DOI: 10.5433/1679-0359.2016v37n5Supl2p3767

Mathematical modeling of bovine brucellosis control using the RB51 vaccine

Modelagem matemática do controle da brucelose bovina com a utilização da vacina RB51

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Abstract

The Brazilian Ministry of Agriculture, Livestock and Food Supply established the National Program for Control and Eradication of Brucellosis and Tuberculosis (PNCEBT) in 2001. One of the main strategies adopted by the program is the mandatory vaccination of heifers between three and eight months of age with the B19 strain. In 2007, Brazil allowed the use of RB51 vaccine in bovine females over 8 months of age as an option for the producer, but kept the B19 strain as a mandatory vaccine. This decision is based on the assumption that combining the two vaccines allows to achieve significant vaccination coverage sooner and, consequently, accelerates the fall speed of prevalence. Thus, this study aimed to measure the impact of the combined use of these two vaccines in reducing the prevalence, using as a tool the mathematical modeling. It was concluded that vaccination by RB51, if adopted as a complement to vaccination by B19, mean decrease in the prevalence of bovine brucellosis in less time.
Key words: Bovine brucellosis. Thematical modeling. Vaccine. B19. RB51.

Resumo

O Ministério da Agricultura Pecuária e Abastecimento brasileiro instituiu o Programa Nacional de Controle e Erradicação da Brucelose e da Tuberculose Animal em 2001. Uma das principais medidas adotadas pelo programa é a vacinação obrigatória de fêmeas entre três e oito meses de idade com a cepa B19. Em 2007, o Brasil permitiu a utilização da vacina RB51 em fêmeas bovinas com mais de 8 anos de idade como uma opção para o produtor, porém manteve como vacina obrigatória a B19 em bezerras de 3 a 8 meses de idade. Essa decisão parte do princípio de que combinando as duas vacinas abrevia-se o tempo para a obtenção de coberturas vacinais expressivas na população de fêmeas em idade de procriar e, consequentemente, acelera-se a velocidade de queda da prevalência. Assim, o presente estudo objetivou medir o impacto do uso combinado dessas duas vacinas na redução da prevalência, utilizando como instrumento a modelagem matemática. Concluiu-se que a vacinação pela RB51, se adotada de forma complementar à vacinação pela B19, significaria queda da prevalência da brucelose bovina em menor intervalo de tempo.
Palavras-chave: Brucelose bovina. Modelagem matemática. Vacina. B19. RB51

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Received: Sept. 26, 2016 – Approved: Sept. 26, 2016

Introduction

Bovine brucellosis is a disease for which most countries have official control programs in place as it is considered a zoonosis and it causes economic losses to producers (ACHA; SZYFRES, 2001; LAGE et al., 2006; PAULIN; FERREIRA NETO, 2003).

In 2001, the Brazilian Ministry of Agriculture, Livestock and Food Supply (MAPA) introduced the National Program for Control and Eradication of Brucellosis and Tuberculosis (PNCEBT) in order to reduce the impact of brucellosis and tuberculosis on human and animal health, and to improve the competitiveness of the Brazilian cattle industry (LAGE et al., 2006).

Since the introduction of the PNCEBT, MAPA's Collaborating Centre for Animal Health, located at the School of Veterinary Medicine and Animal Science, at the University of São Paulo, along with MAPA itself and the official veterinary services of the states, studied the epidemiological situation of these two infections in order to generate high-quality data to best develop disease control strategies and management processes.

Studies on bovine brucellosis were conducted in 18 states, housing 85% of the total Brazilian bovine stock, and the prevalence of herds infected with bovine brucellosis had varied from 0.32% to 41.5% in the states of Santa Catarina and Mato Grosso do Sul, respectively (ALMEIDA et al., 2016; ALVES et al., 2009; AZEVEDO et al., 2009; BORBA et al., 2013; CHATE et al., 2009; CLEMENTINO et al., 2016; DIAS et al., 2009a, 2009b; GONÇALVES et al., 2009a, 2009b; KLEIN-GUNNEWIEK et al., 2009; MARVULO et al., 2009; NEGREIROS et al., 2009; OGATA et al., 2009; ROCHA et al., 2009; SIKUSAWA et al., 2009; SILVA et al., 2009; VILLAR et al., 2009).

In light of these findings, one of the key strategies recommended by PNCEBT to reduce the prevalence of bovine and bubaline brucellosis, was to require farming properties to undergo compulsory B19 vaccination of heifers aged between 3 and 8 months (LAGE et al., 2006). The B19 vaccine is used worldwide because it is considered safe, immunogenic and easy to make. However, administration of the vaccine has its disadvantages which includes the risk of inducing infection in humans, the possibility of induced abortion in pregnant cows and providing a false positive result in serological tests, which can be avoided by restricting the vaccination to cows aged between 3 and 8 months, and by performing serological tests only after 24 months of age (BECKETT; MC DIARMID, 1985; MEYER, 1985; MONTES et al., 1986; NICOLETTI, 1990).

After about ten years from the completion of the first studies on the prevalence of brucellosis, a second study was conducted to investigate the effectiveness of the vaccination programs in the states of São Paulo, Minas Gerais, Espírito Santo, Rondônia, Mato Grosso, Mato Grosso do Sul and Rio Grande do Sul. However, a decrease in the prevalence of infected herds was found only in Mato Grosso, Mato Grosso do Sul, Minas Gerais and Rondônia (BARDDAL et al., 2016; DIAS et al., 2016; ANZAI et al., 2016; INLAMEA et al., 2016; LEAL FILHO et al., 2016; OLIVEIRA et al., 2016; SILVA et al., 2016). The state of Santa Catarina, which had exhibited the lowest prevalence of infected herds and animals, had prohibited the vaccination and had, instead, implemented eradication strategies. Nonetheless, they indicated, in a second study, that there epidemiological situation did not change (BAUMGARTEN et al., 2016).

The search for vaccines that do not interfere with diagnostic tests, and that could be used in adult cows, led to the development of a vaccine derived from the rough strain RB51 (SCHURIG et al., 1991). A rough strain lacks the membrane O-chain component, and as a result, does not stimulate an O-chain-specific immunogenic response that would otherwise allow for antibody detection via serological tests used in the diagnosis of bovine brucellosis (JIMÉNEZ DE BAGÜÉS et al., 1994; SCHURIG et al., 1991; TOBIAS et al., 1993; OLSEN et al., 2003; STEVENS et al., 1994, 1995).

In 2007, Brazil allowed ranchers to use the RB51 vaccine in bovine females over 8 months of age, however, the vaccination of calves aged from 3 to 8 months with the B19 strain remained compulsory (BRASIL, 2007). The underpinning assumption was that the combination of the two vaccines had the effect of potentiating and therefore, shortening the time needed to obtain significant immunization coverage for cows of childbearing age, and consequently, reduce the prevalence of the disease.

Thus, given the importance of the vaccination against brucellosis to PNCEBT, this study aimed at measuring the impact of the combined use of these two vaccines in reducing the prevalence of the disease, through mathematical modeling, similar to that used by Amaku et al. (2009) for the B19 vaccine.

Material and Methods

Mathematical modeling

The mathematical model was based on the model proposed by Amaku et al. (2009). In this model, the population of cows was grouped into seven compartments: susceptible (S), primiparous latent carriers (L1), primiparous infectious cows (I1), multiparous latent carriers (L2) multiparous infectious cows (I2), those vaccinated with the B19 strain (V1) and those vaccinated with the RB51 strain (V2). The compartment diagram shown in Figure 1 illustrates the dynamics of bovine brucellosis between the compartments.

Figure 1. Compartment diagram illustrating the dynamics of bovine brucellosis according to the proposed model.

The following set of differential equations was used for the mathematical representation of this dynamic:

$$(1-p)\eta(t)\{S+V_1+V_2+(1-\rho)[(1-\alpha)L_1+L_2]\}-(\mu+r)S-\lambda(t)S$$

$$\frac{dL_1}{dt}=\lambda(t)S+\rho\eta(t)[(1-\alpha)L_1+L_2]-(\gamma+\mu)L_1$$

$$\frac{dI_1}{dt}=\gamma L_1-(\delta+\alpha)I_1$$

$$\frac{dL_2}{dt}=\delta(I_1+I_2)-(\gamma+\mu)L_2$$

$$\frac{dI_2}{dt}=\gamma L_2-(\delta+\mu)I_2$$

$$\frac{dV_1}{dt}=\rho\eta(t)\{S+V_1+V_2+(1-\rho)[1-\alpha)L_1+L_2]\}-\mu V_1$$

$$\frac{dV_2}{dt}=rS-\mu V_2$$

The force of infection was defined by $\lambda(t) = \beta(I_1+I_2)$, where β is the transmission coefficient expressed by the number of potentially infectious contacts, *per capita*, per unit of time. The extent of vaccination coverage conferred by the B19 strain is defined by p. For simulating the model, p was set to 80%.

The vaccination coverage rate of RB51 was obtained from the following equation, where p_{RB51} is the annual coverage rate of animals vaccinated with RB51:

$$r = I_n(1-p_{RB51})$$

Mortality rate, μ, was estimated assuming that the average life expectancy of cows was seven years. In contrast, the replacement rate was expressed by η. A population of constant size requires equilibrium between these aforementioned parameters, such that the replacement rate must be equal to:

$$\eta(t) = \frac{\mu N}{S + V_1 + V_2 + (1-\alpha)L_1 + L_2}$$

where $N= S+ L_1+ L_2+ I_1+ I_2+ V_1+ V_2$ and refers to the proportion of primiparous cows that have miscarried, estimated at 80% (PAULIN; FERREIRA NETO, 2003).

A fraction, ρ, of the calves born to the infected cows became latent carriers. This fraction was estimated to be 3% (PAULIN; FERREIRA NETO, 2003). Female latent carriers became infectious at a rate, γ, defined from the calving interval. To calculate the parameter, a calving interval of 20 months was adopted for infected cows (FARIA, 1984).

The period in which the cows remained infectious was estimated to be 30 days. The recurrence rate at which these cows became latent carriers was defined by δ, which was equivalent to the inverse of the infectious period.

The model was used to simulate the dynamics of the disease in each of the states where the prevalence was found to be higher than 1% in the initial surveys conducted by PNCEBT. These states were: Espírito Santo, Goiás, Maranhão, Mato Grosso, Rio de Janeiro, Rondônia, São Paulo, Sergipe and Tocantins (AZEVEDO et al., 2009; BORBA et al., 2013; DIAS et al., 2009; KLEIN-GUNNEWIEK et al., 2009; NEGREIROS et al., 2009; OGATA et al., 2009; ROCHA et al., 2009; SILVA et al., 2009; VILLAR et al., 2009).

For the initial conditions of the simulation, it was considered, from the total number of cows over 24 months of age in each state, that the fraction corresponding to the seroprevalence found in the PNCEBT studies would be categorized to the latent L2 compartment. The remaining animals were considered susceptible and were therefore allocated to the S compartment. The other compartments did not contain any individuals at the beginning of the simulations.

Despite the arbitrary initial conditions, a comparative assessment between the associative effects of the RB51 and B19 vaccines was possible.

The value of β was adjusted for each state to yield the prevalence found in this study.

The simulations were performed with the aid of package deSolve (SOETAERT et al., 2010) using the Fourth Order-Runge-Kutta method from the R software (R CORE TEAM, 2015).

Results, Discussion and Conclusion

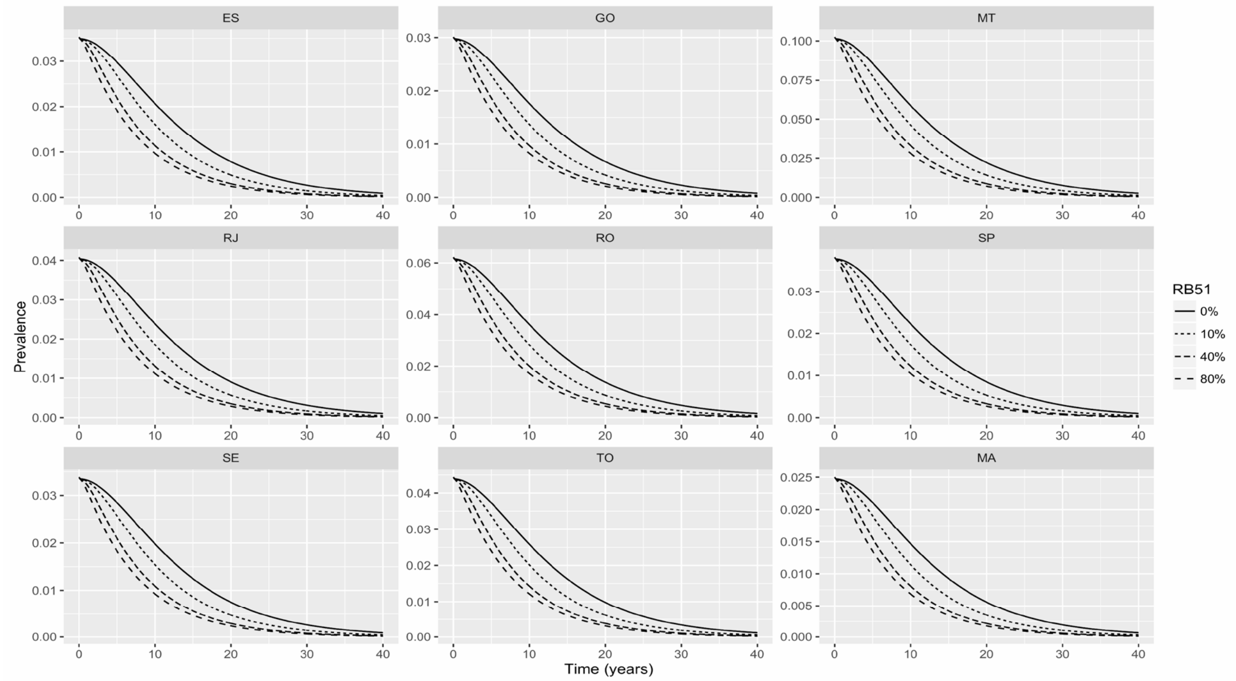
Simulations were run for each state in order to assess the magnitude of the effect produced by the combination of the RB51 and B19 vaccines for the control of bovine brucellosis.

The scenarios that were simulated always included the B19 vaccination into consideration as its efficacy has been proven. Additionally, the PNCEBT guidelines do not advocate for its replacement with the RB51 strain.

Thus, all simulations involved the assumption of an 80% vaccination coverage rate for the B19 strain for heifers aged between 3 and 8 months, whereby in each scenario, the vaccination coverage rate for the rough strain RB51 varied as follows: 0%, 10%, 40% and 80% of animals that were unvaccinated with the B19 strain. The results of the simulation are shown in Figure 2.

Figure 2. Graphs indicating the simulation of the bovine

brucellosis prevalence in the Brazilian States as a result of vaccination of 80% of the heifers with B19, associated with immunization with RB 51 of 10, 40 and 80% of non-vaccinated females with B19.



as the basis for comparison between each scenario. This value was chosen as it was the same value that was determined by the state of Minas Gerais, which implemented a well structured vaccination program with B19 strain for the control of the disease (OLIVEIRA et al., 2016).

Through an analysis of the graphs shown in Figure 2 and Table 1, it is possible to conclude that in all of the states that were evaluated, that the vaccination of adult cows with the B19 strain and adjuvant RB51 strain, had considerably reduced the time required to lower the prevalence of the disease to 1%, particularly when this combination was applied to the scenarios where 40% and 80% of the animals comprised the susceptible population.

Table 1. Estimated time (years) to lower the prevalence to 1% in the different states, considering vaccination of

80% of the heifers with B19, associated with immunization with RB 51 of 10, 40 and 80% of non-vaccinated females with B19.

States	Initial prevalence	Time to reduce the prevalence to 1% (years)			
		B19 only	B19 and RB51 (10%)	B19 and RB51 (40%)	B19 and RB51 (80%)
Espírito Santo	3.53%	17.6	14.0	10.9	9.7
Goiás	3.01%	16.0	12.7	9.7	8.5
Maranhão	2.50%	14.2	11.2	8.3	7.2
Mato Grosso	10.25%	27.5	22.9	19.0	17.5
Rio de Janeiro	4.08%	19.9	15.3	12.0	10.8
Rondônia	6.22%	22.9	18.7	15.2	13.9
São Paulo	3.81%	18.3	14.7	11.5	10.3
Sergipe	3.38%	17.2	13.7	10.6	9.4
Tocantins	4.43%	19.8	15.9	12.6	11.4

In the scenario with an 80% vaccination coverage rate involving the use of the RB51 strain in combination with the B19 strain, the percentage reduction in the time required to lower the prevalence to 1% had varied with respect to the scenario involving the exclusive use of the B19 strain, from 36% to 49%, in extreme cases found in the states of Mato Grosso and Maranhão, respectively.

Intriguingly, the difference in time required to achieve a prevalence of 1% between the scenarios involving RB51 vaccination coverage rates of 40% and 80%, was only a year or two. Nonetheless, in the 40% RB51 vaccination coverage scenario, there is a reduction of 15% of the number of animals vaccinated with RB51, i.e., delay of one or two years to reach the same prevalence is compensated by 15% reduction of the vaccinated animals (Table 2).

Subsequent studies should analyze which strategy is the most economically viable. Nevertheless, it is possible to conclude that vaccination with rough strain RB51, complementarily to the B19 strain, would contribute towards implementing the guidelines proposed by PNCEBT more quickly.

Table 2. Total number of animals vaccinated with the RB51 strain arranged according to the factors of different vaccination coverage rates, and states, required for a prevalence of 1% for bovine brucellosis.

States	Number of animals vaccinated with RB51		
	10% Immunization	40% Immunization	80% Immunization
Espírito Santo	392,097	732,392	859,808
Goiás	4,130,984	7,787,032	9,142,381
Maranhão	1,127,649	2,156,426	2,541,575
Mato Grosso	4,899,907	8,988,640	10,557,806
Rio de Janeiro	491,126	909,232	1,067,809
Rondônia	2,040,025	3,750,213	4,404,337
São Paulo	2,567,059	4,771,408	5,602,371
Sergipe	169,312	316,652	371,721
Tocantins	1,634,091	3,021,791	3,549,954

Acknowledgements

The authors acknowledge the logistical and financial support from MAPA, IMA, CNPq and FAPESP.

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