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Case report

Snakebites as cause of deaths in the Western Brazilian Amazon: Why and who dies? Deaths from snakebites in the Amazon

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ABSTRACT

Snake envenoming represents a major burden for public health worldwide. In the Amazon, the official number of cases and deaths detected is probably underestimated because of the difficulty riverine and indigenous populations have reaching health centers in order to receive medical assistance. Thus, integrated analysis of health information systems must be used in order to improve adequate health policies. The aim of this work is to describe a series of deaths and identify risk factors for lethality from snakebites in the state of Amazonas, Brazil. All deaths from snakebites reported to the Brazilian Notifiable Diseases Surveillance System (SINAN) and to the Mortality Information System (SIM; ICD10-10th revision, X.29), from 2007 to 2015, were included. Variables were assessed by blocks with distal (ecological variables), intermediate (demographics) and proximal (clinical variables) components to identify predictors of case fatality. A total of 127 deaths from snakebites were recorded, with 58 pairs found through linkage of the SINAN and SIM databases (45.7%), 37 (29.1%) deaths found only in SINAN and 32 (25.2%) found only in the SIM. Deaths occurred mostly in males (95 cases; 74.8%) living in rural areas (78.6%). The most affected age group was the ≥61 years old (36 cases; 28.4%). Snakebites were presumably due to Bothrops snakes in 68.5% of the cases and Lachesis in 29.5% based on clinico-epidemiological diagnosis. A proportion of 26.2% of the cases received treatment over 24 h after the bite ocurred. On admission, cases were mostly classified as severe (65.6%). Overall, 28 patients (22.0%). Deceased without any medical assistance Antivenom was given to 53.5%. In the multivariate analysis, a distance from Manaus >300 km [OR = 3.40 (95%CI = 1.99–5.79); ($p < 0.001$)]; age ≥61 years [OR = 4.31 (95%CI = 1.22–15.21); ($p = 0.023$)] and Indigenous status [OR = 5.47 (95%CI = 2.37–12.66); ($p < 0.001$)] were independently associated with case fatality from snakebites. Severe snakebites [OR = 16.24 (95%CI = 4.37–60.39); ($p < 0.001$)] and a lack of antivenom administration [OR = 4.21 (95%CI = 1.30–13.19); ($p = 0.014$)] were also independently associated with case fatality. Respiratory failure/dyspnea, systemic bleeding, sepsis and shock were recorded only among fatal cases. In conclusion, i) death from snakebites was underreported in the mortality surveillance system; ii) older age groups living in remote municipalities and indigenous peoples were the population groups most prone to death; iii) lack or underdosage of antivenom resulted in higher case fatality and iv) systemic bleeding, circulatory shock, sepsis and acute respiratory failure were strongly associated to fatal outcome.

1. Introduction

Animal envenoming represents a major burden for public health worldwide, with a total of 4648 global Disability-Adjusted Life-

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Years (DALYs) and a 62.8 age-standardised DALY rate per 100,000 individuals, in 2015 (GBD, 2015 DALYs and HALE Collaborators., 2016). Numerous animal species have the potential to bite and cause envenoming in humans, but snakes have a major epidemiological importance. Worldwide, up to five million people are bitten by snakes every year and, of these, venomous snakes cause considerable morbidity and mortality (World Health Organization, 2016). At least 421,000 envenomings and 20,000 deaths occur each year due to snakebite globally, but these figures may be as high as 1,841,000 envenomings and 94,000 deaths (Kasturiratne et al., 2008).

In Brazil, it is compulsory to report animal envenoming to the Ministry of Health. Via data system for the collection of diseases from 2000 to 2016, a total of 443,912 snakebites were recorded by the Brazilian official surveillance system, with a mean of 26,000 cases per year; snakebite incidence is higher in the Brazilian Amazon states, representing an occupational health problem for rural and riverine populations, with a rate of 48.8 cases/100,000 inhabitants in 2016 (Brasil Ministério da Saúde, 2016). A total of 1815 deaths from snakebites were recorded in Brazil from 2000 to 2016, with a lethality rate of 0.4% (Brasil Ministério da Saúde, 2016). In the Western Brazilian Amazon, lethality was estimated at 0.6% and was independently associated to an age ≥65 years and time to medical assistance >6 h (E. L. Feitosa et al., 2015a). The number of cases detected officially in the Amazon is probably much lower than the real number due to the difficulty riverine and indigenous populations have in order to reach health centers for treatment of snakebites (Wen et al., 2015). Indeed, an epidemiological survey carried out in the state of Acre, in the Western Brazilian Amazon, found that 13% of tappers and Amerindians were bitten by snakes at least once in their lifetime, with a mortality estimated at about 400 deaths per 100,000 population per lifetime (Pierini et al., 1996).

Bothrops atrox is the most common venomous snake in the Brazilian Amazon, causing 80–90% of the snake envenomings in the region (Wen et al., 2015). In this region, *Bothrops* envenoming causes pain, swelling, regional lymphadenopathy, ecchymosis, blistering, and necrosis as the most common local clinical manifestations (Otero et al., 1996; Pardal et al., 2004; Souza, 2002). Secondary bacterial infections were observed in around 40% (Souza, 2002) and spontaneous systemic bleeding and acute renal injury are common systemic complications (Pardal et al., 2004; Souza, 2002). Incoagulable blood is present in about 50% of *Bothrops* bitten patients in the Brazilian Amazon (Pardal et al., 2004; Souza, 2002). Envenomings caused by *Lachesis* snakes, the bushmasters, are unusual events due to their nonaggressive behavior. Local manifestations are similar to those caused by *Bothrops*, sometimes with an intense tissue damage evidenced by pain, restricted edema or affecting member, blisters, bleeding, and ecchymosis (Torres et al., 1995). Signs and symptoms of vagal stimulation are dizziness, blurred vision, diarrhea, abdominal cramps, sinus bradycardia, severe hypotension and shock are also described (Souza et al., 2007; Torres et al., 1995). *Crotalus* and *Micrurus* envenomings are rarely recorded in the Amazon, and their signs and symptoms are related to neurotoxic, myotoxic and coagulant activities of the rattlesnake venom (Azevedo-Marques et al., 2009) and to neurotoxic effects due to the presence of neurotoxins with pre and postsynaptic activity, in the coral snakes' venom (Dos-Santos, 2009).

Clinical features of snakebite victims demand timely adequate management according to well-defined protocols, including prompt referral to tertiary centers when necessary, as well as an effective response from surveillance systems and policy makers for vulnerable groups. The aim of this work is to describe a series of deaths from snakebites in the state of Amazonas, in the Western Brazilian Amazon, and identify risk factors for lethality in this region.

2. Methods

2.1. Study population and procedures

All deaths from snakebites in the State of Amazonas, Western Brazilian Amazon (Fig. 1A), reported to Brazilian Notifiable Diseases Surveillance System [*Sistema de Informação de Agravos de Notificação* (SINAN)] and to Mortality Information System [*Sistema de Informação de Mortalidade*(SIM)] (ICD-10 - 10th revision, X.29), were included in this study, from 2007 to 2015.

In 1986, a national surveillance system for snakebite control was implemented and it became compulsory to report snakebite envenoming, as part of the Brazilian Ministry of Health's list of notifiable diseases. In 1993, SINAN became the official information system for animal envenomings and since then data became

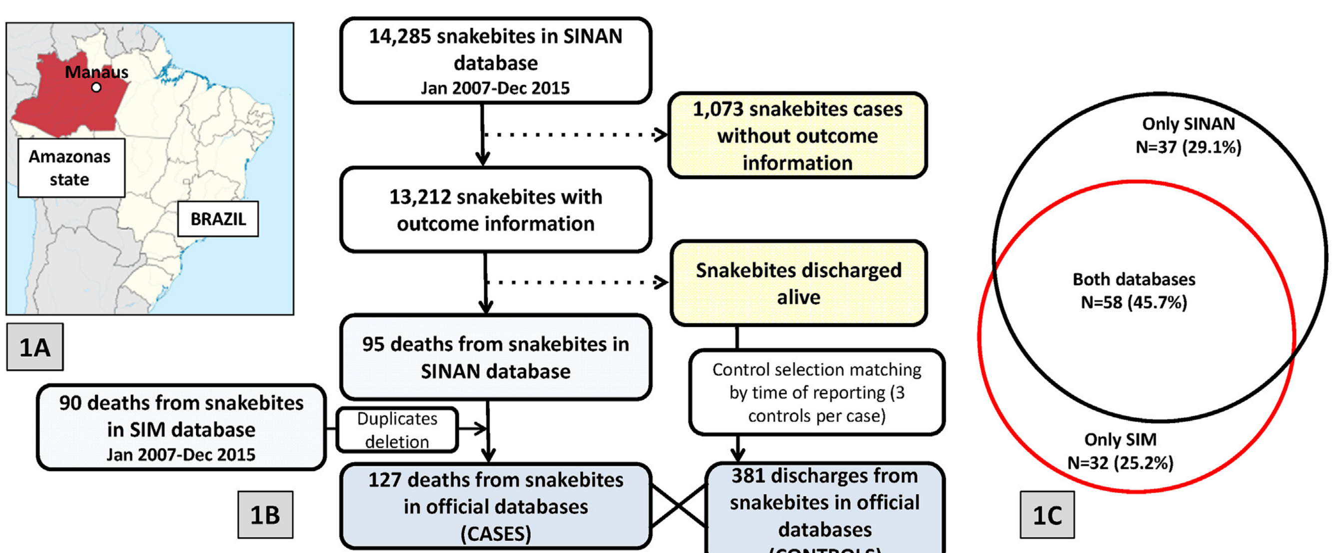

Fig. 1. Research area and study design flow chart.

progressively more reliable. The SIM was developed in 1975 as the official mortality information system. Data are obtained from death certificates, which contain the causes of death, and it is mandatory to be completed by a medical doctor.

The identification of individuals that are common to different databases was made by a manual revision performed by two independent researchers, according to patient's name, mother's name, birth date, snakebite date and municipality of residence. After the final database setting, the variables retrieved were gender, age (in years), anatomical region of the bite, area of occurrence (rural or urban), municipality of occurrence, work-related injury (yes or no), schooling (years of study), occupation, ethnical background, time elapsed from the bite until medical assistance (in hours), presumed perpetrating snake species, pregnancy status, severity grading at admission (mild, moderate or severe), clinical manifestations, clinical complications during patient follow-up and treatment received (antivenom prescription and dosage). Reporting on snakebite severity grading is required by SINAN and is submitted by healthcare providers for case notification, according to the Brazilian Health Ministry guidelines (Azevedo-Marques et al., 2009), as detailed in Supplementary file 1. Regarding death circumstances, information on the immediate and underlying causes of the death, pregnancy status, medical assistance (yes or no) and site of occurrence (domicile, hospital or others) was retrieved.

In order to identify epidemiological and clinical factors associated with lethality from snakebites, a case-control study was used, wherein cases ending in death were classified as the dependent variable. Matching by time of reporting was used as an option to improve efficiency in the estimation of the effect of exposure by protecting against a potential confounder represented by temporal fluctuations in health services access due to high turnover of health professionals and antivenom distribution in remote Amazon areas (Wen et al., 2015). Then, to ensure time comparability between cases and controls, for each case defined as a death from snakebite, the next three discharged cases were chosen as controls from the SINAN study database.

2.2. Statistical analysis

Estimates of internal validity (extent of errors within the system, for example, coding errors) and completeness (underreporting of any surveillance variable) were used to monitor the databases' quality. A checking of both surveillance attributes by two independent researchers before analysis was made to minimize the possible observer-expectancy effect during data handling. Agreement between databases was expressed as proportions. Underreporting of deaths from snakebites in the official surveillance system for snakebites was calculated considering the additional number of deaths reported to SIM, but discharged alive in SINAN.

We obtained the descriptive statistics of epidemiological and clinical variables. Case fatality rate (deaths from snakebites/total of snakebites; adjusted by 1000 snakebites), mortality rate (deaths from snakebites/municipality population; adjusted by 100,000 inhabitants) and proportional mortality (deaths from snakebites/total of deaths; adjusted by 1000 deaths) from snakebites were estimated at the municipality level. Maps were created with the software ArcMap 10.1 in ArcGIS 10.1 (ESRI, USA) using estimates by municipality.

Independent variables were assessed by blocks with distal to proximal components to avoid the underestimation of the effects of distal variables:

1. Block 1 distal components: (1) Mean Municipal Human Development Index (MMHDI) (≥median value or < median value) (Instituto Brasileiro de Geografia e Estatística, 2016); (2) Mean Health System Performance Index (MHSPI) (≥median value or < median value) (Brasil. Ministério da Saúde, 2016); (3) Straight-line distance from the Amazonas state capital Manaus, in kilometers, to the municipality seat (≤300 km or > 300 km); and (4) Area of occurrence (rural or urban);

2. Block 2 intermediate components: (1) Sex; (2) Age group in years (0–15, 16–45, 46–60 and ≥ 61); (3) Ethnicity (Admixed, White, Indian and Black); (4) Education level in years of study (Illiterate, ≤4, 5–8 and >8); (5) Work-related snakebite (yes or no); (6) Anatomical region bitten (lower limbs, upper limbs and other sites); (7) Time in hours from bite until medical assistance (≤6, >6–24 and > 24).

1. Block 3 proximal components: (1) Severity grading at admission (mild, moderate or severe), according to the Brazilian Health Ministry guidelines (Azevedo-Marques et al., 2009); (2) Presumed perpetrating snake genus (*Bothrops*, *Lachesis*, *Micrurus* or non-venomous snakes); (3) Pregnancy status (yes or no); (4) Pain at admission (yes or no); (5) Edema at admission (yes or no); (6) Ecchymosis at admission (yes or no); (7) Necrosis at admission (yes or no); (8) Coagulopathy (abnormal clotting time) at admission (yes or no); (9) Antivenom administration (yes or no); (10) Antivenom dosage (as recommended or underdosage); (11) Secondary infection at bite site during follow-up (yes or no); (12) Necrosis at bite site during follow-up (yes or no); (13) Compartmental syndrome during follow-up (yes or no); (14) Amputation during follow-up (yes or no); (15) Systemic bleeding during follow-up (yes or no); (16) Acute renal failure during follow-up (yes or no); (17) Respiratory failure/acute lung edemaduring follow-up (yes or no); (18) Sepsis during follow-up (yes or no) and; (19) Shock during follow-up (yes or no).

Proportions of independent variables between cases and controls were compared by Chi-square test (corrected by Fisher's test if necessary). The crude *Odds Ratio* (OR) with its respective 95% Confidence Interval (95%CI) was determined. A backward-stepwise logistic regression was used for the multivariable analyses and the adjusted *Odds Ratios* with 95%CI were also calculated. All variables associated with the outcomes at a significance level of $p < 0.2$ in the univariable analysis were included in the multivariable analysis, ranked by previously defined blocks of analysis. Variables were adjusted by covariates of the same level and by significant variables of the previous level, for distal and intermediate components. Proximal variables (clinical complications adjusted by treatment information) were assessed for deriving immediate and intermediates causes of death. Where zeros caused problems with computation of the OR and 95% CI, 1.0 was added to all cells (Deeks and Higgins, 2010; Pagano and Gauvreau, 2000). Statistical significance was considered if $p < 0.05$ in the Hosmer-Lemeshow goodness-of-fit test. Statistical analyses were performed using the STATA statistical package version 13 (Stata Corp. 2013).

2.3. Ethical approval

This study was approved by Ethics Review Board (ERB) of *Fundação de Medicina Tropical Dr. Heitor Vieira Dourado* (FMT-HVD) (approval number 872.520/2014). Since data were obtained exclusively from surveillance databases, the ERB a waiver of informed consent.

3. Results

3.1. Databases analysis

From 2007 to 2015, SINAN included 14,285 snakebite records. No duplicate was found. Removal of entries without outcome information left 1073 notifications (7.5%). A total of 95 deaths were retrieved from this database, with a lethality rate of 0.7% among snakebite patients included in SINAN. The SIM database had 135,676 death records in the period and 90 presented snakebite as one of the causes of death, resulting in an overall proportional mortality rate of 0.07% in the state (Fig. 1B). A total of 58 pairs were found through linkage of the SINAN and SIM databases, with a concordance of 45.7%. A total of 37 (29.1%) deaths were found only in SINAN and 32 (25.2%) were found only in the SIM database (Fig. 1C). Thus, a total of 127 deaths from snakebites were recorded in the period. Six cases recorded as deaths to SIM were *'discharged alive'* according to SINAN. Then, lethality from SINAN was underestimated in 6.0%.

3.2. Population characteristics

Most of the deaths from snakebites occurred in males (95 cases; 74.8%). Regarding the area of occurrence, 78.6% were reported in rural areas. The most affected age group was the ≥61 years old (36 cases; 28.4%). Ethnical background was predominantly admixed (44.9%), followed by Amerindians (42.5%). A total of 55 (57.9%) cases had ≤4 years of education and 22 (23.1%) were illiterate. Deaths occurred mostly at hospital (56 cases; 62.9%) and at home (27.0%). A proportion of 42.7% of the snakebites were related to work activities. The most common formal occupation was farmer/farm caretaker (84.8). Most of the snakebites occurred in lower limbs (89.0%). Snakebites were presumably due to *Bothrops* snakes in 68.5% of cases, *Lachesis* in 29.5%, *Micrurus* in 1.0% and non-identified snake in 1.0%. Regarding time elapsed from the bite until medical assistance, 26.2% of the cases received treatment after 24 h from the bite occurring (Table 1).

3.3. Clinical characteristics at admission

At admission, death cases were classified mostly as severe (65.6%), followed by moderate (26.1%). The most frequent local manifestations were pain (90.8%), edema (88.8%), ecchymosis (34.7%) and necrosis (14.3%). Vagal manifestations (23.9%) and acute renal failure (22.5%) were the most frequent systemic manifestations. Abnormal or incoagulable clotting time was observed in 71.1% of the patients at admission (Table 2).

3.4. Antivenom treatment

From the total, 28 patients deceased without any medical assistance (22.0%). Antivenom was given to 53.5%. Of these, underdosage was observed for 53.8% of the presumed *Bothrops* cases and 78.6% of the presumed *Lachesis* cases. One case of presumed *Micrurus* snakebite was treated according the recommended dosage.

3.5. Frequency of clinical complications

In the follow up, secondary infection was recorded from 18.1%, necrosis in 18.1%, compartmental syndrome in 6.3% and amputation in 0.8% of the patients. The most frequent systemic complications were respiratory failure/acute lung edema (37.0%), acute renal failure (29.1%), sepsis (24.4%), shock (21.3%) and systemic bleeding (15.0%) (Table3). Of the 19 patients who died presenting systemic bleeding, it was possible to identify disseminated intravascular coagulopathy in 7 (36.8%), hypovolemic shock in 4 (21.1%), cerebral hemorrhage in 4 (21.1%) and acute anemia in 1 (5.2%). There were no differences in local or systemic complication prevalences between envenomings caused by presumed *Bothrops*, *Lachesis* and non-identified snakes.

Table 1
Epidemiological characteristics of the patients who died from snakebites, State of Amazonas, from 2007 to 2015.

Characteristics (completeness)	Number	%
Sex (n = 127; 100%)		
Male	95	74.8
Female	32	25.2
Areaofoccurrence (n = 98; 77.16%)		
Rural	77	78.6
Urban	21	21.4
Age group (in years) (n = 127; 100%)		
0–15	22	17.3
16–45	22	17.3
46–60	47	37.0
≥61	36	28.4
Ethnicity (n = 127; 100%)		
Admixed	57	44.9
White	13	10.2
Indian	54	42.5
Black	4	2.4
Education (in years) (n = 95; 74.8%)		
Illiterate	22	23.1
≤4	55	57.9
5–8	13	13.7
>8	5	5.3
Site of the death (n = 89; 70.1%)		
At home	24	27.0
Hospital	56	62.9
Others	9	10.1
Work-related accident (n = 110; 86.6%)		
Yes	47	42.7
No	63	57.3
Formal occupation (n = 72; 56.69%)		
Farmer/Farmcaretaker	61	84.8
Fisher	5	6.9
Others	6	8.3
Anatomical region of the bite (n = 99; 77.95%)		
Lower limbs	89	89.0
Upper limbs	10	10.0
Other sites	1	1.0
Presumed snake **genus (n = 95; 74.80%)**		
Bothrops	65	68.5
Lachesis	28	29.5
Micrurus	1	1.0
Unknown snake	1	1.0
Time elapsed from bite to medical assistance (hrs) (n = 80; 62.99%)		
≤6	37	46.3
>6-24	22	27.5
>24	21	26.2

3.6. Spatial trends and seasonality

Deaths from snakebites were unevenly distributed across the Amazonas State, although there were snakebite cases reported from 43 of the 62 municipalities. The municipalities with the largest number of cases were São Gabriel da Cachoeira (22 cases; 17.3%), Tabatinga (10; 7.9%), Manaus (7; 5.5%) and Maués (7; 5.5%). Case fatality rate (deaths from snakebites/1000 snakebites) was higher in Tapauá (45.9), Tabatinga (41.7) and São Gabriel da Cachoeira (38.5). Mortality rate (deaths from snakebites/100,000 inhabitants) was higher in São Gabriel da Cachoeira (58.1), Santa Isabel do Rio Negro (27.6) and Tapauá (26.1). Proportional mortality (deaths from snakebites/1000 deaths) was higher in Tapauá (11.1), São Gabriel da Cachoeira (10.0) and Santa Isabel do Rio Negro (8.8) (Fig. 2; Supplementary file 2).

There was an increase in the number of snakebites from January to June (Fig. 3).

3.7. Epidemiological associations with case fatality

In the multivariate analysis, a distance from Manaus >300 km

Table 2
Clinical characteristics at admission of the patients who died from snakebites, State of Amazonas, from 2007 to 2015.

Clinical characteristics (completeness)	Number	%
Severity grading at admission (n = 96; 75.6%)		
Mild	8	8.3
Moderate	25	26.1
Severe	63	65.6
Local signs and symptoms at admission (n = 98; 77.2%)		
Pain	89	90.8
Edema	87	88.8
Ecchymosis	34	34.7
Necrosis	14	14.3
Blistering	2	2.0
Bleeding	2	2.0
Secondaryinfection	1	1.0
Systemic signs and symptoms at admission (n = 89; 70.1%)		
Acute renal failure	20	22.5
Respiratoryfailure/dyspnea	3	3.4
Dizziness	2	2.2
Headache	1	1.1
Agitation	1	1.1
Hypotension	1	1.1
Bleeding	1	1.1
Vomiting	1	1.1
Shock	1	1.1
Clotting time (n = 45; 35.4%)		
Normal	13	28.9
Abnormal/Incoagulable	32	71.1

[OR = 3.40 (95%CI = 1.99–5.79); (p < 0.001)]; age 46–60 years [OR = 4.19 (95%CI = 1.32–13.29); (p = 0.015)]; age ≥61 years [OR = 4.31 (95%CI = 1.22–15.21); (p = 0.023)]; and white [OR = 11.78 (95%CI = 3.00–46.20); (p < 0.001)] and indigenous [OR = 5.47 (95% CI = 2.37–12.66); (p < 0.001)] ethnicities were independently associated with case fatality from snakebites (Table 4).

3.8. Clinical risk factors for case fatality

In the univariable analysis, moderate[OR = 3.09 (95% CI = 1.36–7.04); (p = 0.007)] and severe snakebites [OR = 67.33 (95%CI = 28.23–160.60); (p < 0.001)]; pain at admission [OR = 5.61 (95%CI = 2.23–14.15); (p < 0.001)]; ecchymosis at admission [OR = 4.35 (95%CI = 2.50–7.14); (p < 0.001)]; acute renal failure [OR = 16.67 (95%CI = 7.69–33.33); (p < 0.001)]; respiratory failure/dyspnea [OR = 223.70 (95%CI = 42.53–4624.00); (p < 0.001)]; coagulopathy at admission [OR = 4.19 (95%CI = 2.26–8.19); (p < 0.001)]; lack of antivenom administration [OR = 8.85 (95% CI = 5.39–14.54); (p < 0.001)]; antivenom underdosage [OR = 4.72 (95%CI = 2.94–7.57); (p < 0.001)]; secondary infection at bite site [OR = 4.54 (95%CI = 2.32–8.33); (p < 0.001)]; necrosis at bite site [OR = 20.00 (95%CI = 7.14–50.00); (p < 0.001)]; compartmental syndrome [OR = 4.17 (95%CI = 1.45–12.50); (p = 0.009)]; systemic bleeding [OR = 69.50 (95%CI = 12.59–1471.00); (p < 0.001)]; sepsis [OR = 124.80 (95%CI = 23.36–2599.00); (p < 0.001)]; and shock [OR = 104.90 (95%CI = 19.49–2194.00); (p < 0.001)] were significantly associated with higher snakebite fatality. In the multivariate analysis, severe snakebites [OR = 16.24 (95%CI = 4.37–60.39); (p < 0.001)] and lack of antivenom administration [OR = 4.21 (95% CI = 1.30–13.19); (p = 0.014)] were independently associated with case fatality from snakebites. Respiratory failure/dyspnea, systemic bleeding, sepsis and shock were recorded only among fatal cases (Table 5).

Table 3
Frequency of clinical complications of the patients who died from snakebites, State of Amazonas, from 2007 to 2015.

Clinical characteristics (completeness)	Total cases (n = 127)	Presumed *Bothrops* cases(n = 65)	Presumed *Lachesis* cases (n = 28)	Presumed *Micrurus* cases (n = 1)	Non identified snake (n = 33)
Local complications					
Secondaryinfection	23 (18.1)	15 (23.1)	6 (21.4)	0 (0.0)	2 (6.1)
Necrosis	23 (18.1)	13 (20.0)	8 (14.3)	0 (0.0)	2 (6.1)
Functional deficit	17 (13.4)	10 (15.4)	6 (21.4)	0 (0.0)	1 (3.0)
Compartmental syndrome	8 (6.3)	6 (9.2)	2 (7.1)	0 (0.0)	0 (0.0)
Amputation	1 (0.8)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Systemic manifestations					
Acute renal failure	37 (29.1)	22 (33.8)	11 (39.3)	0 (0.0)	4 (12.1)
Respiratory failure/acute lung edema	47 (28.3)	22 (33.8)	13 (46.4)	1 (100.0)	11 (33.3)
Sepsis	31 (24.4)	17 (26.2)	7 (25.0)	0 (0.0)	7 (21.2)
Shock	27 (21.3)	16 (24.6)	6 (21.4)	0 (0.0)	5 (15.2)
Systemicbleeding	19 (15.0)	10 (15.4)	4 (14.3)	0 (0.0)	5 (15.2)

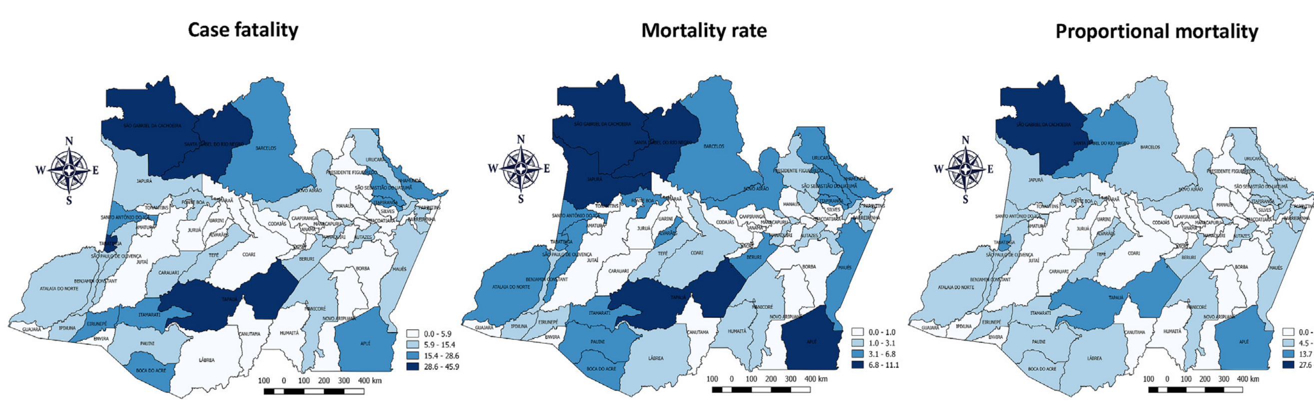

Fig. 2. Spatial patterns of case fatality, mortality rate and proportional mortality in the study area.

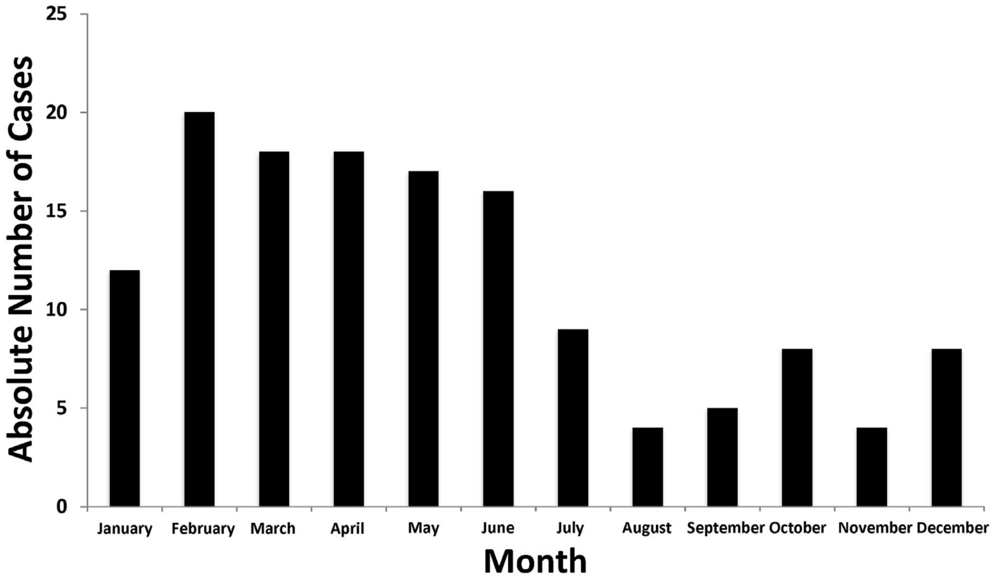

Fig. 3. Month distribution of the deaths from snakebites recorded in the state of Amazonas (2007) to 2015.

Table 4
Distal and intermediate factors associated with deaths from snakebites in the State of Amazonas, Brazil, 2007 to 2015.

Variable	Cases (%)	Controls (%)	Crude OR (IC95%)	p	AOR (CI 95%)	p
Distal components						
MMHDI						
≥medianvalue	62 (48.8)	191 (51.1)	0.95 (0.63–1.42)	0.798	…	…
<medianvalue	65 (51.2)	190 (49.9)				
MHSPI						
≥medianvalue	35 (27.6)	176 (46.2)	**0.44 (0.29–0.69)**	**<0.001**	0.75 (0.42–1.34)	0.329
<medianvalue	92 (72.4)	205 (53.8)				
Distance from Manaus (in km)						
>300	27 (21.3)	182 (47.8)	**3.39 (2.12–5.42)**	**<0.001**	**3.40 (1.99–5.79)**	**<0.001**
≤300	100 (78.7)	199 (52.2)				
Areaofoccurrence						
Urban	21 (21.4)	113 (30.4)	**0.63 (0.37–1.06)**	**0.083**	0.71 (0.41–1.22)	0.212
Rural	77 (78.6)	259 (69.6)				
Intermediate components						
Sex						
Male	95 (74.8)	303 (79.5)	1.31 (0.82–2.09)	0.264	…	…
Female	32 (25.2)	78 (20.5)				
Age group (in years)						
0–15	22 (17.3)	91 (23.9)	1	…	1	…
16–45	22 (17.3)	201 (52.8)	**0.45 (0.24–0.86)**	**0.015**	0.76 (0.26–2.22)	0.615
46–60	47 (37.0)	62 (16.3)	**3.14 (1.72–5.71)**	**<0.001**	**4.19 (1.32–13.29**	**0.015**
≥61	36 (28.4)	27 (7.1)	**5.52 (2.79–10.91)**	**<0.001**	**4.31 (1.22–15.21)**	**0.023**
Ethnicity						
Admixed	57 (44.9)	320 (85.6)	1	…	1	…
White	13 (10.2)	14 (3.7)	**5.21 (2.33–11.67)**	**<0.001**	**11.78 (3.00–46.20)**	**<0.001**
Indian	54 (42.5)	35 (9.4)	**8.66 (5.20–14.43)**	**<0.001**	**5.47 (2.37–12.66)**	**<0.001**
Black	4 (2.4)	5 (1.3)	**3.37 (0.78–14.49)**	**0.103**	5.51 (0.52–57.83)	0.115
Education level in years of study						
Illiterate	22 (23.1)	24 (9.4)	1	…	1	…
≤4	55 (57.9)	106 (41.4)	**0.57 (0.29–1.10)**	**0.093**	2.31 (0.55–9.71)	0.255
5–8	13 (13.7)	78 (30.5)	**0.18 (0.08–0.41)**	**<0.001**	1.10 (0.22–5.50)	0.908
>8	5 (5.3)	48 (18.7)	**0.11 (0.04–0.34)**	**<0.001**	0.20 (0.03–1.31)	0.095
Work-related snakebite						
Yes	47 (42.7)	188 (52.5)	**1.48 (0.96–2.28)**	**0.073**	1.77 (0.89–3.55)	0.105
No	63 (57.3)	170 (47.5)				
Anatomical region bitten						
Lower limbs	89 (89.0)	47 (12.3)	1	…	1	…
Upper limbs	10 (10.0)	329 (86.4)	**0.02 (0.01–0.03)**	**<0.001**	**0.01 (0.01–0.031)**	**<0.001**
Other sites	1 (1.0)	5 (1.3)	**20.96 (1.13–387.10)**	**0.004**	6.78 (0.45–116.65)	0.098
Time from bite until medical assistance (hours)						
≤6	37 (46.3)	264 (72.1)	**1**	…	1	…
>6-24	22 (27.5)	86 (23.5)	**1.82 (1.02–3.26)**	**0.042**	2.40 (0.77–7.53)	0.133
>24	21 (26.2)	16 (4.4)	**9.36 (4.49–19.55)**	**<0.001**	8.20 (0.60–13.42)	0.188

Mean Municipal Human Development Index (MMHDI), Mean Health System Performance Index (MHSPI).
The significance level of $p < 0.2$ in the univariable analysis was considered for included in the multivariable analysis.

4. Discussion

In this work, a low concordance (45.7%) was observed between the two databases, evidencing the importance of the integrated and routine analysis of health information systems with the aim of improving them and expanding their use for the evaluation and formulation of adequate health policies. The results also point out that the use of a single surveillance database in order to build snakebite-related mortality indicators should be viewed with caution, because of the underreporting of cases with fatal outcomes in both systems. Death underreporting is also worrying in Africa (Habib et al., 2015) and Asia (Fox et al., 2006; Kasturiratne et al., 2017; Mohapatra et al., 2011) and represents a limitation for accurately estimating public health and the economic burden of the problem.

Underreporting of deaths to the official mortality system was estimated at almost 30%, showing a challenging problem for the health system. If a case was reported to the surveillance system, the patient was necessarily attended in a health service department, being discharged alive and then dying with no update in the

Table 5
Proximal factors associated with deaths from snakebites in the State of Amazonas, Brazil, 2007 to 2015.

Variable	Cases (%)	Controls(%)	Crude OR (IC95%)	p	AOR (CI 95%)	p
Severity grading admission						
Mild	8 (8.3)	171 (47.0)	**1**	…	1	…
Moderate	25 (26.0)	173 (47.5)	**3.09 (1.36–7.04)**	**0.007**	1.53 (0.48–4.82)	0.470
Severe	63 (65.7)	20 (5.5)	**67.33 (28.23–160.60)**	**<0.001**	**16.24 (4.37–60.39)**	**<0.001**
Presumed perpetrating snake						
Bothrops	65 (68.5)	252 (71.0)	1	…	1	…
Lachesis	28 (29.5)	98 (27.6)	1.11 (0.67–1.83)	0.689	…	
Micrurus	1 (1.0)	0 (0.0)	6.70 (0.49–203.13)	0.279	…	…
Non-identified snakes	1 (1.0)	5 (1.4)	0.77 (0.09–6.75)	0.818	…	…
Pregnancy status						
Yes	1 (7.1)	2 (4.9)	1.49 (0.02–30.84)	0.999	…	…
No	13 (92.9)	39 (95.1)				
Pain at admission						
Yes	89 (88.1)	333 (97.7)	**5.61 (2.23–14.15)**	**<0.001**	2.67 (0.48–6.98)	0.209
No	12 (11.9)	8 (2.3)				
Edema at admission						
Yes	87 (86.1)	281 (82.4)	0.75 (0.40–1.41)	0.378	…	…
No	14 (13.9)	60 (17.6)				
Ecchymosis at admission						
Yes	34 (33.7)	36 (10.6)	**4.35 (2.50–7.14)**	**<0.001**	2.22 (0.78–6.25)	0.133
No	67 (66.3)	303 (89.4)				
Acute renal failure						
Yes	37 (29.1)	9 (2.4)	**16.67 (7.69–33.33)**	**<0.001**	1.35 (0.33–5.55)	0.676
No	90 (70.9)	372 (97.6)				
Respiratoryfailure/dyspnea						
Yes	47 (37.0)	0 (0.0)	**223.70 (42.53–4624.00)**	**<0.001**	…/*	…/*
No	80 (63.0)	381 (100.0)				
Coagulopathy at admission						
Yes	87 (87.0)	156 (61.4)	**4.19 (2.26–8.19)**	**<0.001**	2.56 (0.96–6.83)	0.060
No	13 (13.0)	98 (38.6)				
Antivenom administration						
No	59 (46.5)	34 (8.9)	**8.85 (5.39–14.54)**	**<0.001**	**4.21 (1.3–13.19)**	**0.014**
Yes	68 (53.5)	347 (91.1)				
Antivenom dosage						
Underdosage	62 (63.3)	97 (26.7)	**4.72 (2.94–7.57)**	**<0.001**	1.67 (0.55–5.06)	0.365
As recommended	36 (36.7)	266 (73.3)				
Secondary infection at bite site						
Yes	23 (18.1)	18 (4.7)	**4.54 (2.32–8.33)**	**<0.001**	1.82 (0.26–12.85)	0.551
No	104 (81.9)	363 (95.3)				
Necrosis atbite site						
Yes	23 (18.1)	4 (1.1)	**20.0 (7.14–50.00)**	**<0.001**	3.70 (0.41–33.33)	0.244
No	104 (81.9)	377 (98.9)				
Compartmental syndrome						
Yes	8 (6.3)	6 (1.6)	**4.17 (1.45–12.5)**	**0.009**	5.88 (0.63–50.0)	0.121
No	119 (93.7)	375 (98.4)				
Amputation						
Yes	1 (0.8)	1 (0.3)	3.03 (0.19–50.00)	0.436	…	…
No	126 (99.2)	380 (99.7)				
Systemicbleeding						
Yes	19 (15.0)	0 (0.0)	**69.50 (12.59–1471.00)**	**<0.001**	…/*	…/*
No	108 (85.0)	381 (100.0)				
Sepsis						
Yes	31 (24.4)	0 (0.0)	**124.80 (23.36–2599.00)**	**<0.001**	…/*	…/*
No	96 (75.6)	381 (100.0)				
Shock						
Yes	27 (21.3)	0 (0.0)	**104.90 (19.49–2194.00)**	**<0.001**	…/*	…/*
No	100 (78.7)	381 (100.0)				

…/*: Not calculated.
The significance level of $p < 0.2$ in the univariable analysis was considered for included in the multivariable analysis.

surveillance form and even without any new medical assistance. Usually snakebite patients are discharged after up to 48 h of hospitalization, which may represent a severe risk for some patients, whose clinical condition becomes complicated after leaving the hospital. For instance, these patients may develop secondary infections without proper wound management or from using ineffective preventive antibiotics regimens after discharge (Sachett et al., 2017). Regarding the difficulty for the riverine and indigenous populations living in remote areas that return to health centers for the treatment of this complication, severe clinical conditions such as sepsis and deaths are possible (Wen et al., 2015). Monthly variation of deaths is coincident with the incidence of snakebites, both predominant in the rainy season when snakes come closer to human settings, and is a reflection of the life style routines of riverine populations in Amazon (E. L. Feitosa et al., 2015a).

Conversely, around 25% of the deaths from snakebites were found only in the mortality database. Since late medical assistance was independently associated with the risk of death in the Amazon region (E. L. Feitosa et al., 2015b), a number of patients will die without entering snakebite surveillance statistics. Moreover, the distance from Manaus, where the only tertiary center for snakebites treatment is located, and indigenous patients were independently associated with case fatality from snakebites, highlights the importance of accessing well performing health services to prevent deaths from snakebites. Interestingly, the largest number of deaths was found in São Gabriel da Cachoeira, the municipality with proportionally the highest indigenous population in Brazil and one of most distant municipalities from the capital, Manaus. Indeed, in terms of incidence and mortality in the Amazon, it was found that 13% of tappers and Amerindians were bitten by snakes at least once in their lifetime, with a mortality rate estimated at about 400 deaths per 100,000 population per lifetime (Pierini et al., 1996).

In this case series, 22% died without medical assistance, 46.5% did not receive antivenom and 63.3% received incomplete treatments, resulting in a significant association with case fatality. Antivenoms (AV) are included in the WHO List of Essential Medicines, being the only treatment available for snakebite envenomings (WHO, 2010). In Brazil, the Ministry of Health distributes five types of liquid snake AVs for national use, free of charge to patients. However, in remote areas the lack of health professionals and infrastructure, such as adequate cold chain, impair AV distribution to health facilities resulting in a delay in patient care and a lack of proper antivenom administration (Wen et al., 2015). Furthermore, a low health system performance in treating snakebites is expected, as suggested for other animal envenomings (Oliveira et al., 2016), resulting from absence of systematic training of personnel, poor access to and quality of care for disadvantaged groups such as indigenous patients, ineffective administration and unfair financing in the less developed areas (Kruk and Freedman, 2008). In 16 West African countries, the base-case cost/DALY averted estimate fell below the commonly accepted threshold of one time per capita GDP, suggesting that AV is highly cost-effective for the treatment of snakebites (Hamza et al., 2016). To minimize this problem, the impact of medical assistance descentralization, telehealth platforms in tertiary centers and transport providing to victims and community education should be assessed (Cruz et al., 2009; Sharma et al., 2013; Silva, 2013). Beyond that freeze-drying process was suggested to improve the stability of AVs, but freeze-dried AVs efficacy and safety obtained from clinical trials is still very limited (WHO, 2010). Until then, it is clear the necessity of reviewing the national policy of antivenom distribution, in order to increase availability and promptness of antivenom therapy, especially in cases where distances may impair the transportation of patients from the place of bite, being mostly rural areas, to the site of treatment, usually an urban setting. In Brazil, AV dosage is defined according the severity grading. This work shows that clinical classification used in this country is helpful in death prediction.

Causes of death secondary to snakebites were poorly described worldwide, with unusual descriptions from diagnostic autopsies, the gold standard procedure for determining causes of death, mostly representative from Asian (Farooqui et al., 2016; Kumaranayake, 1971; Sant and Purandare, 1972) and Australian (Sutherland, 1992; Sutherland and Leonard, 1995; Welton et al., 2017) venomous snakes. In this study, *Bothrops* and *Lachesis*en venomings caused most of the deaths. It is known that these genera are the prominent snakes responsible for envenomings in the Amazon (E. S. Feitosa et al., 2015a; Otero et al., 1996; Pardal et al., 2004), but there are no studies regarding causes of death secondary to *Bothrops* and *Lachesis* bites in this region. Since no autopsy was performed in this case series, causes of death from clinical description in death certificates and surveillance reporting forms provided valuable information about the major immediate determinants of death in this groups of patients. Using this integrated approach, it was possible to conclude that deaths were strongly associated to systemic bleeding, circulatory shock, sepsis and acute respiratory failure, with similar frequencies in *Bothrops* and *Lachesis* envenomations.

In this study, circulatory shock and systemic bleeding were seen in 21.3 and 15% of the patients, respectively. Disseminated intravascular coagulopathy, hypovolemic shock and cerebral hemorrhage were common among patients dying with observed systemic bleeding. Considering the prevalence of shock, systemic bleeding occurrence was possibly underestimated since endoscopy or computerized tomography are not available for internal bleeding diagnosis in remote localities in the Amazon. Additionally, hemorrhage cannot be distinguished clinically from thrombosis without imaging. In victims of *B. atrox*, the principal snake responsible for bites in the Amazon, envenoming can be observed with coagulation disorders, such as hypofibrinogenemia, fibrinolytic system activation, and intravascular thrombin generation, resulting from procoagulant (Assakura et al., 1992; López-Lozano et al., 2002) and hemorrhagic activities (Assakura et al., 1992; Freitas-De-Sousa et al., 2015; Jacob-Ferreira et al., 2017; Sanchez et al., 2010; Sousa et al., 2013). In São Paulo, where *Bothrops* was responsible for 87% of the cases, coagulation disorders occurred in 92% and shock in 42% of the patients who died (Ribeiro et al., 1998). In Ecuador, the prevalence of cerebrovascular complications related to *Bothrops* bites was 2.6% (Mosquera et al., 2003). Other reports of cerebral hemorrhage secondary to *Bothrops* envenomings confirm the high lethality of this condition (Kouyoumdjian et al., 1991; Machado et al., 2010; Pinho and Burdmann, 2001; Santos-Soares et al., 2007). Again, underestimation of intracranial hemorrhage is probably underreported in our case series due to the lack of computerized tomography in most health facilities. In older patients, comorbidities leading to vascular disease, such as hypertension and diabetes, may precipitate life-threatening complications after snakebite envenomings (E. L. Feitosa et al., 2015a), as also seen here.

In Southern Brazil, the most common manifestations and complications implicated as possible death causes were acute renal failure, acute respiratory failure, shock and sepsis (Ribeiro et al., 1998). Pulmonary edema and the effects of both fluid overload and metabolic acidosis may complicate management of patients with acute renal failure. Indeed, main complications occurring in patients bitten by *Crotalus* and *Bothrops* and presenting renal failure admitted to ICU were pulmonary edema, respiratory failure, cardiac arrest and hypovolemic shock (da Silva et al., 1979). In this work, sepsis was commonly seen in snakebite envenoming, possibly contributing to renal and respiratory complications. Sepsis is poorly described in snakebites in Latin America and is observed namely in *Bothrops* envenoming (Ribeiro et al., 1998). In the United States, a septic shock syndrome was observed in a patient bitten by a pigmy rattlesnake (Gonzalez et al., 2010). Unfortunately, in this case series circulatory shock lacked the possible etiology, but in *Bothrops* snakebites studies in São Paulo, Brazil, shock was mostly caused by sepsis (Ribeiro et al., 1998). Sepsis in *Bothrops* bites can be explained by the spread of bacteria causing infection in the bite site. Secondary bacterial infection in the bite site was recorded in 40% of the patients in the Brazilian Amazon, and is caused often by *Morganella morganii* (Sachett et al., 2017).

One limitation of our study is the collection of data from surveillance databases. This retrospective design limits the accuracy and therefore the value of the clinical data. Reports of clinical complications and outcome may be not accurate, and may be under suspicious since definition of respiratory and renal failure are not clearly stated as sepsis condition. However, consistency of clinical data and type and severity of envenoming suggest that these independent variables are truly associated with deaths, especially in *Bothrops* envenoming. Another limitation of this study was the imprecision of some estimates due to the small number effect, such as for respiratory failure/dyspnea, systemic bleeding, sepsis and shock prevalences.

In conclusion, i) death from snakebites was underreported in mortality surveillance system and integrated analysis of health information systems must be used for improving adequate health policies; ii) older age and indigenous status were the population groups more prone to death; iii) distance from Manaus, where the only tertiary center for snakebite treatment is located, and indigenous patients were independently associated with case fatality from snakebites, highlighting the importance of accessing well performing health services to prevent deaths from snakebites; iv) lack of antivenom administration or incomplete treatments resulted in a significant association with case fatality and v) case fatality was strongly associated to systemic bleeding, circulatory shock, sepsis and acute respiratory failure, with similar frequencies in *Bothrops* and *Lachesis* envenomations. To minimize this problem, medical assistance descentralization, cold chain improvement, telehealth platforms in tertiary centers and the provision of transport for victims in the Brazilian Amazon is suggested.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.toxicon.2018.02.041.

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