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Bothropic antivenom use, the Region of the Americas

Use of snake antivenom in the Region of the Americas: a systematic review

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Abstract

Objective To evaluate the use of antivenom therapy in *Bothrops* envenomation in the Region of the Americas and to synthesize data on treatment outcomes, adverse reactions and long-term sequelae.

Methods We systematically searched Web of Science, Scopus, Lilacs, PubMed® and Google Scholar for studies published up to 5 May 2025 that reported on the effects of antivenom treatment in humans bitten by *Bothrops* species in the Region of the Americas. We extracted data on patient demographics, adverse reactions, clinical complications and long-term sequelae following antivenom therapy.

Findings Of 2060 articles identified, 38 met the inclusion criteria. *Bothrops* envenomations occurred more frequently in men (75.2%; 3247/4320 individuals), predominantly affected the lower limbs (76.5%; 2494/3295) and typically resulted in moderate-grade envenoming (44.6%; 1553/3483 individuals). We found that adverse reactions to antivenom therapy were common: 19.6% (589/2998) experienced early reactions and 1.6% (16/992) delayed reactions, although incidence declined in recent years. Individuals experienced clinical complications, such as severe oedema (23.2%; 239/1032), secondary infections (22.8%; 452/1985) and incoagulable blood (20.7%; 357/1724). Some patients also experienced permanent sequelae, though these complications were relatively infrequent (3.3%; 50/1512). For studies reporting on deaths, 0.8% (23/3035) of patients died.

Conclusion Antivenom therapy remains central to the management of *Bothrops* envenomation. However, challenges persist in treatment outcomes and long-term sequelae. Addressing these challenges requires ongoing research to strengthen antivenom manufacturing, explore adjunct therapies and improve post-envenomation care. Substantial heterogeneity study methods and reported outcomes, precluded the ability to conduct pooled analyses and generalize findings.

Introduction

Antivenom therapy, developed over a century ago, remains the main treatment for snakebite.[1] However, clinical trials under contemporary standards to ascertain its efficacy and safety were not conducted during its development.[2] Today, producers make quality control assessments of antivenoms in animal models, primarily focusing on the antivenoms' ability to neutralize lethal effects,[3] while disregarding other effects that can contribute to morbidity, such as adverse reactions and prevention of local damage.[4–6] The few well-designed clinical trials that have been conducted on human snakebite treatment with antivenoms,[7] consistently indicate a benefit from using antivenoms.[8–15]

In the Region of the Americas, vipers from the *Bothrops* genus are the primary cause of snakebites. This genus comprises 47 species, and is found from Mexico to Argentina, including the Caribbean and smaller Atlantic coastal islands of Brazil.[16] Envenomation by *Bothrops* snakes triggers a range of haemotoxic effects, typically beginning with local bleeding, and may progress to include symptoms such as oedema, pain, bruising and blisters. Severe complications can arise, including haemorrhagic manifestations, worsening of local effects, infections, necrosis and compartment syndrome caused by increasing oedema. Systemic complications such as acute kidney injury, central nervous system bleeding, shock or sepsis may also occur. Ultimately, *Bothrops* envenomation can result in tissue loss, motor deficits, amputation, renal failure and death.[17]

Compared to other snakebite hotspot areas, Latin America has a lower mortality rate, around 0.04 deaths per 100 000 population.[18] In contrast, a systematic review showed higher rates on the continents of Africa and Asia, at 0.44 and 0.96 deaths per 100 000 population, respectively.[19] A reason for this difference can be the accessibility to high-quality antivenom producers in the Region of the Americas.[20] Despite the availability, several challenges related to snakebite treatment persist in Latin America. These include critical gaps in antivenom distribution and cold-chain logistics that delay on-time administration; the mismatch between antivenom specificity and the high regional diversity of venomous species; and variations in the neutralizing potency of available antivenoms towards the different venom effects.

To comprehensively analyse the use of antivenom therapy against *Bothrops* envenomation in the Region of the Americas, we conducted a systematic review to estimate the local and systemic short- and long-term effects in patients receiving antivenom therapy.

Methods

We registered the systematic review in PROSPERO (CRD42020205978), in accordance with the PRISMA 2020 statement.[21]

Search and data extraction

Up to 5 May 2025, we searched Web of Science, Scopus, Lilacs, PubMed® and Google Scholar using the search string *Bothrops AND (antivenom OR immunotherapy) AND (efficacy OR effectiveness)* to identify studies in any language, conducted in any country or territory in the Region of the Americas that reported on the effects of antivenom in human patients. We also manually examined the bibliographic references of the included articles as well as non-indexed literature.

Two reviewers independently screened the titles of articles, followed by the evaluation of abstracts and complete reading of the article. Agreement between the reviewers was needed for inclusion of a paper. If consensus was not reached, a third reviewer resolved the disagreement. Articles not specifying the snake *Bothrops sp.* as the cause of the snakebite or did not mention an American country or territory as the study location were excluded, as well as systematic reviews, articles without numerical data from clinical studies, and animal studies. We recorded the identified articles in an Excel spreadsheet (Microsoft, Redmond, United States of America).[22]

From the included articles, we extracted study type; number of patients treated; sex; age; snakebite data; antivenom used; antivenom dosage; case evolution; and country or territory where the incident occurred. We also extracted data on variables related to post-antivenom symptoms. As noted in a previous study,[7] snakebite clinical trials often exhibit significant heterogeneity in outcome measurements. Therefore, we focused on the relevant symptoms persisting after antivenom therapy more commonly reported across the articles. Selected variables included: bleeding (systemic or local), incoagulable blood (after 6 hours of serotherapy), local damage (such as blisters, necrosis or gangrene), severe oedema or compartment syndrome, secondary infection or abscess and acute kidney injury. We also recorded adverse reactions to antivenom, as well as other outcomes following treatment such as death, permanent sequelae, need for haemodialysis and length of hospital stay.

Quality

We evaluated the quality of the included studies using an adapted version of a critical appraisal guideline for health research literature,[23] which is suitable for prevalence studies. The guideline considers eight criteria, with each fulfilled criterion receiving one point. We classified studies scoring fewer than three points as low quality, those scoring between 3 and 6 points as sufficient quality and those scoring 7 or 8 points as high quality. No studies were excluded based on methodological quality.

Results

The literature search yielded a total of 2060 articles related to antivenom use in *Bothrops* envenomation. Among these, 1592 articles were off-topic and excluded. We screened 468 abstracts and included 93 articles for full-text assessment, of which 38 met the inclusion criteria (Fig. 1).[9–15,24–54]

Of the included studies, 16 were randomized controlled clinical trials,[9–15,28,32,34,35,37–39,41,42] 14 were prospective studies[24–27,31,33,40,45,47–51,54] and eight retrospective studies.[29,30,36,43,44,46,52,53] While *Bothrops* bites occur across the Region of the Americas, we only identified studies from a handful of countries or territories that have conducted studies on antivenom treatment: Brazil (20 studies),[12,13,15,26,27,30,32,33,35,36,40–43,45,47–49,51,52] Colombia (seven studies),[9,10,14,28,34,37,39] French Guiana (four studies),[24,44,50,54] Martinique (three studies),[29,31,53] Ecuador (two studies),[11,38] Costa Rica (one study)[25] and Uruguay (one study).[46] The included studies were published between 1985 and 2025, with frequent publications in the late 1990s and early 2000s, and a resurgence from 2017 onward, with 39.5% (15/38) published since 2017 (Table 1).

The included studies encompassed data from 4665 victims aged 1 to 93 years (Table 1). Males constituted most of the victims (75.2%; 3247/4320 individuals). The most commonly reported *Bothrops* species involved were *Bothrops asper* (seven studies)[10,14,25,28,34,37,39] and *Bothrops atrox* (eight studies;[11,15,37,38,44,47,48,54] Table 2).

Envenomation severity ranged from mild to severe, with moderate envenomation being the most commonly reported (44.6%; 1553/3483 victims). Of the studies reporting on bite site, 76.5% (2494/3295) of the victims sustained bites to the lower limb.

Notably, 37.5% (965/2570) of victims had received lay first aid interventions, such as tourniquets, incisions and traditional medicine treatments, before receiving antivenom treatment. In one instance, one victim had received an injection of kerosene in the bite site.[39]

These measures may have influenced the treatment outcomes. On average, victims received antivenom treatment 5.7 hours (standard deviation, SD: 0.05) after being bitten, which is within the recommended 6-hour timeframe to prevent clinical aggravation.[50] However, treatment times varied from 1.5 to 19 hours.

The antivenoms administered were from various manufacturers. In Brazil, studies primarily used antivenoms from its health ministry's accredited producers (*Instituto Butantan*, *Instituto Vital Brazil* and *Fundação Ezequiel Dias*). While some studies did not specify the exact product, all antivenoms from these institutes are produced under similar conditions and are comparable.[13] Other producers included *Instituto Clodomiro Picado* from Costa Rica, *Institut Pasteur* and Sanofi Pasteur from France, *Instituto Nacional de Salud* and Probiol from Colombia, Bioclon from Mexico, *Instituto Nacional de Higiene y Medicina Tropical Leopoldo Izquieta Pérez* from Ecuador, and BIOL and Malbran from Argentina. Except for *Instituto Clodomiro Picado and Instituto Nacional de Salud* (Colombia), which manufacture antivenoms composed of integral immunoglobulin G (IgG) molecules, all other antivenoms consist of antibody fragments (F(ab')2) derived from pepsin digestion of horse IgG antibodies. On average, victims received an initial dose of 5.5 (SD: 0.04) vials of antivenom, with each vial containing 10 mL. Doses ranged from 1.5 to 9.1 vials. Intravenous administration was the most common route, only one study administered antivenom via the intramuscular route.[25]

We extracted data on relevant variables related to antivenom treatment outcomes (Table 3). The least reported symptom after antivenom treatment was local or systemic bleeding (7.9%; 123/1551) and the most common symptom was severe oedema, reported in 23.2% of victims (239/1032). Treatment-related adverse reactions occurred in about one fifth of victims: 19.6% (589/2998) experienced early reactions and 1.6% (16/992) delayed reactions. Complications such as permanent sequelae (3.3%; 50/1512), need for haemodialysis (1.5%; 17/1139) and death (0.8%; 23/3035) were less frequently reported. The median length of hospitalization reported was 4.8 days (SD: 0.06).

Discussion

Snakebite envenoming by *Bothrops* species remains a major public health challenge throughout the Region of the Americas, causing substantial morbidity and mortality. These snakebites typically induce severe clinical manifestations, including extensive local tissue damage, coagulopathies, haemorrhage and systemic complications. However, variations exist

in the presenting symptoms depending on the offending snake species.[26,30,53] While antivenom is the only specific treatment and has demonstrated significant lifesaving benefits,[55] it can be less effective for some venom-induced pathologies. This systematic review evaluates these therapeutic limitations in *Bothrops* envenomation, identifying critical gaps to guide future treatment optimization.

We observed a resurgence of publications on antivenom use in *Bothrops* envenomation from 2017 onward, suggesting a renewed interest in the topic following WHO's designation of snakebite as a priority neglected tropical disease in 2017.[56]

We were unable to identify published research on *Bothrops* envenomation from high-incidence countries including the Plurinational State of Bolivia, Guyana, Nicaragua, Panama, Peru and Bolivarian Republic of Venezuela, which report snakebite rates exceeding the regional average.[18] The paucity of data from these countries limits a comprehensive understanding of the full spectrum of antivenom treatment for bothropic envenoming across the Region of the Americas.

The predominant profile of snakebite victims identified in our study corroborates the general understanding that men in rural areas face elevated snakebite risk.[57,58] The reason may be due to male-dominated occupations like farming, livestock herding and resource extraction,[59] activities often conducted without protective gear in low-income communities, reflecting persistent gender roles in these areas.[60]

The included studies only recorded 23 deaths (0.8% of 4665 victims) indicating that antivenom is useful in preventing death, as previously shown.[24,55] However, reversing envenomation symptoms were more challenging. In our review, severe oedema, secondary infections and incoagulable blood were the most frequently reported clinical complications in patients bitten by *Bothrops* snakes, about one-fifth of patients experienced one of these complications. Oedema results from venom toxins and host's inflammatory response to envenomation[61] and may progress to compartment syndrome requiring fasciotomy,[51] which might lead to tissue loss or amputation. While the efficacy of fasciotomy is questioned,[62] antivenom alone may not halt the inflammatory process, suggesting that adjunct anti-inflammatory therapies could be beneficial.

Victims who developed secondary infections, such as abscesses, cellulitis and necrotizing fasciitis, may have permanent impairment. How secondary infections following *Bothrops* snakebites develop remains incompletely understood. However, infection risk

appears to correlate with envenomation severity,[63] indicating that early venom neutralization may reduce incidence. No standardized antibiotic exists and causative pathogens are often unidentified.[35,42] However, resistant bacteria have been identified in the mouths of *Bothrops* snakes,[64] which can further complicate treatment.

Coagulopathy, a hallmark of *Bothrops* envenomation, is primarily caused by venom metalloproteinases and serine proteinases toxins that degrade fibrinogen and impair platelet aggregation.[65] Restoring coagulation is crucial to prevent bleeding, which could potentially lead to lethal complications.[43] Therefore, enhancing antivenom potency, by boosting the concentration of specific antibodies, and using enzyme inhibitors[66,67] may improve outcomes. We chose to report on measurements of incoagulable blood only after 6 hours following antivenom therapy to ensure that the outcome was attributable to the initial treatment. Although clinicians often administer additional doses of antivenom beyond this period until coagulation normalizes. These subsequent treatments were inconsistently documented across reviewed articles, making it difficult to extract precise information on interventions administered after the six-hour mark. Local and systemic bleeding, on the other hand, had a lower prevalence after antivenom therapy, corroborating that *Bothrops* haemotoxic effects can indeed be effectively counteracted by antivenom.[45]

Acute kidney injury, the leading cause of death in *Bothrops* envenomation, occurred in 10 percent of patients, and is characterized by oliguria, increase in serum creatinine levels and may require dialysis.[68] While its pathogenesis is unclear, coagulopathy and venom-caused nephrotoxicity may play a key role,[69] and elevated circulating venom levels correlate with acute kidney injury.[48] Therefore, proper neutralization of circulating venom may be important to prevent acute kidney injury. Notably, we observed that studies involving *Bothrops asper* bites had a greater prevalence of acute kidney injury possibly due to toxin-specific effects. However, further investigations are needed.

About one in 10 patients had local tissue damage, caused by synergistic toxin action and host response. Timely treatment is paramount to prevent disproportionate inflammatory damage. Evidence suggests that endogenous mediators of tissue injury may be counteracted by anti-inflammatory therapies.[70]

Based on our analysis, early adverse reactions are prevalent following antivenom therapy. These reactions result from the administration of large quantities of heterologous proteins, which provoke the patient's immune system. However, most of these adverse

effects were reported to be mild infusion-related reactions, such as cutaneous rash, coughs and swelling, which were effectively reversed with specific treatment. Nevertheless, life-threatening complications may occur, requiring close patient monitoring. In the included studies, late-onset serum sickness, characterized by the deposition of excessive circulating immune complexes, causing fever, headaches, polyarthritis and skin rash,[71] was rare. This finding may reflect prompt antihistamine treatment of early reactions, but can also result from poor patient follow-up, underestimating its occurrence.[28] Encouragingly, adverse events appear to be declining, as more of the recent articles reported fewer events, possibly reflecting improvements in antivenom production. However, despite this progress, the problem persists. While some preventive treatments for antivenom therapy have been tried, they still need validation.[72] Furthermore, antivenom manufactures are urged to improve their purity standards to reduce adverse effects.

While the incidence of permanent sequelae in our analysis was low, the possible poor patient follow-up likely hinders our full understanding of the issue.[17,28] Case reports have shown long-term disabilities following *Bothrops* snakebite injuries, such as disabilities,[73] reduced mobility,[74] renal failure up to 60 months after envenomation[75] and coma due to intracranial haemorrhagic stroke.[76] These examples emphasize the necessity for comprehensive care following envenomation. The limited documentation of long-term effects calls for further research to elucidate the role of appropriate antivenom administration in mitigating these sequelae. Moreover, psychological consequences are often underreported, yet they can represent an important sequela with lasting impact on victims' lives. These effects are not mitigated with antivenom treatments.[77] Both physical and psychological health problems are common in snakebite survivors and can impair quality of life and socioeconomic stability for survivors and their families.[78,79]

The substantial heterogeneity in study designs, treatment protocols and patient demographics of included studies precluded a formal meta-analysis. Therefore, the conclusions in this review should be interpreted within this context of variability. Despite this limitation, we could still make clinically relevant observations based on conserved venom pathobiology across species and antivenom's common mechanism of toxin neutralization via antibody binding. Across studies, some patients continued to experience symptoms after antivenom administration, indicating incomplete venom neutralization. These findings highlight critical gaps in current therapies, emphasizing the need for targeted research on

refractory manifestations to inform antivenom optimization. Ideally, standardized outcome measures should be used to allow future comparisons.

Bothrops envenomation is the most common snakebite in the Region of the Americas and represents a persistent public health concern. Emerging One Health challenges, such as climate change and human-driven landscape changes, are likely to exacerbate the problem.[80,81] Climate change may shift snake distributions and behaviour, potentially altering envenomation epidemiology.[82] Notably, recent evidence demonstrates a direct correlation between elevated temperatures, deforestation and an increase in *Bothrops* snakebite.[83] While such ecological changes may also drive local extinctions of some venomous species,[84] the present clinical challenges justify the need for improved therapeutic strategies, amid an unpredictable epidemiological future.

To conclude, this review underscores the challenges associated with antivenom therapy for treating *Bothrops*-related incidents. Despite advancements in research, adverse reactions following antivenom administration remain prevalent, necessitating continuous efforts to refine antivenom manufacturing processes. Furthermore, persistent clinical complications such as severe oedema, secondary infections and coagulopathy highlight the need for innovative treatment strategies, including the exploration of adjunct therapies and targeted interventions. The disparities in research coverage across affected regions emphasize the importance of global collaboration to effectively address snakebite morbidity. Moving forward, concerted efforts are required to enhance both preventive measures and care following envenomation to mitigate the long-term impact of *Bothrops* snakebites on patient health and well-being.

Competing interests:

None declared.

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Table 1. **Description of included studies on the use of snake antivenom in the Region of the Americas**

Study	Study type	Country or territory	Sample size	Age range of study population, years	Study period
Barrantes et al., 1985[25]	Prospective	Costa Rica	13	NR	1985
Kouyoumdjian et al., 1988[26]	Prospective	Brazil	37	20–83	1982–1987
Kouyoumdjian et al., 1989[27]	Prospective	Brazil	22	1–69	1986–1987
Cardoso et al., 1993[13]	Randomized clinical trial	Brazil	121	7–68	1989–1991
Jorge et al., 1995[12]	Randomized clinical trial	Brazil	170	9–66	1988–1991
Otero et al., 1996[28]	Randomized clinical trial	Colombia	39	NR	1994–1996
Bucher et al., 1997[29]	Retrospective	Martinique	40	8–82	1993–1995
Milani Junior et al., 1997[30]	Retrospective	Brazil	29	NR	1975–1995
Otero-Patiño et al., 1998[10]	Randomized clinical trial	Colombia	79	NR	1994–1996
Thomas et al., 1998[31]	Prospective	Martinique	68	6–82	1993–1997
Fan et al., 1999[32]	Randomized clinical trial	Brazil	101	NR	1994–1995
Otero et al., 1999[9]	Randomized clinical trial	Colombia	53	NR	1996–1997
Bucaretchi et al., 2001[33]	Prospective	Brazil	73	1–14	1984–1999
Otero et al., 2002[34]	Randomized clinical trial	Colombia	39	NR	1999–2000
Pardal et al., 2004[15]	Randomized clinical trial	Brazil	74	5–68	1998–2000
Jorge et al., 2004[35]	Randomized clinical trial	Brazil	251	NR	1990–1996
Smalligan et al., 2004[11]	Randomized clinical trial	Ecuador	210	2–80	1997–2001
Otero et al., 2006[14]	Randomized clinical trial	Colombia	67	NR	2003–2004
Mise et al., 2007[36]	Retrospective	Brazil	665	NR	2001
Otero-Patiño et al., 2007[37]	Randomized clinical trial	Colombia	53	NR	2003
Caron et al., 2009[38]	Randomized clinical trial	Ecuador	129	1–70	1997–2001 and 2004–2006
Otero-Patiño et al., 2012[39]	Randomized clinical trial	Colombia	72	NR	2006–2008
da Silva & Tavares, 2012[40]	Prospective	Brazil	102	12–70	NR
Mendonça-da-Silva et al., 2017[41]	Randomized clinical trial	Brazil	44	> 12	2005–2008
Sachett et al., 2017[42]	Randomized clinical trial	Brazil	186	NR	2014–2016
Oliveira et al., 2019[43]	Retrospective	Brazil	412	NR	2013–2016
Resiére et al., 2020[24]	Prospective	French Guyana	83	29–52	2016–2019
Heckmann et al., 2021[44]	Retrospective	French Guyana	42	16–44	2014–2017
Silva-de-Oliveira et al., 2020[45]	Prospective	Brazil	100	14–79	2016–2017
Negrin et al., 2021[46]	Retrospective	Uruguay	49	NR	2018
Gimenes et al., 2021[47]	Prospective	Brazil	5	NR	NR
Brasileiro-Martins et al., 2022[48]	Prospective	Brazil	127	0–60	2019–2020
Soares et al., 2022[49]	Prospective	Brazil	186	NR	2014–2016
Houcke et al., 2023[50]	Prospective	French Guyana	119	Mean: 41	2016–2022
Toffano et al. 2023[51]	Prospective	Brazil	47	Mean:45	2018–2019
Coutinho et al., 2023[52]	Retrospective	Brazil	268	1–93	2018–2019
Resiére et al., 2024[53]	Retrospective	Martinique	389	Mean:46	2000–2023
Pujo et al., 2025[54]	Prospective	French Guyana	101	Mean:43	2016–2023

NR: not reported.

Table 2. **Description of envenoming characteristics for each included study from the Region of the Americas**

Study	*Bothrops* species	Sex of bite victim, no. (%)		Bite site, no.		Envenoming grade, no.			Received lay first aid interventions,ᵃ no. (%)	Mean time to treatment, hours	Antivenom		
		Male	Female	Inferior limb	Superior limb	Mild	Moderate	Severe			Manufacturer	Molecule	Mean no. of 10mL doses
Barrantes et al., 1985[25]	asper	NR	NR	NR	NR	4 (33.3)	3 (25.0)	5 (41.7)	NR	NR	Instituto Clodomiro Picado	IgG	1.5
Kouyoumdjian et al., 1988[26]	moojeni	28 (75.7)	9 (24.3)	27 (73.0)	10 (27.0)	9 (25.0)	22 (61.1)	5 (13.9)	35 (94.6)	3.4	Brazilian health ministry accredited producers	F(ab')2	6.0
Kouyoumdjian et al., 1989[27]	moojeni	18 (81.8)	4 (18.2)	18 (81.8)	4 (18.2)	5 (23.8)	13 (61.9)	3 (14.3)	NR	4.1	Brazilian health ministry accredited producers	F(ab')2	6.2
Cardoso et al., 1993[13]	jararaca	89 (73.6)	32 (26.4)	98 (81.0)	23 (19.0)	0 (0.0)	89 (73.6)	32 (26.4)	65 (53.7)	4.9	Brazilian health ministry accredited producers	F(ab')2	5.5
Jorge et al., 1995[12]	jararaca	137 (80.6)	33 (19.4)	137 (80.6)	33 (19.4)	NR	NR	NR	82 (48.2)	4.6	Brazilian health ministry accredited producers	F(ab')2	3.5
Otero et al., 1996[28]	asper	NR	NR	NR	NR	15 (38.5)	15 (38.5)	9 (23.1)	26 (66.6)	10.9	Instituto Clodomiro Picado	IgG	NR
Bucher et al., 1997[29]	lanceolatus	30 (75.0)	10 (25.0)	23 (57.5)	17 (42.5)	20 (50.0)	17 (42.5)	3 (7.5)	NR	1.5	Institut Pasteur	F(ab')2	3.0
Milani Junior et al., 1997[30]	jararacussu	19 (65.5)	10 (34.5)	21 (72.4)	8 (27.6)	NR	NR	NR	NR	8.2	Brazilian health ministry accredited producers	F(ab')2	NR
Otero-Patiño et al., 1998[10]	asper	NR	NR	NR	NR	33 (41.8)	22 (27.8)	24 (30.4)	58 (73.4)	8.5	Brazilian health ministry accredited producers; Instituto Nacional de Salud Colombia	IgG and/or F(ab')2	NR
Thomas et al., 1998[31]	lanceolatus	53 (77.9)	15 (22.1)	41 (60.3)	27 (39.7)	41 (63.1)	20 (30.8)	4 (6.2)	NR	4.5	Institut Pasteur	F(ab')2	3.0
Fan et al., 1999[32]	sp.	80 (79.2)	21 (20.8)	NR	NR	76 (75.2)	25 (24.8)	0 (0.0)	NR	NR	Brazilian health ministry accredited producers	F(ab')2	NR
Otero et al., 1999[9]	sp.	NR	NR	NR	NR	NR	NR	NR	NR	NR	Instituto Clodomiro Picado	IgG	NR
Bucaretchi et al., 2001[33]	jararaca	48 (65.8)	25 (34.2)	62 (84.9)	11 (15.1)	19 (26.8)	37 (52.1)	15 (21.1)	13 (17.8)	3.2	Brazilian health ministry accredited producers	F(ab')2	6.0
Otero et al., 2002[34]	asper	31 (79.5)	8 (20.5)	23 (59.0)	16 (41.0)	2 (5.1)	8 (20.5)	29 (74.4)	21 (53.8)	NR	Probiol; Instituto Nacional de Salud Colombia; Bioclon	IgG and/or F(ab')2	9.1
Pardal et al., 2004[15]	atrox	64 (86.5)	10 (13.5)	65 (87.8)	9 (12.2)	43 (58.1)	27 (36.5)	4 (5.4)	28 (37.8)	NR	Brazilian health ministry accredited producers	F(ab')2	5.8

Study	Species										Institution	Antibody	
Jorge et al., 2004[35]	sp.	204 (81.3)	47 (18.7)	NR	NR	NR	NR	NR	126 (50.2)	4.2	Brazilian health ministry accredited producers	F(ab')2	NR
Smalligan et al., 2004[11]	atrox	106 (50.5)	104 (49.5)	101 (52.9)	90 (47.1)	NR	NR	NR	NR	7.8	Brazilian health ministry accredited producers; Instituto Nacional de Salud Colombia; Instituto Nacional de Higiene y Medicina Tropical Leopoldo Izquieta Pérez	IgG and/or F(ab')2	NR
Otero et al., 2006[14]	asper	47 (70.1)	20 (29.9)	54 (80.6)	13 (19.4)	17 (25.4)	35 (52.2)	15 (22.4)	32 (47.7)	7.9	Instituto Clodomiro Picado	IgG	NR
Mise et al., 2007[36]	sp.	510 (76.7)	155 (23.3)	500 (75.2)	165 (24.8)	127 (21.1)	318 (52.8)	157 (26.1)	70 (10.5)	NR	Brazilian health ministry accredited producers	F(ab')2	7.7
Otero-Patiño et al., 2007[37]	asper and atrox	37 (69.8)	16 (30.2)	38 (71.7)	15 (28.3)	13 (24.5)	30 (56.6)	10 (18.9)	23 (44.2)	NR	Bioclon	F(ab')2	5.5
Caron et al., 2009[38]	atrox and bilineatus	67 (51.9)	62 (48.1)	NR	NR	NR	NR	NR	NR	5.2	Brazilian health ministry accredited producers	F(ab')2	2.0
Otero-Patiño et al., 2012[39]	asper	48 (66.7)	24 (33.3)	61 (84.7)	11 (15.3)	19 (26.4)	36 (50.0)	17 (23.6)	27 (37.5)	5.4	Instituto Clodomiro Picado	IgG and/or F(ab')2	NR
da Silva & Tavares, 2012[40]	sp.	NR	NR	NR	NR	NR	NR	NR	NR	NR	Brazilian health ministry accredited producers	F(ab')2	NR
Mendonça-da-Silva et al., 2017[41]	sp.	37 (84.1)	7 (15.9)	40 (90.9)	4 (9.1)	NR	NR	NR	NR	2.8	Brazilian health ministry accredited producers	F(ab')2	6.0
Sachett et al., 2017[42]	sp.	153 (82.3)	33 (17.7)	157 (84.4)	29 (15.6)	80 (43.0)	91 (48.9)	15 (8.1)	46 (24.7)	4.9	Brazilian health ministry accredited producers	F(ab')2	NR
Oliveira et al., 2019[43]	sp.	322 (78.2)	90 (21.8)	360 (87.4)	52 (12.6)	112 (27.7)	219 (54.2)	73 (18.1)	240 (58.2)	3.6	Brazilian health ministry accredited producers	F(ab')2	NR
Resiére et al., 2020[24]	sp.	52 (71.2)	21 (28.8)	NR	NR	32 (42.1)	28 (36.8)	16 (21.1)	NR	9.0	Bioclon	F(ab')2	5.0
Heckmann et al., 2021[44]	atrox	34 (81.0)	8 (19.0)	40 (95.2)	2 (4.8)	0 (0.0)	33 (78.6)	9 (21.4)	NR	11.0	Bioclon	F(ab')2	3.0
Silva-de-Oliveira et al., 2020[45]	sp.	88 (88.0)	12 (12.0)	92 (92.0)	8 (8.0)	27 (27.0)	59 (59.0)	14 (14.0)	29 (29.0)	NR	Brazilian health ministry accredited producers	F(ab')2	8.0
Negrin et al., 2021[46]	alternatus and pubescens	NR	NR	NR	NR	NR	NR	NR	NR	NR	BIOL; Malbran; Brazilian health ministry accredited producers	F(ab')2	NR

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Study	Species										Producer	Antibody	
Gimenes et al., 2021[47]	*atrox*	4 (80.0)	1 (20.0)	5 (100.0)	0 (0.0)	0 (0.0)	3 (60.0)	2 (40.0)	1 (20.0)	5.6	Brazilian health ministry accredited producers	F(ab')2	v
Brasileiro-Martins et al., 2022[48]	*atrox*	110 (86.6)	17 (13.4)	115 (90.6)	12 (9.4)	17 (13.4)	72 (56.7)	38 (29.9)	43 (33.8)	7.7	Brazilian health ministry accredited producers	F(ab')2	NR
Soares et al., 2022[49]	*sp.*	153 (82.3)	33 (17.7)	156 (83.9)	30 (16.1)	80 (43.0)	88 (47.3)	18 (9.7)	NR	NR	Brazilian health ministry accredited producers	F(ab')2	3.4
Houcke et al., 2023[50]	*sp.*	80 (67.2)	39 (32.8)	NR	NR	60 (50.4)	31 (26.1)	28 (23.5)	NR	6.1	Bioclon	F(ab')2	6.0
Toffano et al. 2023[51]	*sp.*	37 (78.7)	10 (21.3)	33 (70.2)	14 (29.8)	6 (16.2)	19 (51.4)	12 (32.4)	NR	6.0	Brazilian health ministry accredited producers	F(ab')2	8.0
Coutinho et al., 2023[52]	*sp.*	206 (76.9)	62 (23.1)	NR	NR	88 (32.8)	106 (39.6)	74 (27.6)	NR	NR	Brazilian health ministry accredited producers	F(ab')2	NR
Resiére et al., 2024[53]	*lanceolatus*	292 (75.1)	97 (24.9)	227 (58.4)	162 (41.6)	241 (70.9)	58 (17.1)	41 (12.1)	NR	4.5	Sanofi Pasteur	F(ab')2	4.2
Pujo et al., 2025[54]	*atrox*	63 (62.4)	38 (37.6)	NR	NR	47 (46.5)	29 (28.7)	25 (24.8)	NR	14.8	Bioclon	F(ab')2	6.0
Total/sample size (%)[b]	**–**	**3247/4320 (75.2)**	**1073/4320 (24.8)**	**2494/3259 (76.5)**	**765/3259 (23.5)**	**1233/3483 (35.4)**	**1553/3483 (44.6)**	**697/3483 (20.0)**	**965/2570 (37.5)**	**5.7 (0.05)[c]**	**–**	**–**	**5.5 (0.04)[c]**

F(ab')2: fragmented antibody; IgG: immunoglobulin G; NR: not reported; *sp.*: species.

[a] Examples of interventions are tourniquet, traditional medicine and incision.

[b] Sample size refers to the total number of participants in studies reporting the variable.

[c] Numbers show weighted averages with standard deviations in the parentheses.

Table 3. **Description of persisting symptoms and outcomes after antivenom treatment, the Region of the Americas**

Study	Sample size	Persisting symptoms after antivenom, no.						Adverse reactions, no		Outcome, no.			Mean hospitalization stay, days
		Local or systemic bleeding	Incoagulable blood[a]	Severe oedema	Local damage[b]	Secondary infection	Acute kidney injury	Acute	Delayed	Death	Permanent sequelae	Received haemodialysis	
Barrantes et al., 1985[25]	13	NR	8	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kouyoumdjian et al., 1988[26]	37	NR	NR	2	4	5	0	NR	NR	1	1	0	8.1
Kouyoumdjian et al., 1989[27]	22	1	NR	2	2	4	0	NR	NR	1	NR	NR	8.9
Cardoso et al., 1993[13]	121	35	19	88	43	NR	NR	72	10	NR	8	NR	3.5
Jorge et al., 1995[12]	170	43	29	NR	NR	NR	NR	NR	NR	NR	1	NR	NR
Otero et al., 1996[28]	39	2	14	5	2	4	8	14	NR	0	2	NR	NR
Bucher et al., 1997[29]	40	NR	NR	6	7	NR	NR	2	1	0	1	NR	5.2
Milani Junior et al., 1997[30]	29	NR	NR	NR	1	5	4	NR	NR	3	1	1	NR
Otero-Patiño et al., 1998[10]	79	3	21	1	2	15	8	32	1	1	2	2	NR
Thomas et al., 1998[31]	68	NR	NR	NR	NR	NR	NR	4	2	1	1	NR	5.2
Fan et al., 1999[32]	101	NR	NR	NR	NR	NR	NR	25	NR	NR	NR	NR	NR
Otero et al., 1999[9]	53	6	6	4	4	6	3	20	0	0	4	0	NR
Bucaretchi et al., 2001[33]	73	NR	NR	NR	13	11	1	25	0	0	3	0	NR
Otero et al., 2002[34]	39	6	10	3	11	12	15	14	NR	4	14	NR	NR
Pardal et al., 2004[15]	74	1	10	20	2	7	NR	14	NR	0	0	NR	3.9
Jorge et al., 2004[35]	251	NR	NR	NR	12	12	NR	NR	NR	NR	NR	NR	NR
Smalligan et al., 2004[11]	210	NR	84	NR	10	NR	NR	114	NR	2	NR	NR	NR
Otero et al., 2006[14]	67	NR	40	NR	NR	21	11	13	NR	NR	1	0	NR
Mise et al., 2007[36]	665	NR	NR	NR	NR	NR	1	57	NR	7	NR	NR	NR
Otero-Patiño et al., 2007[37]	53	1	1	0	NR	16	6	10	1	0	4	0	NR
Caron et al., 2009[38]	129	NR	76	NR	NR	NR	NR	38	NR	NR	NR	NR	NR
Otero-Patiño et al., 2012[39]	72	NR	11	4	1	4	6	18	1	0	4	NR	NR
da Silva & Tavares, 2012[40]	102	NR	NR	NR	NR	NR	NR	21	NR	NR	NR	NR	NR

Study													
Mendonça-da-Silva et al., 2017[41]	44	NR	0	NR	NR	NR	0	12	0	0	0	0	NR
Sachett et al., 2017[42]	186	NR	NR	NR	NR	74	NR	NR	NR	0	0	NR	NR
Oliveira et al., 2019[43]	412	15	21	NR	NR	NR	NR	NR	NR	0	NR	NR	7.0
Resiére et al., 2020[24]	83	NR	NR	35	5	23	4	17	NR	0	NR	NR	NR
Heckmann et al., 2021[44]	42	NR	NR	NR	NR	NR	NR	11	NR	NR	NR	1	3.5
Silva-de-Oliveira et al., 2020[45]	100	4	3	NR	NR	NR	NR	NR	NR	0	NR	NR	4.0
Negrin et al., 2021[46]	49	NR	4	NR	NR	NR	NR	4	NR	NR	NR	NR	NR
Gimenes et al., 2021[47]	5	NR	NR	5	5	4	NR	NR	NR	NR	NR	NR	NR
Brasileiro-Martins et al., 2022[48]	127	NR	NR	v	NR	NR	49	NR	NR	NR	NR	2	NR
Soares et al., 2022[49]	186	NR	NR	NR	NR	NR	NR	22	NR	NR	NR	NR	NR
Houcke et al., 2023[50]	119	NR	NR	NR	NR	31	3	15	NR	NR	NR	3	7.0
Toffano et al. 2023[51]	47	NR	NR	7	NR	20	12	NR	NR	NR	NR	3	NR
Coutinho et al., 2023[52]	268	NR	NR	57	8	148	44	NR	NR	2	3	4	4.0
Resiére et al., 2024[53]	389	6	NR	NR	NR	30	NR	9	0	1	NR	NR	1.4
Pujo et al., 2025[54]	101	NR	NR	NR	NR	NR	19	6	NR	NR	NR	1	9.0
Total/sample size (%)[c]	4665 (100)	123/1551 (7.9)	357/1724 (20.7)	239/1032 (23.2)	132/1495 (8.8)	452/1985 (22.8)	194/2017 (9.6)	589/2998 (19.6)	16/992 (1.6)	23/3035 (0.8)	50/1512 (3.3)	17/1139 (1.5)	4.8 (0.06)[d]

NR: not reported.

[a] Up to 6 hours after antivenom administration.

[b] Such as blisters or necrosis.

[c] Sample size refers to the total number of participants in studies reporting the variable.

[d] Numbers show weighted average with standard deviation in the parenthesis.

Fig. 1. **Flowchart of the selection of studies on the use of snake antivenom in the Region of the Americas**