Fatal Snakebite Envenoming and Agricultural Work in Brazil: A Case–Control Study

Yukari Figueroa Mise,^{1*} Rejane Maria Lira-da-Silva,² and Fernando Martins Carvalho³

¹Instituto de Saúde Coletiva, Federal University of Bahia, Salvador, Brazil; ²Instituto de Biologia, Federal University of Bahia, Salvador, Brazil;

³Faculdade de Medicina da Bahia, Federal University of Bahia, Salvador, Brazil

Abstract. We investigated the association between fatal snakebite envenoming and agricultural work in Brazil, considering the effects of relevant covariables. A nested case–control study was performed using 1,119 fatal cases of snakebite envenoming among persons aged ≥ 10 years, notified to the Brazilian official reporting system, from 2004 to 2015. As controls, 4,476 cases were randomly selected from the 115,723 nonfatal cases of snakebite, without missing data, that occurred in the same time period. The main predictor was occupation in the agriculture sector; the main outcome was death by snakebite envenoming. Logistic regression analysis was used to investigate the main association, controlling for the effects of relevant covariables. Fatal cases had a 20% greater chance (odds ratio [OR] = 1.20; 95% confidence interval [CI]: 1.00–1.39) of being among farmers than the controls. However, late (≥ 6 hours) time to treatment (OR = 2.00; 95% CI: 1.70–2.36); adequate antivenom with an insufficient (OR = 1.25; 95% CI: 1.04–1.50) or excessive (OR = 4.89; 95% CI: 4.10–6.03) number of vials; inadequate antivenom and insufficient or excessive number of vials (OR = 3.87; 95% CI: 2.40–6.24); no use of antivenom (OR = 2.05; 95% CI: 1.60–2.64); and age ≥ 60 years (OR = 1.98; 95% CI: 1.61–2.44) were more strongly associated with lethality. Lethality was 1.0% in the period, being 0.47% among those receiving early and adequate treatment. We concluded that in Brazil, fatal snakebite envenoming was associated with agricultural work, controlling for relevant covariates. However, quality of health care provided and greater age were much more strongly associated with lethality.

INTRODUCTION

Snakebite envenoming is considered an environmental and occupational disease that calls for the attention of national and regional health authorities.¹ Snakebite envenoming takes its toll predominantly among agricultural workers, adults and children, who work in poor rural communities in less developed areas.^{2,3}

The profile of the agricultural worker reveals an individual who is not prepared to deal with the risk of being bitten by a snake and does not have the necessary support for being treated for snakebite envenoming. Agricultural workers are particularly vulnerable to snakebite envenoming.^{4–6} Several epidemiological studies in Latin America and Asia show that rural, subsistence agricultural communities face snakebite envenoming as a daily occupational problem.^{7–9}

The 2010 Brazilian National Census has counted 154,990,266 people aged 10 years and older, 11,606,543 (7.5%) of them occupied in agricultural work.¹⁰ Annually, about 27,200 cases of snakebite occur in Brazil, causing 115 deaths/year, yielding a case fatality rate of 0.42%.¹¹

This study aimed to investigate the association between fatal snakebite envenoming and agricultural work in Brazil, considering the effects of relevant covariables.

MATERIALS AND METHODS

This nested case–control study used cases of snakebite envenoming compulsorily recorded by the Brazilian official reporting system (Sistema de Informação de Agravos de Notificação [SINAN]), from 2004 to 2015.

The main outcome variable was death due to snakebite envenoming, and the main exposure variable was agricultural work, as defined in the SINAN¹² reporting system forms. So,

“agricultural work” is a broad term that involves occupations that cultivate the soil with permanent or temporary crops, including green vegetables and flowers; rearing or fattening of medium or large animals; rearing of small animals; forestry or reforestation; and extraction of plant products.

Eligibility criteria for cases and controls was age ≥ 10 years and having a complete set of data in the SINAN databank. A total of 1,144 deaths occurred from 2004 to 2015, and 1,119 (97.8%) satisfied the eligibility criteria. Among the 227,470 snakebite envenoming patients who did not die, 115,723 (50.8%) had a complete set of data of the variables of interest. The losses of information were statistically significant ($P < 0.05$) according to all variables of interest investigated, except for gender. From these 115,723 individuals, 4,476 were randomly selected, adopting a 1:4 (cases:controls) ratio.

Usually, the patient does not bring the snake responsible for the snakebite with him/her. Therefore, identification of the snake type and decisions about the appropriate antivenom (AV) therapy are made on the basis of the clinical manifestations of the envenoming, which are rather distinctive in Brazil.^{12,13} The Brazilian Health Ministry guidelines recommend the classification of the severity of snakebite cases as mild, moderate, and severe; the number of AV vials to be administered varies from 2 to 20, depending on the type of snake and on the severity of the envenoming. The following types of AVs are freely provided by the Brazilian government and are not available to the private sector: anti-*Bothrops* serum; anti-*Bothrops* plus anti-*Crotalus* serum; anti-*Crotalus* serum; anti-elapidic serum, for *Micrurus* bites¹³; and anti-*Bothrops* plus anti-*Lachesis* serum.¹⁴ For the purposes of this study, the AV treatment was classified according to the AV used and the number of vials used, as follows: adequate AV and adequate number of vials = 0; adequate AV with insufficient number of vials = adequate AV with excessive number of vials = 2; inadequate AV and insufficient or excessive number of vials = 3; and no use of AV = 4.

The other covariates investigated were coded as follows: gender (female = 0 and male = 1); age (10–29 years = 0; 30–59 years = 1; and ≥ 60 years = 2); time to treatment (< 6 hours

* Address correspondence to Yukari Figueroa Mise, Instituto de Saúde Coletiva, Federal University of Bahia, Rua Basílio da Gama, s/n Campus Universitário do Canela, Salvador 41110-040, Brazil. E-mail: yukarimise@gmail.com

[early] = 0 and ≥ 6 hours [late] = 1); perpetrating snake genus (*Micrurus* = 0; *Bothrops* = 1; *Crotalus* = 2; and *Lachesis* = 3). The odds ratio (OR) and its respective 95% confidence interval (CI) were calculated as a measure of association. Chi-square tests were used to compare cases and controls according to agricultural work and covariables.

The attributable-risk percent among the exposed (or its analogous preventable fraction, when appropriate) and the population attributable-risk percent, also known as Levin's attributable fraction,¹⁵ were calculated to estimate the proportions of deaths due to snakebites attributed to agricultural work among those bitten by venomous snakes and in the Brazilian population aged 10 years or older, respectively.

Multiple logistic regression was used to analyze the data, with the backward method, and to calculate adjusted ORs and 95% CI. Effect modification was evaluated by using the maximum likelihood test, adopting a significance level of $P < 0.05$.¹⁶

Data were analyzed by using STATA for Windows, version 12.0 (College Station, TX). The databank of snakebite envenoming cases provided by the Brazilian Ministry of Health and FUNASA (National Health Foundation) did not allow individual identification. Therefore, anonymity was preserved. The Ethical Board of the Collective Health Institute, Federal University of Bahia, approved the research project (#1.370.415).

RESULTS

From 2004 to 2015, for the Brazilian population aged 10 years and older, 116,842 cases of snakebites with a complete set of data were recorded, with 1,119 deaths, yielding a case

fatality rate of 1.0% in the period. Among the 1,119 deaths, 507 (45.3%) were agricultural workers, and among the 4,476 controls, 1,824 (40.8%) were agricultural workers, corresponding to a crude OR of 1.20 and respective 95% CI of 1.06–1.37 (Table 1).

Cases and controls were similar according to gender ($P < 0.48$), but differed markedly according to age groups, time to treatment, snake genus, and AV treatment ($P < 0.001$). Late (≥ 6 hours) time to treatment occurred in 28.3% (317/1,119) of the cases and in 15.3% (683/4,476) of the controls. Adequate AV treatment (adequate AV and adequate number of vials) was administered to 42.4% (474/1,119) of those who died (the cases) and to 63.2% (2,827/4,476) of the controls (Table 1).

Table 1 also shows crude and adjusted ORs for the associations between lethality and agricultural work and the covariates investigated, using logistic regression. The main association was not affected by confounding or effect modification. The result of the maximum likelihood test for the model was 445.72 ($P < 0.001$), indicating that data have adequate goodness of fit. The magnitude of the OR for the main association between lethality and agricultural work remained practically the same after adjustment (OR = 1.20; 95% CI: 1.00–1.39; $P < 0.012$) and the lower limit of its 95% CI reached unity.

Based on data from Table 1, we estimated the percentage of risk of death by snakebite envenoming attributed to agricultural work among people aged 10 years and older who were bitten by venomous snakes (attributable-risk percent among the exposed): 16.7% ($=1.20-1.0/1.20$). Levin's population attributable risk among Brazilian people aged 10 years and older who were bitten by venomous snakes was estimated as 7.6% ($=16.7\% \times 507/1,119$).

TABLE 1

Adjusted OR and respective 95% CIs for the association between agricultural work and lethal snakebite envenoming according to covariables among 1,119 cases and 4,476 controls in Brazil, 2004–2015

Variable	Cases		Controls		$P <$	OR _{adj.} *	95% CI	$P <$
	<i>n</i>	%	<i>n</i>	%				
Agricultural work					< 0.006			
Yes	507	45.3	1,824	40.8		1.20	1.00–1.39	< 0.012
No	612	54.7	2,652	59.2		–	–	–
Age (years)					< 0.001			
10–29	389	34.8	1,893	42.3		1	1.00–1.36	–
30–59	530	47.4	2,114	47.2		1.17	1.61–2.44	< 0.044
≥ 60	200	17.9	469	10.5		1.98	1.61–2.44	< 0.001
Gender					< 0.48			
Female	252	22.5	964	21.5		1	–	–
Male	867	77.5	3,512	78.5		0.90	0.76–1.07	< 0.228
Snake type					< 0.001			
<i>Micrurus</i>	6	0.6	39	0.9		1	–	–
<i>Bothrops</i>	910	81.3	3,902	87.2		2.29	0.94–5.60	< 0.069
<i>Crotalus</i>	148	13.2	368	8.2		2.38	0.96–5.91	< 0.062
<i>Lachesis</i>	55	4.9	167	3.7		1.16	0.45–2.98	< 0.756
Time-to-treatment					< 0.001			
< 6 hours	802	71.7	3,793	84.7		1	–	–
≥ 6 hours	317	28.3	683	15.3		2.00	1.70–2.36	< 0.001
Antivenom (AV) treatment					< 0.001			
Adequate AV and adequate number of vials	474	42.4	2,827	63.2		1	–	–
Adequate AV with insufficient number of vials	195	17.4	899	20.1		1.25	1.04–1.50	< 0.017
Adequate AV with excessive number of vials	315	28.1	397	8.9		4.98	4.10–6.03	< 0.001
Inadequate AV with insufficient or excessive number of vials	32	2.9	63	1.4		3.87	2.40–6.24	< 0.001
No antivenom administered	103	9.2	290	6.4		2.05	1.60–2.64	< 0.001

CI = confidence interval; OR = odds ratio.

* OR adjusted for age, sex, snake type, time-to-treatment, and antivenom (AV) treatment.

Aside from agricultural work, other covariates were very strongly associated with snakebite lethality: age ≥ 60 years (OR = 1.98; 95% CI: 1.61–2.44); age 30–59 years (OR = 1.17; 95% CI: 1.00–1.36); late time to treatment (OR = 2.00; 95% CI: 1.70–2.39); and aspects related to the AV treatment: adequate AV with insufficient number of vials (OR = 1.25; 95% CI: 1.04–1.50); adequate AV with excessive number of vials (OR = 4.98; 95% CI: 4.10–6.03); and inadequate AV with insufficient or excessive number of vials (OR = 3.87; 95% CI: 2.40–6.24), and no AV treatment (OR = 2.05; 95% CI: 1.60–2.64). Antivenom was not administered to 9.2% of the cases (103/1,119) and to 6.5% (290/4,476) of the controls ($X^2 = 10.18$; $P < 0.002$) (Table 1).

Based on data from Table 1, we also estimated the percentage of risk of death due to snakebite envenoming attributed to late (≥ 6 hours) time to treatment among people aged 10 years and older (attributable-risk percent among the exposed) as 50.0% ($=2.0-1.0/2.0$). The percent of risk of death due to snakebite envenoming attributed to late time to treatment among Brazilian people aged 10 years and older who were bitten by venomous snakes (population attributable-risk percent) was estimated as 35.8% ($=50.0\% \times 802/1,119$).

Table 2 shows that 353 (31.5%) of the 1,119 people who died because of snakebite envenoming received early (< 6 hours) and adequate AV treatment; among the controls, this proportion was 54.5% (2,440/4,476) ($X^2 = 188.9$; $P < 0.001$). Among the cases and among the controls, the proportions of early and adequate AV treatment with excessive number of vials were 26.8% ($=215/802$) and 8.5% ($=323/3,793$), respectively ($X^2 = 148.3$; $P < 0.001$).

Data for the entire study group of 1,119 cases and 4,476 controls reveal that the use of early and adequate AV treatment was more frequent (54.5%) among patients who survived snakebite envenoming than among those who died (31.5%). Early and adequate treatment was strongly associated with lower lethality (OR = 0.38; 95% CI: 0.33–0.44) and presented an estimated effectiveness of 62% (Table 3).

DISCUSSION

This study among Brazilian patients confirmed the hypothesis that agricultural work is associated with snakebite envenoming lethality. Despite the borderline 95% CI (1.00–1.39) of the estimate, 20% more of patients who died from

TABLE 2

Number of patients with lethal (1,119 cases) and nonlethal (4,476 controls) snakebite envenoming according to AV treatment and to time to treatment, Brazil, 2004–2015

AV treatment	Cases		Controls	
	Time to treatment		Time to treatment	
	< 6 hours	≥ 6 hours	< 6 hours	≥ 6 hours
Adequate AV and adequate number of vials	353	121	2,440	387
Adequate AV with insufficient number of vials	153	42	753	146
Adequate AV with excessive number of vials	215	100	323	74
Inadequate AV with insufficient or excessive number of vials	19	13	55	8
No AV administered	62	41	222	68
Total	802	317	3,793	683

AV = antivenom.

TABLE 3

Frequencies of early and adequate treatment (time to treatment < 6 hours and adequate antivenom with adequate number of vials) compared with frequencies of other antivenom treatments and/or no treatment among patients who died because of snakebite envenoming (cases) and among those who survived (controls), Brazil, 2004–2017

Treatment	Cases		Controls	
	<i>n</i>	%	<i>n</i>	%
Early and adequate	353	31.5	2,440	54.5
Others plus none	766	68.5	2,036	44.5
Total	1,119	100.0	4,476	100.0

Odds ratio (OR) = 0.38; 95% confidence interval = 0.33–0.44; $X^2 = 188.9$; $P < 0.001$. Effectiveness (OR - 1, in %) = 62%.

snakebite envenoming were occupied in agriculture than those who survived. Exposure (agricultural work) was relatively high among the victims of snakebite envenoming: 45.3% among the 1,119 patients who died and 40.8% among the 4,476 controls. These proportions are disproportionately high, considering that only 7.5% of people aged 10 years and older were occupied in agricultural work in Brazil.¹⁰ We estimated the percent of risk of dying because of snakebite envenoming attributed to agricultural work among the exposed (people aged 10 years and older who were bitten by venomous snakes) to be 16.7%. On the nationwide scale in Brazil, we estimated that 7.6% of the deaths among people aged 10 years and older who were bitten by venomous snakes were attributed to agricultural work. Farmers and laborers presented increased high lethality by snakebite than business and salaried individuals aged more than 15 years in a large survey in India.¹⁷

The heaviest burden of snakebite lethality was more strongly associated with age ≥ 60 years, adequacy of the AV treatment, and late time to treatment than with agricultural work. The sharp discrepancies in the attributable-risk percentages among the exposed for those with late time to treatment (50.0%) and those with agricultural work (16.7%) illustrate the greater importance of the factors related to AV treatment. Analogously, the population (aged 10 years or older) attributable-risk percent for late time to treatment was 35.8%, but was only 7.6% for agricultural work.

In our study, late time to treatment was relatively common among those who died (28.3%) and among those who survived (15.3%) snakebite envenoming. Indeed, cases presented a two-fold greater chance (OR = 2.0: 1.70–2.36) than controls of having had a late time to treatment. Time to treatment ≥ 6 hours has been reported as an important predictor of lethality by snakebite envenoming.^{18,19} Late time to treatment is a bad prognostic factor because AV can only neutralize the circulating venom but cannot hamper the local lesions that are useful in staging the clinical picture. Because of this, the snakebite AV must be administered before the physiopathological effects associated with the venom appear.²⁰

Delay in medical treatment usually depends on the patient's displacement to a health center capable of providing adequate treatment.⁵ Nowadays, combatting fatal snakebite envenoming requires access to AV of high quality and to medical staff adequately trained to deal with this public health problem.²¹ The health teams involved should be well qualified and periodically trained in correct diagnosis, prescription, and administration of AV, as well as detection and dealing with adverse reactions to AV.¹²

In our study, patients who received inadequate AV treatment or no AV treatment at all presented higher lethality. In Brazil, serum therapy is usually decided on the basis of the clinical manifestations presented by each particular snakebite poisoning case.¹² The AVs used in Brazil are produced by a few laboratories, following standardized methods, under control of the government. Antivenoms are distributed free of charge to patients attended to in health centers and hospitals all over the country.^{5,20}

Unacceptably high proportions of patients did not receive AV treatment (9.2% of the cases and 6.5% of the controls), even when they arrived early at the health service providers (7.8% of the cases and 5.9% of the controls). These figures are probably related to lack of AV and/or poorly trained medical staff, and reveal the low quality of public health services in Brazil.

The frequency of adequate AV treatment (adequate AV and adequate number of vials) of 42.4% among cases and 63.2% among the controls (Table 1) was very low, even when patients arrived early at the health service providers: 44.0% and 64.3%, respectively (Table 2). Such low figures reinforce the idea of the poor quality of the health services provided to snakebite envenoming cases in the country. The production and distribution of AV in Brazil are planned on the basis of cases registered in the national reporting system (SINAN).⁵ The shortage or absence of AV in the hospitals that provide health care to snakebite cases can denote problems in the production and/or distribution of AVs in the vast Brazilian national territory. Or, it might also denote that the health team is not well trained in estimating the severity of the snakebite clinical picture and administering AV therapy according to the recommended strength. The usage of AV cannot regenerate tissue lesions. However, AV can neutralize the circulating venom and prevent new lesions.²² New lesions, in turn, can generate more tissue residuals that, in the bloodstream, could impair renal physiology.²³ In Brazil, acute renal failure is the main cause of death due to snakebite envenoming.²⁴

In this study, the administration of AV in strength (number of vials) lower than that recommended was associated with a 25% higher chance of lethality (adjusted OR = 0.25; 95% CI: 1.04–1.50). This finding contradicts the results of a study from Turkey, where low-dose AV treatment effectively treated patients with venomous snakebites.²⁵

We found that the administration of AV in number higher than the recommended one was associated with an almost five times greater chance of lethality (adjusted OR = 4.98; 4.10–6.03). Early treatment and adequate AV with excessive number of vials were observed among 26.8% of the cases and among 8.5% of the controls (Table 2). The excessive number of vials administered to these patients can reflect greater severity of envenoming presented by the patients, inducing the medical team to administer an excessive number of vials, even among those with early time to treatment. However, we can also hypothesize that the excessive number of vials was iatrogenic and contributed to increase the lethality. Antivenom administration can entail some severe adverse effects. Furthermore, it is very difficult to differentiate between the adverse effects attributable to the AV and those resulting from the venom itself.²⁶

Older age was identified as an important risk factor for snakebite envenoming lethality. Snake venom causes tissue physiopathological alterations that are better overcome by younger people. Furthermore, older age favors the

occurrence of comorbidities, such as diabetes and cardiovascular diseases, that potentiate the risk of renal failure, the main cause of death in snakebite envenomings in Brazil.^{18,27}

In the study population of Brazilians aged 10 years and older, with complete sets of data, for the period 2004 to 2015, lethality was 1.0%. In the state of Amazonas, Brazil, among people from all age groups, with complete sets of data, for 2007 to 2012, lethality was 0.6%.¹⁸ Our data revealed that lethality could decrease from 1.0% to 0.47% if all patients received early and adequate AV treatment.

Lethality did not vary markedly according to snake genus and gender; late time to treatment and adequacy of AV treatment were much more relevant. Such findings are in disagreement with Brazilian government directives that reinforce patients' attributes and snake genus as the most important risk factors in snakebite severity and lethality.¹²

The interpretation of the results of this study must take into account the limited quality of the data reported to the national reporting system. In the Brazilian national database, snakebite envenoming notification forms are filled in by various people without prior validation and poor standardization of the criteria. Furthermore, it is impossible to solve in the official statistics because the accuracy of identification of offending snakes is very limited. The findings of our study suggest that a more complete study needs to be performed based on a prospective and standardized protocol. We must consider the possibility of underreporting of mild cases of snakebite envenoming. Furthermore, lethal cases probably had a better registration of their characteristics than patients from the control group. In our study, eligibility criteria were met by 97.8% of the cases, but only by 50.8% of the controls.

In conclusion, lethality due to snakebite envenoming in Brazil is associated with agricultural work, even after controlling for relevant covariates. However, factors related to older age and particularly to the poor quality of the health care provided, such as late time to treatment, use of inadequate AV, and inadequate number of vials administered, were much more strongly associated with lethality.

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Authors' addresses: Yukari Figueroa Mise, Instituto de Saúde Coletiva, Federal University of Bahia, Salvador, Brazil, E-mail: yukarimise@gmail.com. Rejane Maria Lira-da-Silva, Instituto de Biologia, Federal University of Bahia, Salvador, Brazil, E-mail: rejanelirar2@gmail.com. Fernando Martins Carvalho, Faculdade de Medicina da Bahia, Federal University of Bahia, Salvador, Brazil, E-mail: fmc.ufba@gmail.com.

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