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ORIGINAL ARTICLE

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Accidental exposure to *Brucella abortus* vaccines and occupational brucellosis among veterinarians in Minas Gerais state, Brazil

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Abstract

Brucellosis is an important occupational disease, mainly among veterinarians, because of their frequent contact with sick animals, contaminated secretions and live attenuated anti-*Brucella* vaccines. This study aimed to determine the prevalence of accidental exposure to S19 and RB51 vaccine strains and occupational brucellosis among veterinarians registered to administer vaccinations in Minas Gerais, Brazil, as well as to identify the risk factors associated with accidental exposure to anti-*Brucella abortus* vaccines. Data were collected through an online questionnaire. Three hundred and twenty-nine veterinarians were included in the analyses using stratified random sampling. A multivariate logistic regression analysis was used to evaluate the predictors of accidental exposure to S19 and RB51 strains. Nearly one third of the veterinarians registered to administer bovine brucellosis vaccination in Minas Gerais, 32.83% (108/329) (95% confidence interval [CI]: 27.78–38.19%), reported having been accidentally exposed to S19 or RB51 vaccine strains. The exposure factors associated with this outcome included a score of personnel protective equipment (PPE) use during work (odds ratio [OR], 0.94; 95% CI: 0.89–0.98) and a score of knowledge about brucellosis symptoms, classified as poor (base category), intermediate (OR, 0.26; 95% CI: 0.07–0.87) or good (OR, 0.22; 95% CI: 0.07–0.62). In addition, 4.56% (15/329) (95% CI: 2.57–7.41%) of veterinarians reported that they had brucellosis, of which 46.67% (7/15) considered that the disease was due to accidental exposure to anti-*B. abortus* live attenuated vaccine. The prevalence of accidental exposure to *B. abortus* vaccine strains among veterinarians from Minas Gerais enrolled in the control of bovine brucellosis was high. The reduced knowledge about human brucellosis symptoms and lack of appropriate PPE use were risk factors from unintentional contact with S19 and RB51 vaccine strains.

KEYWORDS

job-related, malta fever, RB51, S19, vaccine

1 | INTRODUCTION

Brucellosis is one of the most common bacterial zoonoses worldwide and is associated with reproductive failure in domestic animals and debilitating febrile illness in humans (Corbel, Elberg, & Cosivi, 2006; Pappas, Papadimitriou, Akritidis, Christou, & Tsianos, 2006). Despite great diversity in *Brucella* genus, the majority of human infections are caused by *Brucella melitensis* and *B. abortus* (Franco, Mulder, Gilman, & Smits, 2007). The disease has a great impact on public health, since it is a zoonosis of strong occupational character (McDermott & Arimi, 2002), associated with chronic debilitating infection and high treatment costs (McDermott, Grace, & Zinsstag, 2013). Cattle farmers, slaughterhouse workers, microbiologists, veterinarians and their assistants are often exposed to infected animals, contaminated biological materials or live attenuated anti-*Brucella* spp. vaccines capable of causing the disease to humans (Corbel et al., 2006; Pereira et al., 2020,). Moreover, these professionals, as well as the general population, can also become infected by non-occupational transmission route through the ingestion of raw milk and milk products prepared with raw milk (Young, 1995).

In Brazil, bovine brucellosis caused by *B. abortus* is endemic and present in all states, whereas *B. melitensis* is exotic in the country (Ferreira Neto et al., 2016; Poester, Goncalves, & Lage, 2002). However, the seroprevalence of positive herds exhibits a heterogeneous distribution across the country, ranging from 0.91% (95% confidence interval [CI]; 0.30–2.11) in Santa Catarina state (Baumgarten et al., 2016) to 30.60% (95% [CI]; 27.40–34.00) in Mato Grosso do Sul state (Leal Filho et al., 2016). To reduce the bovine brucellosis prevalence, the Programa Nacional de Controle e Erradicação da Brucelose e da Tuberculose Animal—PNCEBT (National Program for the Control and Eradication of Animal Brucellosis and Tuberculosis) was created in 2001 and reviewed in 2017 (Brasil, 2001, 2017). The PNCEBT is mainly based on compulsory vaccination of young females aged between 3 and 8 months with S19 and the vaccination of females that were not vaccinated at this age with RB51 (Dorneles, Oliveria, & Lage, 2017). In addition, the programme also includes transit control for breeding animals and the slaughter of positive cattle (Ferreira Neto et al., 2016).

Since S19 and RB51 are live anti-*B. abortus* vaccines, which are effective and fundamental in the control of bovine brucellosis but pathogenic to humans (Ashford et al., 2004; Dorneles, Sriranganathan, & Lage, 2015; Joffe & Diamond, 1966; Nicoletti, Ring, Boysen, & Buczek, 1986), vaccination against brucellosis in Brazil is only performed by PNCEBT accredited veterinarians or by registered vaccinators under their responsibility (Brasil, 2017). This implies that veterinarians and their assistants are among the most susceptible occupational groups to human brucellosis, because, in addition to directly dealing with infected animals, aborted materials or delivered calves, they are also exposed to live attenuated anti-*Brucella* spp. vaccines (Ashford et al., 2004; Proch et al., 2018).

In this context, Minas Gerais is among the pioneer states in the control of bovine brucellosis in Brazil, enforcing compulsory vaccination of cattle and buffalo heifers in all its territories since 1994 (Minas Gerais, 1993; Oliveira et al., 2016). Nonetheless, although this strategy has led to a significant reduction in the prevalence of seropositive herds in comparative studies on the epidemiological situation of bovine brucellosis in Minas Gerais carried out almost 10 years apart (2002–2011) (Ferreira Neto et al., 2016), the disease is still prevalent in cattle herds, with different rates among producing regions, ranging from 2.02% (95% [CI], 0.41–3.62) in Leste to 5.06% (95% [CI], 2.56–7.56) in Triângulo Mineiro (Gonçalves et al., 2009; Oliveira et al., 2016). In 2018, to control the disease in cattle, approximately 1.70 million heifers were vaccinated in Minas Gerais state (Minas Gerais, 2017). This large volume of vaccinations greatly increased the chance of accidental exposures to *B. abortus* vaccines. Indeed, based on an estimate of four involuntary needle-stick injuries per thousand inoculations among health professionals in North American hospitals (Henderson et al., 1990), it can be supposed that approximately 6,800 accidental inoculations with anti-*B. abortus* vaccines occurred among veterinarians and their assistants in Minas Gerais in 2018 alone. Furthermore, since the conditions for handling and performing vaccinations in cattle are usually more adverse than those in human hospitals (Ashford et al., 2004), this prediction is probably underestimated. Despite this, the incidence of human brucellosis in Minas Gerais state is unknown, and the legislation implementing the compulsory notification human brucellosis cases in the state was only established in December 2018 (Minas Gerais, 2018).

Thus, the aims of the present study were (*a*) to estimate the prevalence of accidental exposure to S19 and RB51 vaccines and occupational brucellosis among PNCEBT accredited veterinarians in Minas Gerais, (*b*) to identify the risk factors associated with accidental exposure to anti-*B. abortus* vaccines and (c) to understand the main behaviours related to vaccine exposure and occupational brucellosis.

2 | MATERIAL AND METHODS

2.1 | Study design and area

This cross-sectional study was conducted from November 2018 to May 2019 in Minas Gerais state, located in southeastern Brazil, with an area of 588,383 km^2. The state was divided into seven regions (strata) of bovine production, as previously proposed in epidemiological studies conducted in cattle (Figure 1) (Gonçalves et al., 2009; Oliveira et al., 2016) and validated by (Alves et al., 2018). Each stratum exhibits different regional characteristics related to livestock activities, such as production systems, average herd size and sanitary practices (Alves et al., 2018; Gonçalves et al., 2009; Oliveira et al., 2016).

2.2 | Study population and eligibility criteria

The inclusion criterion was to be an accredited veterinary residing in Minas Gerais, enrolled in PNCEBT to perform brucellosis vaccination and who were actively vaccinating heifers from January to June

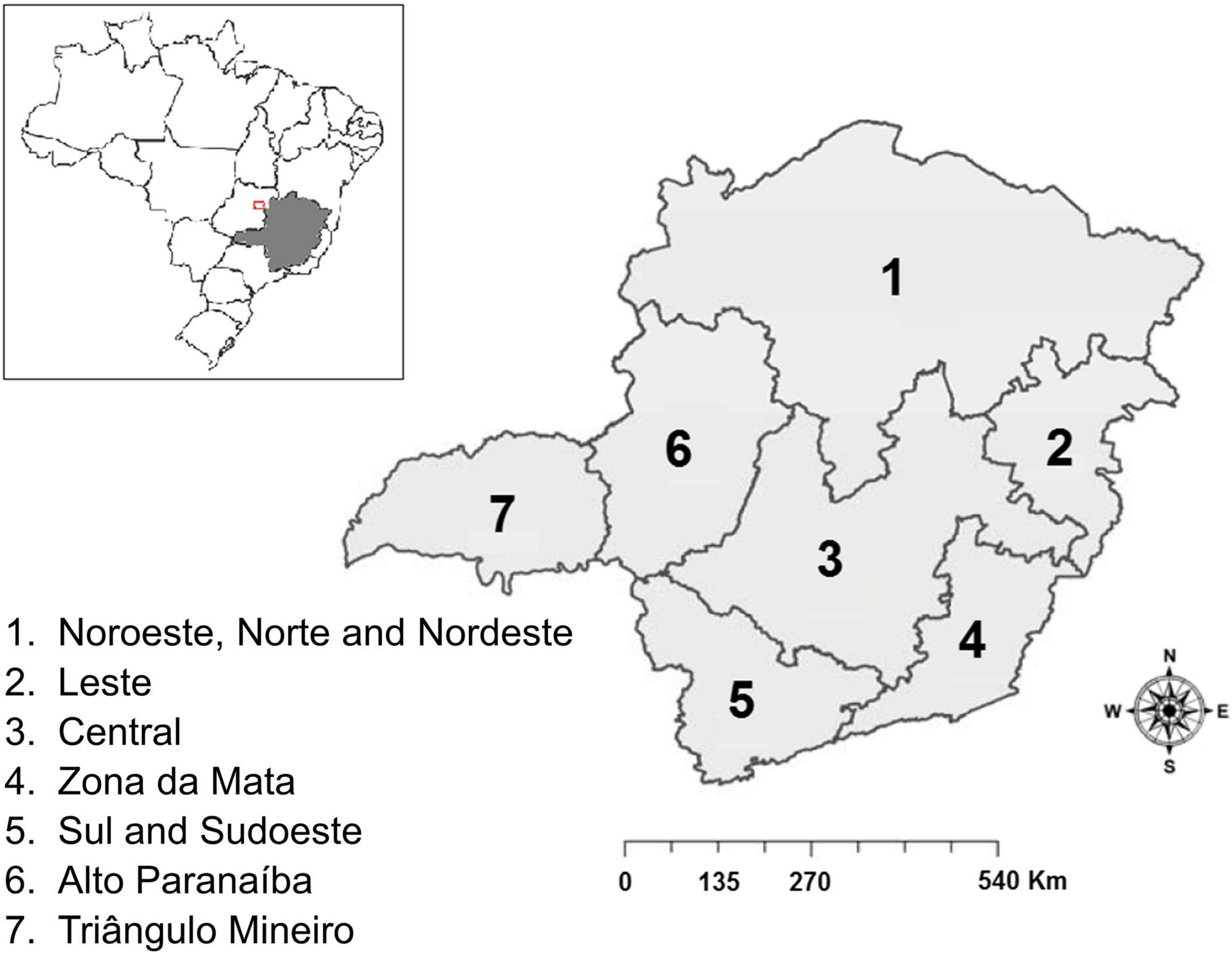

FIGURE 1 Map of the state of Minas Gerais, showing the regions (strata) defined in the current study. The state was divided into seven regions: 1. Noroeste, Norte and Nordeste; 2. Leste; 3. Central; 4. Zona da Mata; 5. Sul and Sudoeste; 6. Alto Paranaíba; and 7. Triângulo Mineiro

2018. The exclusion criterion was to be a professional with outdated contact information (email address) in the register of accredited veterinarians able to perform brucellosis vaccination from the Instituto Mineiro de Agropecuária—IMA, the health authority of Minas Gerais state.

2.3 | Sample size

The sample size was calculated using the following formula (Dohoo, Martin, & Stryhn, 2009):

$$n_0 = \frac{Z^2 * p * (1-p)}{e^2} n_0 = \frac{(1.96)^2 * 0.50 * (1-0.50)}{0.05^2} n_0 = 384.16$$

where "n_0" is the minimum sample size required, "Z" is the normal quantile for a given desired confidence level, "*p*" is the estimated proportion of the event to be studied and "*e*" is the desired level of precision. Since the estimated prevalence of brucellosis among the study population was not known, *p* = .5 was assumed to obtain the largest sample size, with maximum variability (Dohoo et al., 2009). The desired confidence level was 0.95, and the precision was 0.05. The study population was considered finite ($n \leq 0.05$), where "*N*" is the number of individuals in the population:

$$\mathrm{n} = \mathrm{n_0/N}\ \mathrm{n} = 384.16/2{,}154\ \mathrm{n} = 0.18$$

The sample was then corrected using the finite population correction formula:

$$\mathrm{n} = \frac{\mathrm{n_0}}{1 + \frac{\mathrm{n_0}}{\mathrm{N}}}\ \mathrm{n} = \frac{384.16}{1 + \frac{384.16}{2{,}154}}\ \mathrm{n} = 326.02$$

In order to ensure the representativeness of the sample in all regions of the Minas Gerais state, which has 853 municipalities, and to assess a possible association between the occurrence of brucellosis in animals and humans, the veterinarians were proportionally assigned to each cattle producing region in state, according to their residential address in the IMA record. The division of the state of Minas Gerais into seven strata was evaluated and validated by two different studies conducted approximately 10 years apart to assess the prevalence of bovine brucellosis in the state (Gonçalves et al., 2009; Oliveira et al., 2016). This division consider the different bovine productive characteristics of each stratum (Alves et al., 2018). Therefore, a stratified sampling was used to calculate the population to be sampled in each stratum, according to the heterogeneous distribution of the population of veterinarians working in each region of the state (Table 1). The number of veterinarians randomly selected from the IMA register was four times greater (proportional per stratum) than the final calculated sample size considering a 25% response rate. A total of 1,316 veterinarians were contacted by e-mail, which contained the invitation for participation in the study, informed consent terms and questionnaire link (Google Forms). The questionnaires were sent to participants until the minimum required sample size was reached for each stratum, totalling 329 respondents (surplus responses were ruled out due to saturation, according to the pre-determined proportion of participants in each stratum).

2.4 | Ethical considerations

This study was approved by the Human Ethics Research Committee (Comitê de Ética em Pesquisa com Seres Humanos) from Universidade Federal de Lavras (UFLA) (86861018.2.0000.5148). Informed consent was obtained from all participants before questionnaire administration.

2.5 | Questionnaire survey

Data were obtained through an online questionnaire (Appendix S1 and S2) based on a similar study conducted in Turkey (Kutlu et al., 2014), with some modifications. The questionnaire, translated from the original English version into Portuguese, the local language, was pretested in a pilot study with 20 veterinarians to guide improvements in the data collection instrument. To prevent 'leading line questioning', general questions (containing closed, semiclosed and open questions), such as age, job experience, area of expertise, disease perceptions, infection control practices and risky procedures (vaccine administration and veterinary care related to bovine reproduction) were asked first. Then, specific questions related to accidental unprotected S19 and RB51 contact and occupational *B. abortus* infection were asked. Individuals who reported unintentional exposure to live attenuated anti-*B. abortus* vaccines or brucellosis were asked about the probable causes of the outcome, type of exposure to the S19 and RB51 strains, prophylaxis measures adopted, diagnostic methods used, symptoms occurrence and duration, treatments implemented and possible relapses of the disease.

TABLE 1 Distribution of veterinarians residing in Minas Gerais, registered to perform brucellosis vaccination and who were actively vaccinating calves from January to June of 2018, according to bovine productive regions in the state

Strata	*N*	Relative frequency (%)	*n* †
Noroeste, Norte and Nordeste	200	9.29	31
Leste	116	5.39	18
Central	647	30.04	98
Zona da Mata	252	11.70	39
Sul and Sudoeste	462	21.45	70
Alto Paranaíba	220	10.21	34
Triângulo Mineiro	257	11.93	39
Total	2,154	100.00	329

Note: *N*, population; *n*, sample † always rounded up

2.6 | Outcome definitions

Accidental anti-*B. abortus* vaccine exposure and *B. abortus* infection data were based on self-reporting by the participants.

2.7 | Descriptive analysis

After reaching the minimum required sample size for each stratum, all responses were imported into R statistical software 3.5.2 (R Team, 2018), cleaned and checked for duplicates. To perform the analysis, participants' data had to include at least the 28 required questions (Appendix S3). Descriptive statistics of the variables were examined; frequency distributions for categorical variables and medians, means, interquartile ranges and standard deviations for continuous variables were calculated (Appendix S3).

2.8 | Transformations of variables

To assess the knowledge about human brucellosis (transmission and clinical signs) and prevention measures adopted by the respondents, three recategorizations of variables were performed. Variables concerning the use of gloves, coat, protective goggles and masks and their respective frequencies of use (X13 to X16 –Appendix S3) were grouped into a single variable: personal protective equipment (PPE) use. For this, scores were awarded for both the equipment, according to their importance in the prevention of the disease, and for the frequency of use (never, sometimes and always). The variables of gloves, mask, goggles and coat were recategorized using the weights 4, 4, 2 and 1 (according to the importance of the PPE to human brucellosis transmission), respectively. The mask received a weight equal to 4 since human brucellosis is transmitted mainly by aerosol, due to the large amount of bacteria that can be inhaled from contaminated biological materials. The gloves also received a weight equal to 4, as they protect the hands from microlesions that can facilitate the entry of the pathogen in the organism. The goggles, on the other hand, received weight equal to 2, as it is a PPE that protects the conjunctival mucosa from vaccine sprays. The coat was assigned a weight equal to 1, since it protects the arms from contact with vaccine and contaminated biological materials. The weights of the frequency of use were 2 for always, 1 for sometimes and 0 for none. Then, the sum of the values of each equipment multiplied by its respective frequency of use was calculated, generating values between 0 (never used any PPE) and 22 (always used all the recommended PPE).

To identify the knowledge of participants on brucellosis transmission (X22 –Appendix S3), a score was established considering the following, in order of decreasing importance: transmission routes related to occupational risks ("self-inoculation with vaccine strains S19 and RB51" and "unprotected contact with products of potentially contaminated abortions"—weight = 2), infection sources not related to labour activities ("ingestion of milk and milk products ingestion prepared with raw milk"—weight = 1) and wrong answers about the disease spread ("direct contact with saliva of cattle/buffalo" and "ingestion of undercooked meat"—weight = 0). Then, the number of points for each participant was summed, and their brucellosis transmission knowledge was scored as good (4 or 5 points), intermediate (1, 2 or 3 points) or poor (0 points).

Last, the knowledge of the participants about the main symptoms of human brucellosis (X23—Appendix S3) was also evaluated. A similar principle was used, attributing scores to the alternatives based on the frequency of symptoms most related to the clinical manifestation of *B. abortus* infection in humans. The values assigned for each alternative were 2 for "pain in the joints, sweating, fever and chills", 1 for "endocarditis and orchitis can occur in severe cases" and 0 for "mainly reproductive clinical signs, similar to those in cattle/buffaloes" and "staggered walking and mental disorientation on the first day after infection". Then, the number of points of each participant was summed, and their knowledge about brucellosis main symptoms was scored as good (2 or 3 points), intermediate (1 points) or poor (0 points).

2.9 | Statistical analysis

The apparent prevalence of accidental vaccine exposure and occupational brucellosis was calculated by dividing the number of self-reported outcomes by the total number of veterinarians sampled. The confidence intervals (CI) of these prevalences were obtained by the exact binomial distribution. A model for accidental exposure to anti-*B. abortus* vaccines was fitted. The independent variables for the model are summarized in the Appendix S3. The model was built using the purposeful selection of variables for the logistic regression according to Hosmer, Lemeshow, and Sturdivant (2013).

In brief, preliminary analyses were carried out for each of the variables considered as potential predictor variables. A chi-square test (χ^2) or Fisher's exact test was performed for the qualitative variables, and a univariate logistic regression model was carried out for the quantitative variables. Variables that had a *p*-value less than 0.25 in the univariate test were considered as possible candidate variables for the first multivariate model. Second, a multivariate logistic model containing all the variables that reached the inclusion criterion was fitted. The importance of each of them was assessed through the Wald test; variables that had a *p*-value greater than .05 were removed and a new model was fitted. The partial likelihood ratio test was used to compare the new and more parsimonious model to the previous one. In the third step, it was evaluated whether there was a variation greater than 20% in each one of coefficients of the remained variables when the variable was excluded from the model. If it was the case, the variable was added back into the model. The second and third steps were repeated for all non-significant variables. Next, all the variables not selected in the first step were added in the model one at a time. The fifth step consisted of verifying whether the logit of each continuous variable in the model showed a linear relation as a function of the covariate. Then, the interactions of the variables were checked and adjusted in the sixth step. The goodness of fit of the full model was assessed in the seventh step by the receiver operating characteristic (ROC) curve and the Hosmer–Lemeshow test. The association among the dependent and independent variables in the final logistic regression model was calculated by odds ratios (ORs) and their respective 95% CIs. All statistical analyses were performed in R statistical software 3.5.2 (R Team, 2018).

3 | RESULTS

3.1 | Descriptive analysis

A total of 418 veterinarians completed the questionnaire. However, only 329 were included in the analysis according to the stratification proposed in the study and to the limit of responses saturation required in each stratum (Table 1). Of the 329 participants, 273 (82.98%) were male and 56 (17.02%) were female. Detailed descriptive statistics of all variables are shown in Appendix S3. The average age and years of professional experience were 40.63 (±12.13) and 14.49 (±11.65) years, respectively. The main working sectors reported were dairy (214 = 65.05%) and beef cattle (59 = 17.93%), followed by others (56 = 17.02%). Moreover, 235 (71.43%) of the veterinarians were self-employed, 67 (20.36%) worked for a private company and 27 (8.21%) were public workers. The knowledge about brucellosis transmission to humans was considered good for 156 (47.42%), intermediate for 171 (51.98%) and poor for 2 (0.61%) of the participants, while the knowledge about human brucellosis symptoms was evaluated as good for 275 (83.59%), intermediate for 37 (11.25%) and poor for 17 (5.17%) of the respondents (Figure 2).

When asked about the number of veterinary procedures performed in the last 6 months, 309 (93.92%) reported vaccination against bovine brucellosis, 240 (72.95%) reported parturition assistance, 179 (54.41%) reported manual placenta removal and 177 (53.80%) reported contact with aborted material (more than one answer was allowed). The

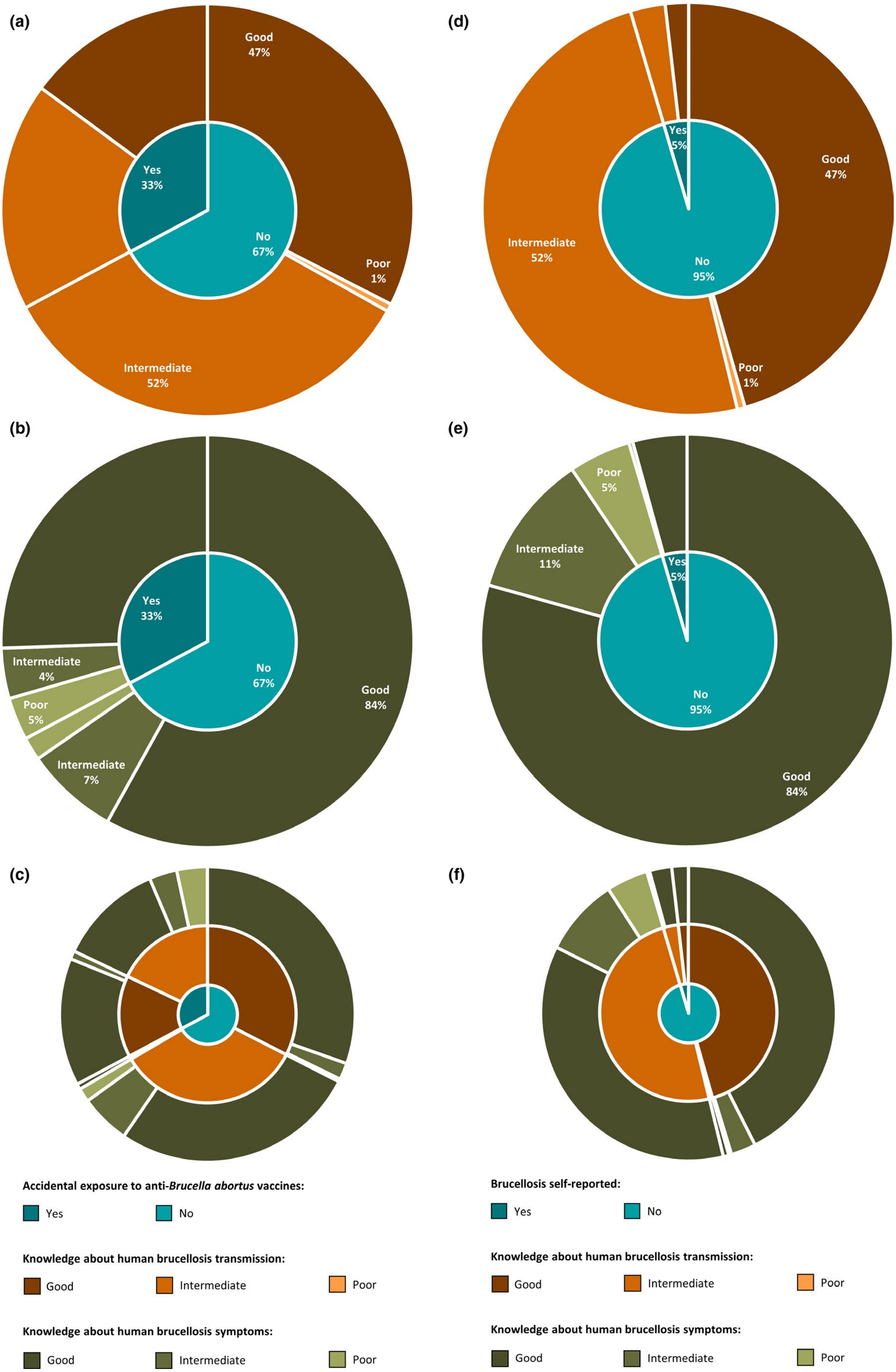
(a)
Good
47%
Yes
33%
No
67%
Poor
1%
Intermediate
52%
(d)
Yes
5%
Good
47%
Intermediate
52%
No
95%
Poor
1%
(b)
Yes
33%
Intermediate
4%
Poor
5%
No
67%
Good
84%
Intermediate
7%
(e)
Poor
5%
Intermediate
11%
Yes
5%
No
95%
Good
84%
(c)
(f)
Accidental exposure to anti-*Brucella abortus* vaccines:
Yes
No
Knowledge about human brucellosis transmission:
Good
Intermediate
Poor
Knowledge about human brucellosis symptoms:
Good
Intermediate
Poor
Brucellosis self-reported:
Yes
No
Knowledge about human brucellosis transmission:
Good
Intermediate
Poor
Knowledge about human brucellosis symptoms:
Good
Intermediate
Poor

FIGURE 2 Self-report of accidental exposure to anti-*Brucella abortus* vaccines among PNCEBT accredited veterinarians to perform bovine brucellosis vaccination in Minas Gerais, Brazil, 2018/2019, related to knowledge about brucellosis transmission to humans (a), to knowledge of human brucellosis main symptoms (b) and to both knowledges (c). Self-report of brucellosis among PNCEBT accredited veterinarians to perform bovine brucellosis vaccination in Minas Gerais, Brazil, 2018/2019, related to knowledge about brucellosis transmission to humans (d), to knowledge of human brucellosis main symptoms (e) and related to both knowledges (f)

frequencies of wearing gloves, coat, goggles and coat during these procedures and the reasons for not using PPE are shown in Figure 3. Among the reasons for not using the PPE, the most reported ones was lack of habit (369/790 [46.71%]), difficulty in performing the procedure using protection (220/790 [27.85%]), not having the equipment (102/790 [12.91%]), not considering it important (81/790 [10.25%]) and lack of time (18/790 [2.28%]) (Figure 3) (responses for not using PPEs were grouped into a single variable). The main forms of S19 and RB51 vaccines disposal reported were infectious waste (104/329 [31.61%]), rural property general waste (93/329 [28.27%]), urban general waste (38/329 [11.55%]), burying on rural property (37/329 [11.25%]), burning (sometimes using iron heaters) (29/329 [8.81%]) and return to the veterinary store (28/329 [8.51%]).

Approximately one-quarter of the sampled veterinarians (85/329 [25.84%]) had a vaccinator registered under their responsibility, and 81 (95.29%) of them reported having provided training to these professionals to carry out animal brucellosis vaccinations. The knowledge of the veterinary about the use of PPE by the vaccinators indicated that 64.71% (55/85) did not wear a mask, 52.94% (45/85) did not wear a coat, 51.76% (42/85) did not wear goggles, and 2.35% (2/85) did not wear gloves. Eleven of the respondents reported that vaccinators were accidentally exposed only to the S19 strain; seven (63.64%) were exposed once, one (9.09%) was exposed twice, and three (27.27%) were exposed more than twice. Among these individuals, only six (54.55%) sought medical attention; two (18.18%) reported pain at the site of inoculation and fever, one (9.09%) had associated muscle pain and the other (9.09%) reported weakness and headaches.

The prevalence of accidental exposure to anti-*B. abortus* vaccine strains among the sampled individuals was 32.83% (108/329) (95% CI: 27.78–38.19%), and exposure to the S19 strain was more frequent (106/108) than exposure to the RB51 strain (4/108) (Figure 4). Among those, 45.37% (49/108) were exposed once, 27.78% (30/108) were exposed twice, and 23.15% (25/108) were exposed more than twice to S19, whereas exposure exclusively to RB51 was reported by two individuals, one who was exposed once and another that was exposed more than twice. Furthermore, two individuals described exposure to both vaccine strains. The forms of exposure reported were needle-stick injury (60/159 [37.74%]), contact of non-wounded skin with vaccine content (49/159 [30.82%]), spraying of vaccine content into eyes (33/159 [20.75%]) or into oral/nasal mucosa (10/159 [6.29%]), and contact of wounded skin with vaccine content (7/159 [4.40%]) (more than one answer was allowed). The accidents occurred mainly during manipulation of vaccine bottles (61/134 [45.52%]), followed by livestock vaccination (54/134 [40.30%]), disassembling the syringe (7/134 [5.22%]), recapping the needle (7/134 [5.22%]) and disposing of materials (5/134 [3.73%]) (more than one

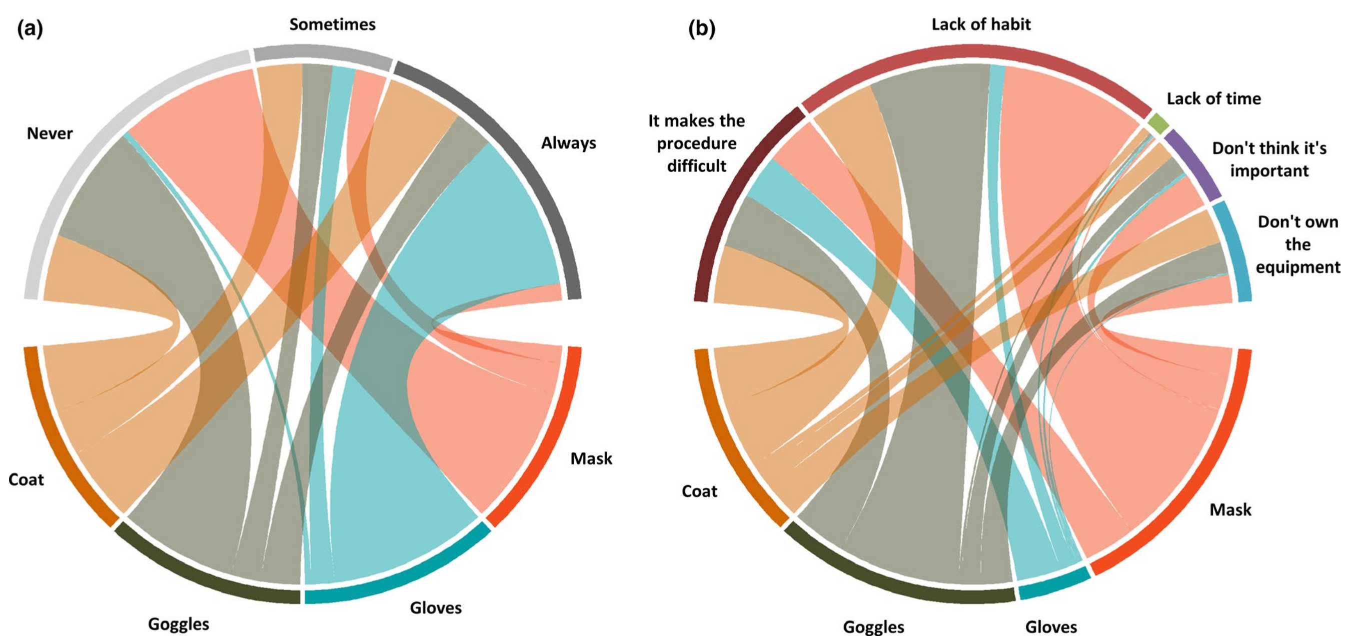

FIGURE 3 Frequency of wearing personal protective equipment (PPE) (a) and reasons for not using it during work (b) reported by PNCEBT accredited veterinarians to perform bovine brucellosis vaccination in Minas Gerais, Brazil, 2018/2019

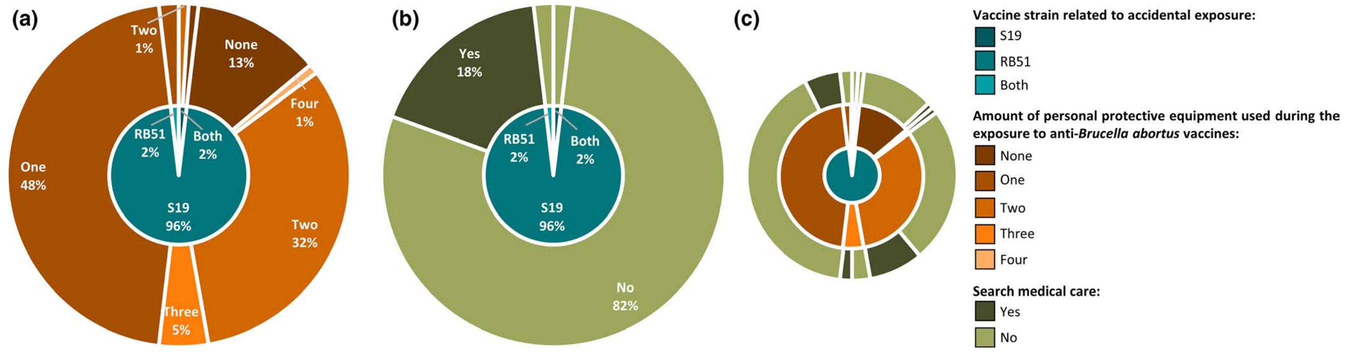

FIGURE 4 Vaccine strain involved in accidental exposure to anti-*Brucella abortus* vaccines among veterinarians registered to perform bovine brucellosis vaccination in Minas Gerais, Brazil, 2018/2019, related to amount of personal protective equipment used (PPE) during unintentional contact with the vaccines (a), to the search to medical care (b) and to both (c)

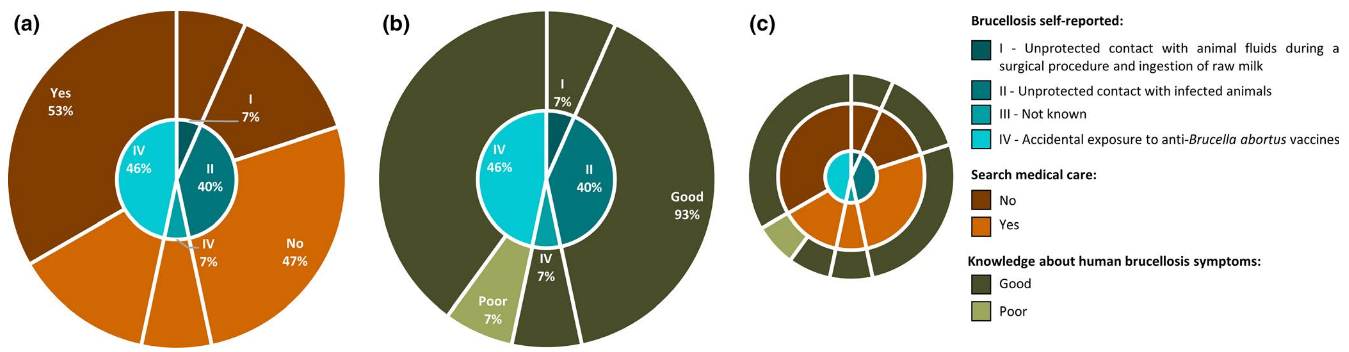

FIGURE 5 Probable source of *Brucella abortus* self-reported infection among veterinarians registered to perform bovine brucellosis vaccination in Minas Gerais, Brazil, 2018/2019, related to the search to medical care (a), to knowledge of human brucellosis main symptoms (b) and to both (c)

answer was allowed). Among the probable reasons for accidental exposure to S19 and RB51 strains were the lack of infrastructure of the property to carry out the vaccination (43/124 [34.68%]), adoption of inadequate protection measures (33/124 [26.61%]), temperament of the animal (cattle breed) (22/124 [17.74%]), lack of attention or hurry (9/124 [7.26%]), pressure inside the vaccine bottle when the needle was inserted (6/124 [4.84%]), lack of knowledge about risks associated with brucellosis vaccination (2/124 [1.61%]) and other reasons (9/124 [7.26%]) (more than one answer was allowed). Among the protection measures adopted during the accidental exposures, only 0.93% (1/108) of the respondents reported using all the PPE recommended for brucellosis vaccination (coat, gloves, mask and goggles); 48.15% (52/108) use only one PPE equipment, 33.33% (33/108) used two, 4.63% (5/108) used three and 12.96% (14/108) used none (Figure 4). After unintentional contact with anti-*B. abortus* vaccine, 47.09% (81/172) washed the local contact area, 32.56% (56/172) performed disinfection with an antiseptic, 11.05% (19/172) sought medical attention, 4.07% (7/172) self-medicated, 1.74% (3/172) performed cauterization of the contact area, and 3.49% (6/172) did nothing (more than one answer was allowed). The drugs used for self-medication were doxycycline (2/7 [28.57%]), amoxicillin (1/7 [14.29%]), rifampicin + tetracycline (1/7 [14.29%]) and sulphonamide (1/7 [14.29%]), with some of the respondents reporting used of combination of drugs for self-medication (Appendix S3). In addition, interestingly, 28.57% (2/7) reported using a veterinary spray of tetracycline at the site of vaccine contact.

The prevalence of self-reported occupational brucellosis among the veterinarians sampled was 4.56% (15/329) (95% CI: 2.57–7.41%). Among these individuals, 46.67% (7/15) considered brucellosis infection to be due to accidental exposure to S19 or RB51, 40.00% (6/15) attributed the disease to unprotected contact with uterine secretions from infected animals, 6.67% (1/15) attributed the disease to ingestion of raw milk or unprotected contact with uterine secretions from infected animals during a surgical procedure, and 6.67% (1/15) did not know the probable source of the *B. abortus* infection (Figure 5). The most frequent clinical signs reported were muscle and joint pain (6/15 [46.67%]); weakness, chills and sweating (5/15 [33.33%]); fever (4/15 [26.67%]); headaches (3/15 [20.00%]); weight loss (2/15 [13.33%]); and diarrhoea (1/15 [6.67%]). Two individuals who had brucellosis described relapses with joint involvement (a) and skin allergy (b). The diagnostic methods used, seeking for medical care and therapeutic protocols implemented among the participants that self-declared *B. abortus* infection are shown in Table 2.

TABLE 2 Diagnostic methods used, medical care sought and therapeutic protocols implemented among veterinarians from Minas Gerais, Brazil (2018/2019), that self-reported *Brucella abortus* infection

Patient	Probable source of *B. abortus* infection	Medical care	Diagnostic methods[a]				Therapeutic protocol
			iELISA	PCR	RBT	Culture	
1	Unprotected contact with uterine secretions from infected animals	Yes	Positive	-	Positive	-	Penicillin or cephalosporin (8–14 days) and aminoglycoside (8–14 days)
2	Accidental exposure to S19 and RB51 strains	No	-	-	-	-	-
3	Unprotected contact with uterine secretions from infected animals	Yes	Positive	Positive	Positive	-	Doxycycline (more than 30 days) and rifampicin (22–30 days)
4	Unprotected contact with uterine secretions from infected animals	No	Positive	-	-	-	-
5	Accidental exposure to S19 and RB51 strains	Yes	Positive	-	Negative	-	Doxycycline (22–30 days) and rifampicin (22–30 days)
6	Unprotected contact with uterine secretions from infected animals	No	Positive	-	-	-	-
7	Accidental exposure to S19 and RB51 strains	Yes	-	-	-	Positive	Doxycycline (more than 30 days) and rifampicin (15–21 days) and trimethoprim + sulfamethoxazole (more than 30 days)
8	Unprotected contact with uterine secretions from infected animals during a surgical procedure and ingestion of raw milk	Yes	-	-	Positive	-	-
9	Not known	No	Positive	-	-	Negative	Doxycycline (more than 30 days) and rifampicin (more than 30 days)
10	Unprotected contact with uterine secretions from infected animals	No	-	-	-	-	-
11	Accidental exposure to S19 and RB51 strains	Yes	Positive	-	-	-	Doxycycline (more than 30 days) and rifampicin (more than 30 days) and aminoglycoside (1–7 days)
12	Unprotected contact with uterine secretions from infected animals	No	-	-	Positive	-	-
13	Accidental exposure to S19 and RB51 strains	Yes	-	-	Positive	-	Other tetracycline (15–21 days)
14	Accidental exposure to S19 and RB51 strains	Yes	Positive	-	-	-	Doxycycline (more than 30 days)
15	Accidental exposure to S19 and RB51 strains	No	Positive	-	-	-	Aminoglycoside (22–30 days)

Abbreviations: "-", not performed; iELISA, indirect enzyme-linked immunosorbent assay; RBT, rose bengal test.

[a]*Brucella* standard agglutination test, 2-Mercaptoethanol and Coombs test were not performed.

3.2 | Logistic regression model

Variables that exhibited *p*-values lower than .25 in the univariate analysis and were therefore selected for the first multivariate logistic regression analysis of potential risk factors for accidental anti-*B. abortus* vaccine exposure are summarized in Table 3.

The final multivariate logistic model for accidental exposure to anti-*B. abortus* vaccine is shown in Table 4. The variables score of knowledge about the symptoms of human brucellosis and score of PPE use during labour activities were significantly associated with accidental exposure to S19 and RB51 and were included in the final model. The Receiver Operating Characteristic (ROC) value was 0.62.

TABLE 3 Results of the univariate analysis for accidental anti-*Brucella abortus* vaccine exposure among veterinarians from Minas Gerais, Brazil, 2018/2019

Variable	Method	*p-value*
Year of birth	Fisher's exact test	.25
Sex	Pearson's chi-squared test	.11
Use gloves during work	Fisher's exact test	.04
Use coat during work	Pearson's chi-squared test	.13
Use mask during work	Pearson's chi-squared test	.07
Score of knowledge (brucellosis symptoms)	Pearson's chi-squared test	.01
Score of PPE use during work	Univariate logistic regression	.01

Abbreviation: PPE, Personal protective equipment

TABLE 4 Multivariate analysis of accidental anti-*Brucella abortus* vaccine exposure among veterinarians from Minas Gerais, Brazil, 2018/2019

Variable	OR	95% CI	*p*-value
Score of knowledge about human brucellosis symptoms:			
Poor	-	-	-
Intermediate	0.26	0.07–0.87	.03
Good	0.22	0.07–0.62	.01
Score of PPE use during work:			
Unit increase in PPE use score	0.94	0.89–0.98	.01

Abbreviations: CI, confidence interval; OR, odds ratio; PPE, personal protective equipment.

4 | DISCUSSION

Veterinarians are one of the most important risk groups for occupational brucellosis because of the high rate of exposure to infected animals, their contaminated fluids and to live attenuated anti-*Brucella* spp. vaccines. Hence, this study identified the epidemiological situation of accidental exposure to S19 and RB51 among veterinarians from PNCEBT in Minas Gerais, Brazil, and characterized the practices and perceptions of veterinarians related to occupational brucellosis. Nearly one third of the interviewed professionals had already been accidentally exposed to S19 and RB51 vaccines. It was observed that the adoption of individual protection measures and good knowledge about the disease were very important factors in the prevention of occupational exposure to *B. abortus*. These results are crucial to direct public health policies aimed at worker health surveillance and strategic actions based on continuing education and awareness of veterinarians, mainly considering the risks and characteristics of brucellosis as an occupational disease.

A great difficulty in studies conducted by means of online questionnaires is the low response rate of participants; to minimize this issue, an adherence rate of 25% was considered. This rate was adopted after the application of a pilot questionnaire (data not shown) and was corroborated by a study involving British veterinarians, in which even with a forecast of 30% adherence, the minimum number of participants required was not reached (Robin, Bettridge, & McMaster, 2017). On the other hand, the use of online platforms makes epidemiological surveys less expensive and faster than classical methodologies. Furthermore, it is important to consider that, as the proportion of men (87%) and women (13%) in the population of veterinarians registered to perform brucellosis vaccination in Minas Gerais was very close to that in sampled population (83% men and 17% women), it can be inferred that the chosen sampling strategy probably allowed the obtainment of a representative sample.

The high proportion of males observed among the participants can be explained by the profile of the occupation described in the country 15 years ago, the average job experience of the participants, which showed a predominance of male veterinarians among those working with large animals (CFMV, 1999). In this field, veterinary services related to reproduction and vaccination against bovine brucellosis are frequent, which implies that professionals working with dairy and beef cattle have a greater probability of contact with *B. abortus*, compared with professionals that work in other fields. Considering that unprotected contacts with animal biological fluids and live attenuated vaccines pose a greater risk for occupational brucellosis (Pereira et al., 2020), questions regarding protection measures adopted by the participants, PPE adherence and barriers to the non-use of PPE were asked. More than half of the participants reported never wearing mask or goggles, which are considered very important for human brucellosis prevention. Moreover, it is alarming that a fairly high proportion of the participants (6.19% for goggles and 10.59% for mask) did not consider the use this PPE important, and 12.46% (41/329) were classified as having insufficient knowledge about disease transmission to humans, not considering the following alternatives transmission routes as true: "self-inoculation with vaccines S19 and RB51" and "unprotected contact with potentially contaminated abortions". Likewise, a poor understanding of the main clinical signs of human brucellosis was identified and is further discussed as a probable cause of the low prevalence of self-reported occupational brucellosis.

Additionally, inadequate disposal of the anti-*B. abortus* vaccines was also identified. Proper disposal of biological products at the farm is as important as proper use (Gunn et al., 2013). Indeed, vaccine bottles and vaccination residues disposed of at the property in rural general waste or buried are potential sources of infection to other animals, both domestic and wild, and can contaminate the environment (soil and water). Similarly, the disposal of vaccination residues in urban waste is inappropriate and can lead to infection in workers from disposal companies who are not prepared to handle infectious products (Compés Dea et al., 2017). Another improper form of disposal reported by the respondents was incineration, since the vaccine bottle can burst and spray aerosols, which are frequently associated with the transmission of human brucellosis (Kaufmann et al., 1980).

Concerning vaccine exposure among veterinary assistants (vaccinators registered under accredited veterinary responsibility), most of the veterinarians reported that their assistants did not wear a mask, coat or goggles during occupational activities, although they also affirmed having trained these assistants to handle the anti-*B. abortus* vaccines. S19 vaccine accident among vaccinators, who carried out vaccination under accredited veterinary's responsibility, have been informed by 12.94% (11/85) of participants; however, this rate was approximately three times lower than that of unintentional contact with vaccine strains among veterinarians [108/329 (32.83%)]. These results were different from those observed by Proch et al. (2018), in India, who found more occupational brucellosis among assistants than among veterinarians. This difference probably occurred because our study did not perform laboratory tests and the outcome was reported by the veterinarian and not by the vaccinator. Moreover, as already identified in the present study, the lack of knowledge on human brucellosis symptoms by the studied accredited veterinarians could also impaired the identification of the disease in the vaccinators under their responsibility. All those factors could have lead to underreporting brucellosis cases among vaccinators. For these reasons, the prevalence and information about the main causes and consequences of brucellosis accidental exposure among veterinarians could be considered more precise than that among vaccinators. Furthermore, the prevalence of accidental exposure to anti-*B. abortus* vaccines (32.83%) among the veterinarians from Minas Gerais observed in the present study was almost two times higher than that reported among veterinary and veterinary assistants in 2011 in Turkey (17.34%) (Kutlu et al., 2014). This finding is alarming due the great importance of brucellosis vaccine exposure related to labour activities among veterinarians in Minas Gerais (Table 2) and is probably associated with farm infrastructure that is insufficient to safely perform vaccinations. In fact, the state of Minas Gerais has predominantly small properties (median of 54 animals per herd), and the structures of the facilities are usually deficient (Alves et al., 2018; Gonçalves et al., 2009; Oliveira et al., 2016). Moreover, Minas Gerais has the third largest cattle herd in the country (IBGE, 2017) and performs approximately 1.70 million brucellosis vaccinations per year (Minas Gerais, 2017), which promotes more opportunities for involuntary exposure to vaccines.

For both veterinarians and veterinary assistants, exposure to S19 was more frequent than exposure to RB51, which was expected since in Brazil, vaccination of young heifers against brucellosis is compulsory and usually performed with S19; RB51 is more commonly used than S19 when animals exceed 8 months of age or to increase herd immunity during brucellosis outbreaks (Brasil, 2017). Moreover, in Brazil, in last years, the production of S19 exceed the production of RB51 by a 40-time factor (Ferreira Neto et al., 2016). In addition, S19 usually costs a third of the price of RB51 and is more easily found in the market. All contributes to the more frequent use of S19. Regarding the form of accidental exposure to vaccines, our data are in accordance with previously published studies, where more than half of the participants reported needle-stick injuries (Ashford et al., 2004; Blasco & Díaz, 1993; Joffe & Diamond, 1966; Kutlu et al., 2014; Nicoletti et al., 1986; Proch et al., 2018), which happened mainly during the handling of the vaccine bottle or during vaccination. Furthermore, as mentioned previously, exposure may also be due to involuntary contact with the vaccine, the poor infrastructure of the property, which was attributed as the cause of the accident by most of the respondents, followed by the inappropriate use of protective measures and animal temperament. In fact, vaccine bottle manipulation, disassembling the syringe, recapping the needle and disposing of materials are frequent causes of reported accidents among health professionals (Cullen et al., 2006; Fowler, Holzbauer, Smith, & Scheftel, 2016; Weese & Jack, 2008), and most professionals reported using only one, two or no PPE equipment during accidental contact with anti-*B. abortus* vaccine strains. Corroborating these findings, a study carried out in Italy also demonstrated that three fourths of needle-stick injuries were due to incorrect needle handling by healthcare workers and that one third could have been avoided by the use of safety devices (Castella, Vallino, Argentero, & Zotti, 2003). However, exposure through aerosols to the oral/nasal mucosa and eyes should be highlighted as another possible mode of contact with anti-*B. abortus* vaccines due to the low adherence to the use of mask and goggles. Additionally, it should be noted that inadvisable practices were described by some of the participants, including self-medication, use of veterinary drugs or even skin cauterization following the vaccination accident, which were likely associated with the low rate of medical care. These practices, in addition to being inadequate, can be invasive and dangerous.

The prevalence of self-reported brucellosis (4.56%) in this study was lower than the prevalence (11.8%) found by Kutlu et al. (2014) among veterinarians and veterinary assistants in Turkey in 2011. Nonetheless, it is important to consider that unlike Brazil, both *B. abortus* and *B. melitensis* were endemic in Turkey, with the latter being responsible for more severe clinical signs in humans than *B. abortus* (Franco et al., 2007), which could lead to an increased perception of the participants about the occurrence of the disease. Indeed, human brucellosis caused by *B. melitensis* tends to be less underdiagnosed than brucellosis caused by *B. abortus* (Pappas, Akritidis, Bosilkovski, & Tsianos, 2005). Moreover, as well as field strains, the *B. melitensis* vaccine strain REV-1 is much more virulent to humans than *B. abortus* vaccine strains S19 and RB51, which could also explain the higher (60.71%) percentage of Turkish professionals depicted infected by *Brucella* spp. after unprotected contact with vaccines than that in the present study (46.67%). In addition, the risk of contracting brucellosis was 5.40 times higher [95% (CI), 3.16–9.30] among professionals exposed to vaccine antigens than among professionals who were never exposed to anti-*Brucella* spp. strains in this country (Kutlu et al., 2014). Not surprisingly, followed by a vaccine accident, the second major cause attributed to occupational brucellosis was unprotected contact with uterine secretions from infected animals. Even individuals that accounted his infection to the consumption of raw milk also considered the possibility of becoming infected due to unprotected contact with animal fluids during a surgical procedure. Additionally, in agreement with the literature (Young, 1995), the most frequently reported clinical signs were joint involvement, weakness, fever, chills and headaches. However, it is worth mentioning that an important deficiency was identified regarding knowledge about the clinical signs of human brucellosis among the veterinarians. Almost a quarter of the respondents failed to identify the most common symptoms of the disease, which may have resulted in a possible inaccurate number of self-reported outcomes. Indeed, the self-report of brucellosis in the present study is impaired as the individuals did not identify the major common symptoms of the disease in humans. Furthermore, the results revealed a predominance of indirect methods in the diagnosis of the disease, similar to results reported in a systematic review and meta-analysis on occupational brucellosis (Pereira et al., 2020), which could be explained by considering the decreased risks and costs of indirect methods compared with bacterial isolation and molecular techniques. Other results that deserve special attention are medical attention and the treatment received among those who reported brucellosis since among the fifty per cent of veterinarians who sought specialized medical care, some were inadequately treated for the disease (Table 2). We must consider that infections caused by facultative intracellular bacteria such as *Brucella* spp. are often chronic (Gorvel & Moreno, 2002), and a minimum period of 4–6 weeks of treatment with a combination of drugs is recommended to avoid relapse (Yousefi-Nooraie, Mortazhejri, Mehrani, & Sadeghipour, 2012). Some of the most commonly used and recommended brucellosis treatment regimens, those that combine doxycycline and an aminoglycoside or rifampicin (Ariza et al., 2007), were found among those reported by the accredited veterinarians in the present study. However, in Brazil, a high rate of resistance and intermediary susceptibility to rifampicin was observed (Barbosa Pauletti et al., 2015) which could raise questions on its efficacy in brucellosis treatment in the Brazilian population. Two cases of relapse were reported despite prolonged treatment and a combination of drugs; however, it was not possible to identify whether the protocol was initiated before or after the resurgence of clinical signs. These results demonstrate the lack of knowledge and the unprepared nature of many health professionals to address this disease; this scenario exacerbates the neglected situation of human brucellosis, especially in developing countries.

In the multivariate logistic regression model of accidental vaccine exposure, it was observed that each one-point increase in the PPE use score, the likelihood of being accidentally exposed to S19 or RB51 strains was reduced by 0.94 times (95% CI: 0.89–0.98). In fact, PPE limits human exposure to infectious sources; gloves and coats provide skin protection against splashing of vaccines, and masks and goggles prevent airborne and conjunctival brucellosis transmission (Cash-Goldwasser et al., 2018). Additionally, individuals with poor knowledge of human brucellosis symptoms were more likely to experience accidental exposure to anti-*B. abortus* vaccines than veterinarians with intermediate (OR, 0.26; 95% CI: 0.07–0.87) or good (OR 0.22; 95% CI: 0.07–0.62) knowledge. This probably occurs because exposure to the vaccine is directly related to knowledge of the professional about the risk; the greater the knowledge, the less the chances of exposing themselves to hazards.

A model of risk factors for occupational brucellosis was constructed (data not shown); however, it was not possible to construct a robust model with a satisfactory fit, probably because the low rate of occupational brucellosis observed, which could be due to the self-report by professionals who demonstrated insufficient knowledge about the main signs of the disease. Thus, despite the stratification of the sampling, the possible association between the prevalences of human and bovine brucellosis in the different cattle producing regions of Minas Gerais (strata) could not be tested. The insufficient knowledge about human brucellosis clinical signs observed among the accredited veterinary population in the present study certainly contributed to the low prevalence of self-reported occupational brucellosis and, consequently, to a poor fit of the logistic model. All stress the high risk of occupational brucellosis that this specific population is submitted to.

The sampling carried out in the present study among the veterinarians from Minas Gerais accredited to the PNCEBT allowed us to create a profile of individuals who carry out routine vaccinations against bovine brucellosis and thereby to elucidate whether these professionals understand and how they address the inherent risks associated with vaccination and their work activities. In future studies, to estimate a more accurate prevalence of occupational brucellosis than that estimated here, it will be interesting to perform laboratory diagnosis on the individuals to control for underdiagnosis bias due to self-reporting. Moreover, the results of the present study could help animal and human health policy makers to establish strategies to improve knowledge on human brucellosis and to reduce the occupational risk among PNCEBT accredited veterinarians and the vaccinators under their responsibility.

In conclusion, our results showed that the prevalence of accidental exposure to anti-*B. abortus* vaccines among veterinarians from Minas Gerais accredited by the PNCEBT was high, and the risk factors observed for unintentional contact with S19 and RB51 vaccine strains were the score of knowledge about human brucellosis symptoms and score of PPE use.

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CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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