# Time to treatment and severity of snake envenoming in Brazil

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**ABSTRACT**

**Objective.**   *To analyze the relationship between time to treatment and severity of snakebite envenomation in Brazil.*

**Methods.**   *This case-series retrospective study analyzed 144 251 snakebite cases in Brazil between 2007 and 2015, as reported to the Brazilian Notifiable Diseases Information System. The main dependent variable was snakebite envenomation severity (mild/moderate/severe). The main predictor was time to treatment (early (< 6 hours) vs. delayed (≥ 6 hours)). Covariables were snake type (Bothrops/Crotalus/Micrurus/Lachesis), patient's age and sex, bite site, and treatment at a specialized care center (center/noncenter). Polytomous logistic regression techniques were used to control the covariates and assess confounding and effect modification.*

**Results.**   *The time to treatment variable was strongly associated with the severity of snakebite envenomation. Snake type and treatment at specialized care center modified the main association effect. The association between delayed time to treatment and envenomation severity was consistently stronger among patients treated at specialized care centers than among those who were not treated at such centers. Odds ratios tended to increase significantly from moderate to severe envenomation for cases within the subgroups "Center + Bothrops" (1.37 to 2.05), "No center + Bothrops" (1.25 to 1.47), "Center + Crotalus" (1.35 to 3.03), "No center + Crotalus" (0.97 to 2.72), and "Center + Lachesis" (1.22 to 1.89).*

**Discussion.**   *This study confirmed the classical hypothesis that the time between snakebite and initiation of medical care is associated with severity of snakebite envenomation. It is therefore necessary to provide snakebite victims early access to specialized medical care, particularly to antivenom therapy.*

**Keywords**   Snake bites; patient acuity; time to treatment; Brazil.

The number of snakebite envenomation victims in the Americas is high, particularly in Latin America, where it represents a serious public health problem. One study estimated that, in 2007, there was an incidence of between 80 329 and 129 084 cases in Latin America (1).

In South America and Central America, there is a predominance of snakebites by the *Bothrops* species, while rattlesnakes (*Crotalus)* are responsible for most cases that occur in North America (2).

Snakebites in Brazil are underreported, and the available clinical and epidemiological data on them is often insufficient or of poor quality (3). In Brazil, in 2007, the coefficient of snakebite incidence was relatively low (13.50 per 100 000 inhabitants), but lethality varied markedly, according to snake type (4).

Severe and lethal snakebite cases are strongly associated with a delay in specific medical treatment (serum therapy), usually considered to be six hours following the snakebite (4). Delayed treatment is a factor in poor prognosis. That is because even though the circulating venom is neutralized by the antivenom, this does not apply to the local lesion.

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Antivenom only acts on the circulating venom and does not reverse the local lesion effects caused by envenomation. This information is critical for clinical staging and envenomation treatment and prognosis (5).

This study aims to analyze the relationship between the time interval from snakebite to initiation of serum therapy care and the severity of snakebite envenomation in patients in Brazil.

## MATERIAL AND METHODS

This case-series retrospective study included all 144 251 snakebite envenomation cases caused by snakes of medical importance, compulsorily reported to the Brazilian Notifiable Diseases Information System (Sistema de Informação de Agravos de Notificação (SINAN)), that occurred in Brazil between 2007 and 2015. The study included individuals over 15 years old, for whom the following information set was available: envenomation severity (snakebite envenomation staging); time to treatment (the interval between the snakebite and the initiation of medical care); and other covariables of interest: age, sex, snake type, anatomic region of the bite, and treatment at specialized care center. Other supportive therapies can be added to patient treatment, especially when local or systemic manifestations, such as acute renal failure, hypotension, and shock, also occur. However, the antivenom is the cornerstone of snakebite envenoming therapy.

The 144 251 cases with complete information did not differ significantly ($p > 0.05$, chi-square tests) from the 232 868 cases with incomplete information according to sex and anatomic region of the bite, although they did differ ($p < 0.05$) in terms of age, snake type, and treatment at specialized care center.

The main outcome variable ("envenomation severity") was classified as mild, moderate, or severe. Envenomation staging is established at patient admission to the medical service, taking into account the intensity of local and/ or systemic manifestations, according to Brazilian Ministry of Health criteria for the diagnosis and treatment of ophidian accidents (4). The main predictor variable (time to treatment) was classified as early (< 6 hours) or delayed (≥ 6 hours).

The medical care at the specialized medical center *should* necessarily include the administration of the specific antivenom, as soon as possible (4). Patients who did not receive antivenom therapy were classified as having a delayed time to treatment.

Dummy variables were constructed to classify the covariables: age (15 to 34 years old = 0; 35 to 59 years old = 1; and 60 years old or older = 2); snake taxon (*Bothrops* = 0; *Crotalus* = 1; *Lachesis* = 2; *Micrurus* = 3); and anatomic region of the bite (central axis = 0; upper limbs = 1; lower limbs = 2). The Brazilian Government strategy to increase accessibility to antivenom treatment ensures that municipalities either have their own specialized center for the care of victims of accidents caused by venomous animals or that the nearest center is located in a neighboring district. Patients were classified according to the place where they received their first medical care: in a specialized care center or not (center = 0; noncenter = 1). Sex was analyzed as male = 0 and female = 1. The main association, time to treatment and envenomation severity, was measured by the odds ratio (OR) and its respective 95% confidence interval (CI).

The relative importance of the main association for the covariables of patient's sex and age, treatment at specialized care center, snake taxon, and anatomic region of the bite was evaluated using polytomous logistic regression. Using the backward stepwise method, we considered the existence of confounding when the difference between the adjusted and crude ORs was 20%. Based on the scientific literature and on our data structure, interaction terms were built and tested for all the models, in order to estimate the presence of effect modification for the main association (6). Goodness-of-fit was estimated using the log likelihood ratio test, with a $p$ value of $p < 0.05$.

We created a database for individual data using the Statistical Package for the Social Sciences (SPSS) version 20.0.0 (IBM Corp., Armonk, New York, United States of America) and then exported the data to Stata 12.0 (StataCorp, College Station, Texas, United States) for processing and analysis.

The data bank of cases of snakebite envenoming provided by the Brazilian Ministry of Health and National Health Foundation (FUNASA) did not allow individuals to be identified. Therefore, anonymity was preserved. The Ethical Board of the Collective Health Institute, Federal University of Bahia, approved the research project (#052/06).

## RESULTS

Out of the 144 251 patients, 71 143 (49.3%) were classified as mild cases of snakebite envenomation, 61 334 (42.5%) as moderate cases, and 11 774 (8.2%) as severe cases. Delayed serum treatment (≥ 6 hours after bite) was administered to 22 483 (15.6%) of the 144 251 patients. Receiving delayed serum treatment occurred with 13.0% of the mild cases, 17.1% of the moderate cases, and 23.4% of the severe cases.

Antivenom was not used in 7 781 (5.4%) of the 144 251 patients. This was the case for 9.8% of the mild cases, 2.0% of the moderate cases, and 2.0% of the severe cases. Nonuse of antivenom occurred in 4.8% of the 130 140 patients who were attended in specialized centers, and in 10.4% of those 14 103 who were attended in other centers.

Envenomation severity was strongly ($p < 0.001$) associated with sex, age, snake, bite site, and treatment at a specialized care center. Within the covariable strata, severe envenomation was more frequent among males aged 60 years or over who were bitten by *Micrurus* in the central axis and treated at a specialized care center (Table 1).

The strength of the association between time to treatment and envenomation severity increased from the moderate cases (crude OR = 1.37; 95% CI, 1.33-1.42) to severe cases (crude OR = 2.04; 95% CI, 1.94-2.14). Crude ORs also increased from moderate cases to severe cases in those 35 to 59 years old and those 60+ and with *Crotalus* and *Micrurus* envenomation (Table 2).

Polychromous logistic analysis included the variables time to treatment, envenomation severity, age, sex, bite site, treatment at specialized care center, and snake taxon. "Snake taxon" (likelihood ratio 70.33) and "treatment at a specialized care center" (likelihood ratio 11.88) modified the effect of association between time to treatment and envenomation severity. Consequently, the database was divided into the eight subgroups formed by these two covariables, in

**TABLE 1. Envenomation severity according to time to treatment and relevant variables in 144 251 snakebite cases in Brazil, 2007–2015**

| Variable | Envenomation severity | | | | | | $p^a$ |
|---|---|---|---|---|---|---|---|
| | Mild | | Moderate | | Severe | | |
| | n | % | n | % | n | % | |
| Time to treatment | | | | | | | |
| Delayed (≥ 6 hours) | 9 260 | 41.2 | 10 471 | 46.6 | 2 752 | 12.2 | < 0.001 |
| Early (< 6 hours) | 61 883 | 50.8 | 50 863 | 41.8 | 9 022 | 7.4 | |
| Sex | | | | | | | |
| Female | 14 940 | 51.0 | 12 024 | 41.1 | 2 300 | 7.9 | < 0.001 |
| Male | 56 023 | 48.9 | 49 310 | 42.9 | 9 474 | 8.2 | |
| Age (years) | | | | | | | |
| 15 to 34 | 32 567 | 51.0 | 26 707 | 41.8 | 4 631 | 7.2 | < 0.001 |
| 35 to 59 | 30 530 | 48.5 | 27 127 | 43.0 | 5 353 | 8.5 | |
| 60+ | 8 046 | 46.4 | 7 500 | 43.3 | 1 790 | 10.3 | |
| Snake | | | | | | | |
| *Bothrops* | 62 597 | 50.3 | 52 623 | 42.2 | 9 326 | 7.5 | < 0.001 |
| *Crotalus* | 6 099 | 45.9 | 5 519 | 41.6 | 1 660 | 12.5 | |
| *Lachesis* | 1 883 | 36.3 | 2 877 | 55.4 | 429 | 8.3 | |
| *Micrurus* | 564 | 45.6 | 315 | 25.4 | 359 | 29.0 | |
| Site of bite | | | | | | | |
| Central axis | 940 | 49.9 | 752 | 39.9 | 193 | 10.2 | < 0.001 |
| Upper limb | 16 315 | 50.3 | 13 095 | 40.4 | 2 996 | 9.3 | |
| Lower limb | 53 888 | 49.0 | 47 487 | 43.2 | 8 585 | 7.8 | |
| Treatment at specialized care center | | | | | | | |
| Center | 63 757 | 49.0 | 55 672 | 42.8 | 10 719 | 8.2 | < 0.001 |
| No center | 7 386 | 52.4 | 5 662 | 40.1 | 1 055 | 7.5 | |

[a] Chi-square tests.

order to proceed with the appropriate regression analyses.

Delayed time to treatment was the only variable present in all eight subgroups. The association between delayed time to treatment and envenomation severity was consistently stronger among groups of patients treated at specialized care centers than those not treated at such centers. Further, the ORs tended to increase significantly from moderate to severe envenomation, compared to results within the subgroups "Center + *Bothrops*" (1.37 to 2.05), "No center + *Bothrops*" (1.25 to 1.47), "Center + *Crotalus*" (1.35 to 3.03), "No center + *Crotalus*" (0.97 to 2.72), and "Center + *Lachesis*" (1.22 to 1.89). Note that the 95% CI for "moderate" does not include the OR for the respective "severe" cases within the same subgroup. For example, in the subgroup "Center + *Bothrops*," the OR = 1.37 is not included in the 1.94-2.17 95% CI of the "severe" stratum, nor is the OR = 2.05 included in the 1.32-1.42 95% CI of the "moderate" stratum (Table 3).

Covariables strata "male," and age groups "35 to 59 years old," and "60+ years old" also demonstrated strong associations with envenomation severity. The association between "60+ years old" and severity of *Bothrops* envenomation in patients treated at specialized care centers was particularly relevant. These ORs increased from 1.23 (95% CI: 1.18-1.28) among cases with moderate envenomation to 1.58 (95% CI: 1.48-1.70) among those with severe envenomation, representing a significant increase in risk of severe envenomation. Males were significantly more affected than females in *Bothrops* and *Crotalus* envenomation, but only in cases treated at specialized care centers. Further, the strength of association increased from moderate to severe cases only in cases involving "Center + *Crotalus*," with the OR going from 1.14 to 1.24 (Table 3).

## DISCUSSION

The variable time to treatment was strongly associated with the severity of

snakebite envenomation. The Brazilian Ministry of Health has already noted the importance of time to treatment in snakebite severity (4). A study of 9 191 snakebite cases in the Brazilian Amazon reported that, between 2007 and 2012, a delay of six or more hours in medical care was associated with increased severity of envenomation (7).

Snake antivenoms are highly effective remedies (8), but they must be adequately distributed to the necessary locations and administered by trained medical staff (9).

The Brazilian Government maintains exclusive control over antivenom production and with distribution at a reasonable cost, making it available to the entire population (10). At least one antivenom center capable of providing specialized snakebite care is strategically located near every Brazilian municipality. The amount of antivenoms delivered to each center depends on epidemiological criteria, principally the number of envenomation cases the center reports to the Notifiable Diseases Information System.

According to our data, the presence of a specialized care center acted as an effect modifier, increasing the severity of snakebite envenomation. It is possible that "mild" accidents did not motivate patients to seek immediate specialized medical care. However, there was a delay in seeking health care once the envenomation worsened (10). This process may have increased the demand of severe cases for specialized care centers.

Envenomation severity is usually associated with snake taxon. Snake venom is a complex mixture of components, such as proteins, peptides, and biologically active substances, which vary widely among the different snake types that exist on the planet (11). Enzymes present in the venom are related to tissue necrosis, coagulant activity, anticoagulants, and pain. Different snake types have different types of venom, which can result in distinct clinical manifestations and lethality (3, 12, 13).

In our study, snake taxon had an important modification effect on the main association between time to treatment and envenomation severity. Cases with *Bothrops* envenomation predominated in our case series. The genus *Bothrops* is reported to be the main etiological

**TABLE 2. Crude odds ratio (OR) and respective 95% confidence interval (CI) for the association between time to treatment and envenomation severity, according to covariable strata in 144 251 snakebite cases in Brazil, 2007–2015**

| Variable | Envenomation severity | | | |
| | Moderate[a] | | Severe[a] | |
| | OR | 95% CI | OR | 95% CI |
|---|---|---|---|---|
| Time to treatment | | | | |
| Early (< 6 hours) | 1.00 | - | 1.00 | - |
| Delayed (≥ 6 hours) | 1.37 | 1.33-1.42 | 2.04 | 1.94-2.14 |
| Sex | | | | |
| Female | 1.00 | - | 1.00 | - |
| Male | 1.09 | 1.07-1.12 | 1.08 | 1.04-1.13 |
| Age (years) | | | | |
| 15 to 34 | 1.00 | - | 1.00 | - |
| 35 to 59 | 1.10 | 1.07-1.12 | 1.23 | 1.10-1.29 |
| 60+ | 1.16 | 1.11-1.20 | 1.55 | 1.46-1.65 |
| Snake | | | | |
| *Bothrops* | 1.00 | - | 1.00 | - |
| *Crotalus* | 1.08 | 1.05-1.13 | 1.86 | 1.75-1.92 |
| *Lachesis* | 1.73 | 1.63-1.84 | 1.39 | 1.24-1.54 |
| *Micrurus* | 0.70 | 0.60-0.80 | 4.43 | 3.87-5.08 |
| Site of bite | | | | |
| Central axis | 1.00 | - | 1.00 | - |
| Upper limb | 1.01 | 0.92-1.13 | 0.91 | 0.78-1.07 |
| Lower limb | 1.11 | 1.00-1.22 | 0.81 | 0.69-0.95 |
| Treatment at specialized care center | | | | |
| Center | 1.00 | - | 1.00 | - |
| No center | 0.89 | 0.86-0.92 | 0.84 | 0.78-0.90 |

[a] Reference group: "mild" envenomation severity.

agent of snakebite envenomation in Brazil (3) and Argentina (14). *Bothrops asper* and *B. atrox* cause the most bites and fatalities in Central and South America (2, 15). The genus *Bothrops* comprises a large number of species, which display aggressiveness and ecological plasticity and adapt to environmental changes, including anthropized environments (16). *Crotalus* snakes are found in open areas, while *Lachesis* is seen in dense forest environments, and these two are thus less likely to be involved in ophidian accidents (3, 4, 17). *Micrurus* has a wide distribution across all of Brazil, but accidents are rare, because of its coloration (conspicuous), dentition (small, fixed, and corrugated front tusks) and the fact that they do not strike (17).

Our study revealed that the association between male sex and poisoning severity increased from moderate to severe cases for victims of *Crotalus* treated at specialized care centers. Men are more likely to suffer snakebites than are women, principally because of men's work in agriculture (16, 18).

In our study, snakebite envenomation was particularly severe among patients aged 60+ treated for *Bothrops* envenomation at specialized care centers. In the Brazilian Amazon, individuals aged 65+ presented more severe envenomation (7).

Antivenom therapy was not used in 7 781 (5.4%) of reported cases. All these cases were classified as presenting "delayed" time to treatment. However, these cases only represented a tiny proportion (2.0%) of those with severe or moderate envenomation. Antivenom was not used in 4.8% of the patients who were attended at specialized centers, and in 10.8% of those who were attended at other centers. The shortage or the absence of antivenom, particularly in the specialized centers that provide health care to snakebite cases, may denote problems in the production and/or the distribution of antivenoms in the vast territory of Brazil. Or it could also

indicate that the health team is not well trained about how to estimate the severity of snakebite clinical picture and, more likely, about how to administer antivenom therapy according to the recommended strength.

We should note that treatment failures cannot be attributed to nonvenomous snakebites, since this study only included cases attributed to venomous snakes from four genera occurring in Brazil: *Bothrops*, *Crotalus*, *Micrurus*, and *Lachesis*.

One positive aspect of our study is its large sample size, which allowed us to perform statistical analyses unavailable to smaller studies, such as subdividing the database in order to investigate effect modification.

Limitations inherent to cross-sectional studies may have occurred, since subjects for the study population were selected from a secondary database, sourced from compulsory notification. Since the data was not obtained from a primary source, mistakes may have occurred in the way the exposure information was obtained (information bias). Selection bias should also be considered, since this study only included cases with a complete set of variables. The study population represented only 38.3% of the 377 119 snakebite envenomation cases reported between 2007 and 2015. Further, the population presents important differences according to age group, snake type, and treatment at a specialized care center.

The study found that snake type modified the effect for the association between time to treatment and envenomation severity, although the analyses were not valid for each of the eight identified subgroups. The small sample size of certain strata decreased study power. The study classified its main outcome into three categories, which may have contributed to the smaller sample size of certain subgroups and, consequently, decreased study power.

## Conclusions

This study confirmed the classical hypothesis that time to treatment is associated with snakebite envenomation severity in Brazil. Medical care at a specialized center and snake type, particularly *Bothrops*, *Crotalus*, and *Lachesis*,

**TABLE 3. Results of the polytomous logistic regression analysis for the association between time to treatment and envenomation severity, with odds ratio (OR) and 95% confidence interval (CI), according to snake type and treatment at specialized care center, in 144 251 snakebite cases in Brazil, 2007–2015**

| Subgroup/Variable(s) in analysis | n | Moderate[a] | | Severe[a] | |
|---|---|---|---|---|---|
| | | OR | 95% CI | OR | 95% CI |
| Center + *Bothrops* | 112 820 | | | | |
| Delayed time to treatment[b] | | 1.37 | 1.32-1.42 | 2.05 | 1.94-2.17 |
| Male[c] | | 1.08 | 1.05-1.11 | 1.05 | 1.01-1.11 |
| 35 to 59 years old[d] | | 1.11 | 1.09-1.14 | 1.10 | 1.06-1.16 |
| 60+ years old[d] | | 1.23 | 1.18-1.28 | 1.58 | 1.48-1.70 |
| No center + *Bothrops* | 11 726 | | | | |
| Delayed time to treatment[b] | | 1.25 | 1.11-1.40 | 1.47 | 1.19-1.80 |
| Center + *Crotalus* | 11 305 | | | | |
| Delayed time to treatment[b] | | 1.35 | 1.19-1.53 | 3.03 | 2.60-3.53 |
| Male[c] | | 1.14 | 1.04-1.25 | 1.24 | 1.08-1.42 |
| No center + *Crotalus* | 1 973 | | | | |
| Delayed time to treatment[b] | | 0.97 | 0.70-1.36 | 2.72 | 1.86-3.98 |
| Center + *Lachesis* | 4 939 | | | | |
| Delayed time to treatment[b] | | 1.22 | 1.07-1.39 | 1.89 | 1.51-2.35 |
| No center + *Lachesis* | 250 | | | | |
| Delayed time to treatment[b] | | 0.54 | 0.23-1.28 | 0.34 | 0.04-2.77 |
| Center + *Micrurus* | 1 084 | | | | |
| Delayed time to treatment[b] | | 1.22 | 0.81-1.85 | 0.72 | 0.46-1.13 |
| No center + *Micrurus* | 154 | | | | |
| Delayed time to treatment[b] | | 0.56 | 0.15-2.10 | 0.38 | 0.08-1.81 |

[a] Reference group: mild envenomation severity.
[b] Reference group: early time to treatment.
[c] Reference group: female.
[d] Reference group: 15 to 34 years old.

modified the effect of this association. Envenomation severity was associated with older age groups (only in envenomation by *Bothrops*) and with male sex (in *Bothrops* and *Crotalus* envenomation). Snakebite victims must be provided with early access to specialized medical care, particularly to antivenom therapy.

**Disclaimer.** The authors hold sole responsibility for the views expressed in the manuscript, which does not necessarily reflect the opinion or policy of the *RPSP/PAJPH*, the Pan American Health Organization, CNPq, or FUNASA/MS. These institutions had no role in study design, data analysis, decision to publish, or preparation of the manuscript.

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**RESUMEN**

**Tiempo hasta el tratamiento y gravedad del envenenamiento por mordedura de serpiente en el Brasil**

*Objetivo.* Analizar la relación entre el tiempo transcurrido hasta el tratamiento y la gravedad del envenenamiento por mordedura de serpiente (ofidismo) en el Brasil.

*Métodos.* En este estudio retrospectivo de una serie de casos se analizaron 144 251 casos de mordedura de serpiente en el Brasil entre el 2007 y el 2015, notificados al Sistema Brasileño de Información sobre Enfermedades de Notificación Obligatoria. La principal variable dependiente fue la gravedad del ofidismo (leve, moderado o grave). El principal factor predictivo fue el tiempo hasta el tratamiento (temprano [menos de 6 horas] o tardío [6 horas o más]). Las covariables fueron el tipo de serpiente (*Bothrops, Crotalus, Micrurus* o *Lachesis*), la edad y el sexo del paciente, la localización de la mordedura y el tratamiento en un centro de atención especializada (sí o no). Se usaron técnicas de regresión logística politómica para controlar las covariables y evaluar el fenómeno de confusión y la modificación del efecto.

*Resultados.* La variable de tiempo hasta el tratamiento se asoció estrechamente con la gravedad del ofidismo. El tipo de serpiente y el tratamiento en un centro especializado modificaron el principal efecto de asociación. La asociación entre el tratamiento tardío y la gravedad del ofidismo fue sistemáticamente más estrecha en los pacientes tratados en los centros especializados de atención que entre los no tratados en tales centros. Las razones de posibilidades tendieron a aumentar significativamente del ofidismo moderado al ofidismo grave para los casos en los subgrupos "centro + *Bothrops*" (1,37 a 2,05), "no tratados en un centro + *Bothrops*" (1,25 a 1,47), "centro + *Crotalus*" (1,35 a 3,03), "no tratados en un centro + *Crotalus*" (0,97 a 2,72) y "centro + *Lachesis*" (1,22 a 1,89).

*Discusión.* Este estudio confirmó la hipótesis clásica de que el lapso entre la mordedura de serpiente y el inicio de la atención médica se asocia con la gravedad del ofidismo. Por consiguiente, es necesario dar a las víctimas de mordeduras de serpiente acceso temprano a la atención médica especializada, en particular al tratamiento con el antídoto.

**Palabras clave** Mordeduras de serpientes; gravedad del paciente; tiempo de tratamiento; Brasil.

**RESUMO**

**Tempo para tratamento e gravidade do envenenamento ofídico no Brasil**

*Objetivo.* Examinar a relação entre tempo para tratamento e gravidade do envenenamento ofídico no Brasil.

*Métodos.* Neste estudo retrospectivo de série de casos foram analisados 144.251 casos de picadas de cobras registrados no Sistema de Informação de Agravos de Notificação do Brasil entre 2007 e 2015. A principal variável dependente foi gravidade do envenenamento ofídico (leve/moderado/grave). O principal fator de predição foi tempo para tratamento (rápido <6 horas ou demorado ≥6 horas). As covariáveis foram gênero da serpente (*Bothrops/Crotalus/Micrurus/Lachesis*), idade e sexo do paciente, local da picada e tratamento em centro especializado de atendimento (em centro/não em centro). Um modelo de regressão logística politômica foi usado para controlar as covariáveis e avaliar os fatores de confusão e modificadores de efeito.

*Resultados.* A variável tempo para tratamento apresentou marcante associação com gravidade do envenenamento ofídico. O gênero da serpente e o tratamento em centro especializado modificaram o principal efeito da associação. A associação entre demora para o tratamento e gravidade do envenenamento foi consistentemente mais marcante nos casos tratados em centros especializados em comparação aos casos não tratados nestes centros. Os odds ratios tenderam a aumentar significativamente nos casos de envenenamento moderado a grave nos subgrupos "em centro + *Bothrops*" (1,37 a 2,05), "não em centro + *Bothrops*" (1,25 a 1,47), "em centro + *Crotalus*" (1,35 a 3,03), "não em centro + *Crotalus*" (0,97 a 2,72) e "em centro + *Lachesis*" (1,22 a 1,89).

*Discussão/Conclusão.* Este estudo confirmou a clássica hipótese de que o tempo decorrido entre a picada de cobra e o início do atendimento médico está associado à gravidade do envenenamento ofídico. Portanto, é necessário prover às vítimas de acidentes ofídicos acesso rápido à atenção médica especializada, sobretudo o acesso ao tratamento com soro antiofídico.

**Palavras-chave** Mordeduras de serpentes; gravidade do paciente; tempo para o tratamento; Brasil.