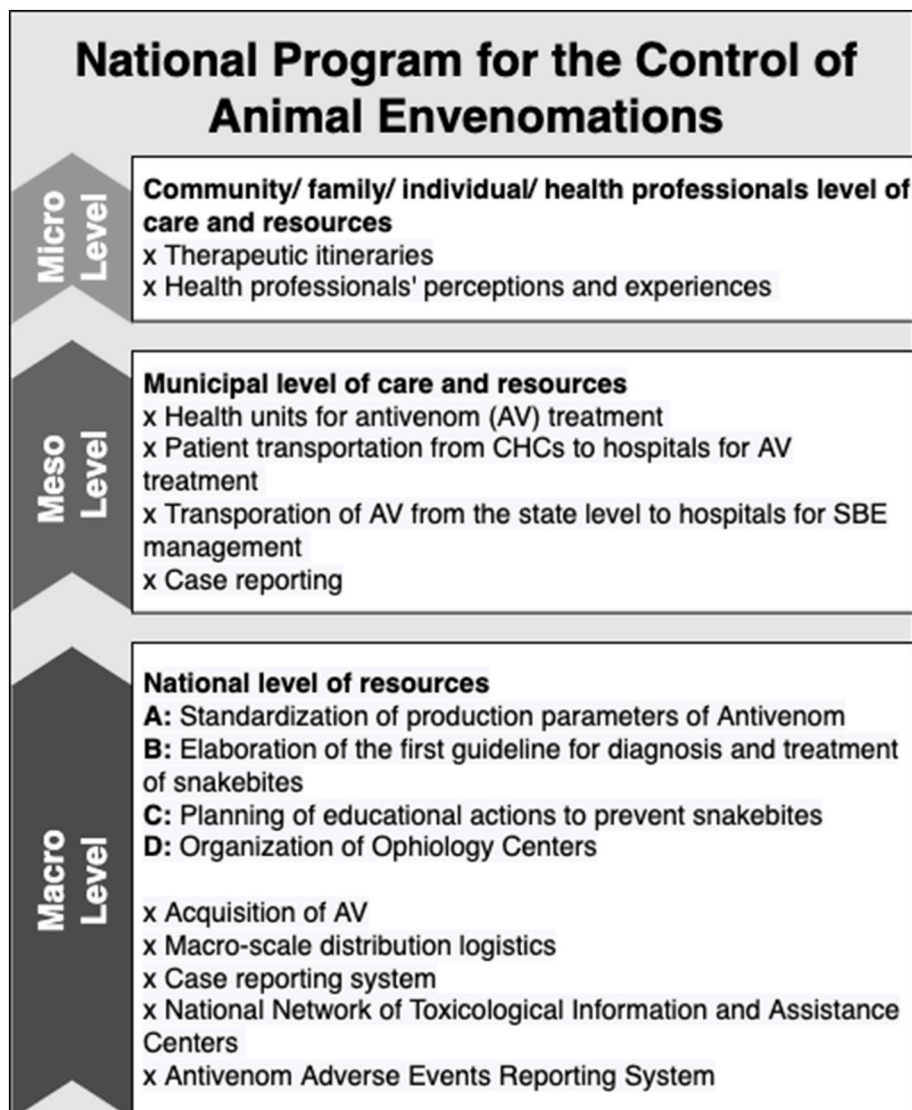


Fig. 1. Multilevel identification of actors and activities into the service ecosystem for treating envenomings triggered by venomous animals in Brazil.

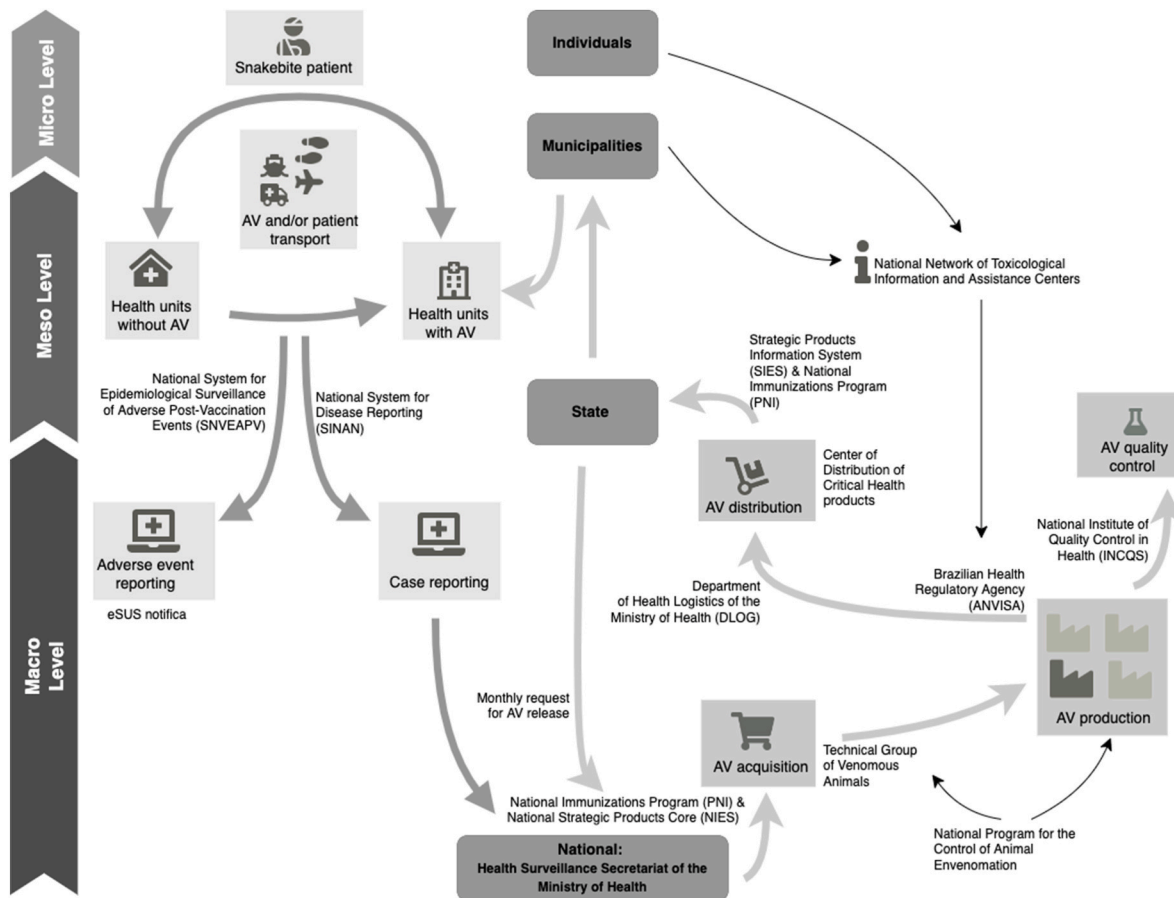


Fig. 2. Flow of resources into the service ecosystem for treating envenomings by venomous animals in Brazil.

plants of the national public antivenom manufacturers and complete acquisition of the AVs produced, taking responsibility for distributing monthly quotas to the states based on epidemiological surveillance data. AV manufacturing processes were standardized, as the criteria for AV administration in terms of the number of ampoules or vials, according to snakebite severity. Four public manufacturers produced >300,000 vials per year of horse-derived F(ab')₂ immunoglobulin fragment AVs (Fig. 1) for VAE treatment: *Bothrops*, *Crotalus*, *Bothrops-Crotalus*, *Bothrops-Lachesis*, and *Micrurus* snake AVs; *Tityus* scorpion AV; one polyvalent AV that neutralizes *Loxosceles* and *Phoneutria* spider venom, as *Tityus* scorpion venom; and one AV for *Lononia* caterpillar envenomings (da Silva Souza et al., 2018). In 2013, new sanitary legislation from the Brazilian Health Regulatory Agency (Agência Nacional de Vigilância Sanitária - ANVISA) required laboratories to improve good manufacturing practices (GMP). Instituto Butantan was the first national manufacturer to obtain a GMP certification for hyperimmune AVs, making it so far the only AV manufacturer which is currently providing antivenoms to the Brazilian MoH. The current supplies are sufficient but there is no strategic stock to supply AVs in case of stock-out. If the four laboratories were manufacturing normally, the quantity would be far from sufficient. In case of excess in the stock of a specific AV, the laboratory usually exports small amounts of AVs to other countries. The MoH is usually requested to donate AVs to attend emergencies.

Case-reporting system: In Brazil, VAEs are considered mandatory reporting conditions from municipalities to states and the MoH via the National System for Disease Reporting (Sistema de Informação de Agravos de Notificação - SINAN). The system allows for the collection, transmission, and dissemination of data from both notification and investigation of all the mandatory reporting diseases from the MoH list to monitor healthcare delivery and ensure access to services. Daily

notifications are sent to the state level via electronic interface, where they are consolidated and forwarded to the MoH. Additionally, the MoH has made investments in real-time notification systems via a web-based SINAN.

Acquisition of antivenoms: The Health Surveillance Secretariat of the MoH is responsible for planning annual necessities of antivenoms, according to informed requests from the Brazilian states. The technical group that monitors the occurrence of VAEs (*Grupo Técnico de Animais Peçonhentos*, in Portuguese) establishes the demand of antivenoms and the National Immunization Program organizes the distribution to the 27 federal units. The process of annual acquisition of AVs begins with calculating the quantity of AVs necessary for providing AVs, taking into account: 1) the quantity of AV vials in stock, 2) expected demand of the states, 3) historical number of VAEs needing AV treatment based on official reports, 4) weighted average of AV vials for each type of VAE, and 5) an extra-amount in case of the need to expand treatment, underreporting cases, and AV losses. The administrative process for purchasing antivenoms is carried out by the Strategic Health Products Core (Núcleo de Insumos Estratégicos - NIES) of the SVS/MS and annual contracts are signed with the AV-manufacturing laboratories.

There are four public antivenom-manufacturing laboratories, which destinate with priority the amount of vials demanded by the MoH. Currently, one is GMP-certified by the national regulatory entity and the others are under refurbishing to adequate and modernize infrastructure and processes. Annual contracts are established with monthly deliveries, according to the national necessity and manufacturing capacity of the laboratories. In the last few years, 450 to 500,000 vials of antivenoms have been distributed to the referral health units. This represents an annual cost of US\$ 12,5 million, supported by the MoH. AV treatment is offered free of charge to all patients.

Macro-scale distribution logistics: Manufacturers transport AV batches to the central warehouse of biological products (Center of Distribution of Strategic Health Products, or *Centro de Distribuição de Insumos Estratégicos de Saúde* – CDIES), located in the state of São Paulo, which is managed by an outsourced company hired by the Department of Health Logistics (*Departamento de Logística em Saúde* - DLOG) of the MoH. Samples of each antivenom batch are destined to the National Institute of Quality Control in Health (*Instituto Nacional de Controle de Qualidade em Saúde* - INCQS), for quality control analysis and release for distribution, by the PNI, to the 26 states and the Federal District, where they are stored for distribution to different municipalities. The quantity of AV vials received from the manufacturers is informed to the Strategic Products Information System (*Sistema de Informação de Insumos Estratégicos* - SIES) and the Material Administration System (*Sistema Integrado de Administração de Material* - SISMAT) of the MoH.

Each state requests AVs through the SIES online platform every month following a pre-established schedule. GT-Peçonhentos staff evaluates the requests, taking into account the highest number of VAEs in the corresponding month of the previous three years for each state; a 30% potential increase in notifications or events; available stocks at the national and state levels; laboratory delivery schedules; and health emergencies, such as in case of floods.

Fig. 3 shows the spatial flows of AV transportation from the macro to micro level of care.

Toxicological Information and Assistance Centers (*Centros de Informação e Assistência Toxicológica* - CIATOX): In Brazil, a science-based toxicological consulting network comprises 36 centers, in 19 Brazilian states, responsible to provide toxicology and human health consulting services to the health professionals and public and private sectors. The centers teams have specific scientific expertise of toxicology, risk assessment, industrial hygiene, occupational health, and response to emergencies or other events involving release or threat of release of chemicals and envenomings caused by animals. The centers,

operating in university hospitals and state or municipal-level health organizations, support health professionals in the case management and/or correct referral to hospital units. Currently, there are three centers operating in the Amazon region. When an individual uses this service, the free call is transferred to the closest CIATOX from where the call originated. The system operates 24 h a day, seven days a week, throughout the year ([Ministério da Saúde, 2015](#)).

Antivenom adverse events reporting system: The frequency of early adverse reactions is around 20% in the Brazilian Amazon, and most of them are mild, according to hospital-based observational studies ([Mendonça-da-Silva et al., 2017](#)). The AV-related adverse events are reported to the National System for Epidemiological Surveillance of Adverse Post-Vaccination Events (*Sistema Nacional de Vigilância dos Eventos Adversos Pós-Vacinação* - SNVEAPV), which is composed by the Inter-institutional Committee on Pharmacovigilance Vaccines and other Immunobiologicals (*Comitê Interinstitucional de Farmacovigilância de Vacinas e outros Imunobiológicos* - CIFAVI) (with representatives of the PNI, ANVISA, INCQS, and the Strategic Health Surveillance Information - Center *Centro de Informações Estratégicas de Vigilância em Saúde* - CIEVS) ([Ministério da Saúde, 2022b](#)). A notification is filled out in the *eSUS notifica* (<https://notifica.saude.gov.br>) and analyzed by PNI technicians. Any healthcare professional or citizen can submit the notification of an adverse event. Notifications are harmonized internationally, and consolidated information is interoperable with the international databases.

3. Meso (municipal) levels of care and resources

Health units for VAE treatment: The decision regarding which municipalities would have referral health units to receive AVs, the corresponding quantities, and types of AVs are based on: (a) epidemiological risk of envenoming supported by the official surveillance system described above; (b) conditions for adequate storage and

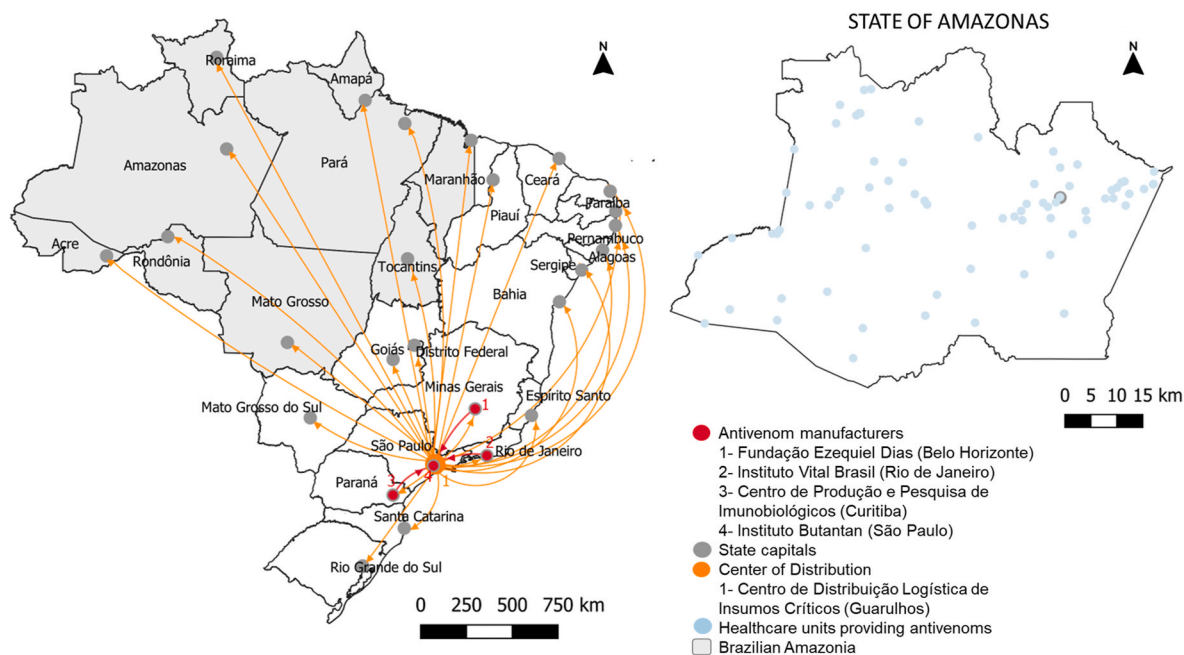


Fig. 3. Distribution logistics of antivenom (AV) in Brazil: from manufacturers to local levels. In Brazil, there are four public AV manufacturers: 1. Instituto Butantan (São Paulo); 2. Fundação Ezequiel Dias (Belo Horizonte); 3. Instituto Vital Brasil (Rio de Janeiro); and 4. Centro de Produção e Pesquisa de Imunobiológicos (Curitiba). In the state of Amazonas (the biggest state of the country, in the Western Brazilian Amazonia, with 1,570,745.7 km² and 4,207,714 inhabitants in 2020), 77 registered health units provide AVs, located in 61 of the 62 municipalities of the state. Many of these units, especially the military units located on the state borders, do not have a continuous supply of AVs. Not all these health units provide all eight AVs produced in Brazil. In 75 health units (97.4%) there available: *Bothrops*, *Lachesis*, *Micrurus*, scorpion and spider AVs. *Crotalus* and *Lonomia* AVs are available in four (5.2%) and two (2.6%) health units, respectively. Base used to create map is from the Brazilian Institute of Geography and Statistics (Instituto Brasileiro de Geografia e Estatística - IBGE), which is freely accessible for creative use in shapefile format, in accordance with the Access to Information Law (12,527/2011) (<https://portaldepapas.ibge.gov.br/portal.php#homepage>).

administration; (c) existence of hospitals and knowledgeable health staff; (d) access to health centers in a relatively short time interval; and (e) availability of referral hospitals to treat severe cases (Wen et al., 2015). In Brazil, in 2021, AV treatment was available in 2190 registered health units in 2004 municipalities (36% of the 5568 Brazilian municipalities) and Brasília, in the Federal District. In the Amazon region, 553 registered health units provide AV, located in 490 municipalities (63.5% of the municipalities in this region) of the nine states (Ministério da Saúde, 2022c).

In *Bothrops* SBEs, acute kidney injury, systemic bleeding, circulatory shock, sepsis and acute respiratory failure are the major complication associated to deaths (da Silva Souza et al., 2018). These complications often require patient care in the ICU. In Brazil, there are 28,364 public ICU beds (13.1/100,000 inhabitants), with 2388 ICU beds (10.1/100,000 inhabitants; 47.6/100,000 km²) in the Amazon region and 25,976 (13.8/100,000 inhabitants; 742/100,000 km²) in the rest of the territory (Saldanha et al., 2019). While in the Extra-Amazonian Region ICU beds are relatively well distributed throughout the territory, in the Amazon they are almost entirely concentrated in state capitals, which creates large gaps in coverage of care for critically-ill patients. Acute kidney injury is a complication that occurs in 13% of SBE patients in Manaus, Brazilian Amazon (Alves et al., 2018). In addition, patients may remain with chronic renal failure after SBE episodes (Pucca et al., 2020). In both cases, renal replacement therapy may be necessary. Availability of clinics performing this procedure again is very uneven across the country, with 58 renal replacement therapy clinics in the Amazon (0.2/100,000 inhabitants; 1.2/100,000 km²) and 530 in the Extra-Amazonian Region (0.3/100,000 inhabitants; 15.1/100,000 km²) (Saldanha et al., 2019).

Patients' transportation from communities to hospitals for AV treatment: VAE patients can be admitted directly in hospitals with AV available; usually public health units belonging to the Emergency Care Network in the Unified Health System (*Rede de Atenção às Urgências no Sistema Único de Saúde*) (Saldanha et al., 2019), or in community health centers (CHCs) and other healthcare units. In the latter case, the patient is expected to receive first aid, wound care, analgesics, and be transported to the healthcare unit to assess the AV treatment. Transport from these units to hospitals can be carried out by various modes, depending on the available resources. In areas where transport takes place by land, there are ambulances of the Mobile Emergency Care Service (*Serviço de Atendimento Móvel de Urgência - SAMU*), a public service for pre-hospital emergencies, or ambulances of the municipality. In CHCs located in the riverine and indigenous communities, transport is usually by boats belonging to the respective cities. In the Amazon region, the SAMU river transport is restricted to the area of Manaus (*Secretaria Municipal de Saúde de Manaus*, 2022). In a limited number of indigenous districts there are ambulance service motorboats from the SAMU for Indigenous Health (*Serviço de Atendimento Móvel de Urgência da Saúde Indígena - SAMUSI*) (Ministério da Saúde, 2022d). There are also some CHCs located in areas so remote that transport is only possible by air, carried out by companies contracted by the government. Communication generally takes place by intermittently available radio which leads to considerable delays in medical care. In practice, VAE victims often use their own transportation between health units, due to communication or mechanical difficulties of transportation modalities.

Transportation of AV from state level to hospitals for VAE treatment: The type and quantity of AVs delivered to each hospital registered for AE treatment is communicated to the responsible department at the state level and to the state coordination of immunizations, as the distribution of AVs is linked to that of vaccines. The municipality is responsible for the storage and transportation of AVs to the referral units. Depending on their geographical situation, the municipalities use land, river, or air transport for health products, including AVs. When additional doses of AVs are demanded in emergencies, which is common during the rainy season when the number of SBEs increases. Replacement of AV stock may occur if there are spare amounts, or relocation of vials between

municipalities is also possible. In parallel, the state informs the need for additional AV vials to the MoH.

In the state of Amazonas, the municipalities around Manaus allow transport by road. In more distant places, most of the time, transport is done by boats, and occasionally via air. In general, AV is transported in a Styrofoam thermal box, with enough dry ice to maintain the appropriate temperature until arrival in the destination municipality. In this state, the amount of AV for each municipality is made by the Zoonoses Department of the Health Surveillance Foundation (*Gerência de Zoonoses da Fundação de Vigilância em Saúde do Amazonas - GZ/FVS-AM*), based on the evaluation of the SINAN reports from that municipality. In the last week of each month, the Zoonoses Management sends the quantity of all AV to be released to each treatment point in the municipalities, to the State PNI, from where the municipal representative pick up the AVs.

Stock-out may occur when 1) there is an unusual demand in consequence of climate change, causing rainfall extremes; 2) shortage in delivering the necessary amount due to manufacturing delay (it is important to highlight that national AV stocks are due to only one laboratory), and 3) cold-chain impairment, usually at local level.

Case reporting: VAE is of compulsory report, and any health professional may report an envenoming case treated at the health unit. The procedure begins by filling an MoH standardized paper form, which consists of eight blocks of information: 1. Health unit information; 2. Patient demographics; 3. Patient's address; 4. Case epidemiology (the areas where the cases occurred - rural or urban, time to medical care, anatomical site of the AE); 5. Clinical information; 6. Type of envenoming; 7. Treatment information; 8. Outcome (discharge or death). After gathering those filled paper forms, the epidemiological surveillance department from the municipality enters the local information into an offline SINAN interface.

Despite the MoH routines for reporting being widely disseminated, AE underreporting remains a concern in the Amazon. A hospital-based survey showed that in Manaus the percentage of underreporting is 6.2% in SBEs and 59.8% in caterpillar envenomings. In the municipalities of the interior of the state of Amazonas (Barcelos, Coari, Lábrea and Maués), underreporting rates are even higher, ranging from 18.5% for SBEs to 100% for caterpillar envenomings.

4. Micro (community/family/individual/health professionals) levels of care and resources

Therapeutic itineraries: In Brazil, several indigenous and riverine populations live in rural areas, at constant risk of VAEs during agricultural, cattle raising and hunter-gathering activities. In agricultural settings and hunter-gathering populations, middle aged males are more susceptible to SBEs, due to greater contact with snakes in their habitats, without the use of individual protective equipment (Feitosa et al., 2015). These populations present higher severity and case-fatality rates from SBE compared to urban populations, due to AV underutilization (not using the AV despite of patient's need) or underdosing (not giving enough AV dosage) (Monteiro et al., 2020; da Silva Souza et al., 2018). In this region, major barriers to SBE care are the low number of hospitals offering AV treatment, long travel distances, absence of an adequate transport, and resistance to seek medical care (Ministério da Saúde, 2011). For example, different ethnic or cultural groups use a variety of folk medicines in place of or prior to accessing healthcare (Salazar et al., 2021; Cristino et al., 2021; da Silva et al., 2019). Practices such as the use of tourniquets, incisions in the affected area, and use of substances of several origins are often ineffective or even deleterious selfcare practices, lead to delayed medical assistance and are dangerous due to the risk of necrosis and secondary bacterial infection (Salazar et al., 2021; da Silva et al., 2019). In the Brazilian Amazon, 22% of patients who died from SBEs had no medical assistance and 47% had no antivenom treatment (da Silva Souza et al., 2018).

Health professionals' perceptions and experiences: In the Brazilian Amazon, health professionals report insecurity when providing care to

SBE patients, due to lack of training on VAE management during their medical and nursing undergraduate training programs (Rocha et al., 2022). Some erroneous care practices including errors in the clinical classification of SBEs and in deciding antivenom dosage, use of non-validated premedication protocols for preventing adverse reactions, inappropriate use of preemptive antimicrobial therapy, and traditional practices such as use of black stones and advice for patients not to drink water were cited by the health staff.

5. Final remarks

Comparing to neighbouring countries, the Brazilian national system of information covers a broader spectrum of VAEs, which allows the MoH to have more reliable data about the burden of venomous animal envenomings and estimate antivenom demands. On the other hand, in less developed countries, when AV is available, non medical professionals are allowed to diagnose and treat patients bitten by venomous animals in primary rural healthcare units. However, differently from sub-Saharan African countries, AV in Brazil is preferentially allocated in urban hospitals, even in the Amazon region, where epidemiological scenario is similar to the less developed regions. Lessons from the experiences of AV administration by nurses and other health professionals, rather than medical doctors, should be disseminated.

SBE is a significant public health problem in Brazil, especially in the Amazon region, where the highest incidence and severity and case-fatality rates are recorded. During the last few decades, significant advances were made to achieve self-sufficiency in antivenoms of a high standard across the country, with an expansion of free-of-charge antivenom treatment to more than 2000 hospitals. However, it has become clear the persistent access barriers due to the lack of culturally appropriate interventions to increase antivenom treatment coverage to include non-urban populations in this care network.

The treatment of envenomings triggered by venomous animals in the country involves an organized and highly hierarchical set of public institutions that work from the antivenom manufacture to the clinical treatment of patients at the local level of care. The orchestration of these different actors involves a great effort through the collaboration between several MoH departments and the manufacturers that incorporates an epidemiological surveillance system in order to dictate the amount of AV to be produced and distributed to the health units. Communication of the macro and state level organizations and definitions of rules and common language for VAE care by a MoH guideline is crucial to maintain the quality of care in the care sites. The most vulnerable part of this complex chain is at the local level, due to the limited access of VAE patients to capable health facilities. Thus, based on our resource mapping presented here, we suggest that increasing the coverage of AV treatment should be a priority of the health system in Brazil, especially in the Amazon region.

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Ethics statement

Not applicable.

Credit author statement

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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.

Data availability

Data will be made available on request.

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