Research Article

The scenario tree epidemiological model in estimation effects of *B. melitensis* Rev 1 vaccination on disease prevalence

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Abstract: The aim of this study was to evaluate the effects of the vaccination program in Bosnia and Herzegovina on annual prevalence of small ruminant brucellosis. The stochastic scenario tree model was used to simulate vaccination and surveillance implementation during 8 years. Outputs were annual proportions of true positive, true negative, false positive, and false negative flocks. Vaccination coverage was described by the Pert distribution with average 70% and min and max 50% and 80%, respectively. Effects of risk factors (high prevalence-areas and transhumance) were considered. The model was separately simulated for three levels of initial average flock prevalence (2%, 5%, and 10%). In the following years, flock prevalence arising from the fitted distribution of the false negative flocks from the previous year increased by the estimated reproductive number. Average within flock prevalence was provided separately for the vaccinated and unvaccinated flocks, indirectly accounting for the vaccine efficacy. Specificity of the diagnostic tests (Rose Bengal plate and Complement fixation) was reduced by 5% for the vaccinated flocks to represent the increased occurrence of false positive results. Each simulation was iterated 1000 times using @Risk, providing average prediction and 5th and 95th percentile of outputs. According to our estimates, only consistent vaccination combined with systematic removal of diseased animals can result in significant reduction of disease prevalence.

Key words: Small ruminant brucellosis, vaccination, prevalence, modeling

1. Introduction

Brucellosis is a globally distributed zoonotic disease with negative consequences on human health and animal production, welfare and health, as well as direct and indirect implications on trade, economy, and biosecurity (1,2). At the same time, brucellosis is a long known and extensively investigated disease, but scientists still do not have complete answers for all issues resulting from its occurrence and aftereffects. In most countries, control of animal brucellosis is an important segment of national animal health activities, even in those with brucellosis-free status achieved decades ago (2,3). Human exposure is prevented through the control and eradication of disease in animals, provided by test and slaughter and vaccination programs applied either simultaneously or consecutively (3). In developed countries, human brucellosis seldom occurs, mostly as a consequence of contracting disease in other countries with endemic brucellosis (1,4), whereas if animal brucellosis is present at all, it is limited to wildlife (5,6). In developing countries, human brucellosis is common, acquired either through direct contact with diseased animals or as alimentary infection, depending on the level of the disease in animals and habits and costumes in animal rearing, processing, and consumption of particularly milk and milk products (1,5). This is especially evident in countries of the Mediterranean basin, which includes Bosnia and Herzegovina (BiH). In this country, brucellosis of ruminants, especially sheep and goats, poses a significant problem for animal health and production, and even more for (veterinary) public health (7). After failed attempts to control the disease by inconsistent test and slaughter measures, in 2009 the mass vaccination became mandatory using the Rev 1 vaccine applied conjunctively for all small ruminants older than 3 months, except for pregnant ewes (8). After 2009, the vaccination continued on annual basis with replacement animals and those not vaccinated earlier, and vaccination was planned to cease entirely in 2017. Decision on vaccination and its implementation has been followed by many controversies and debates between stakeholders, and now we are in the final year of its application waiting to see the results of vaccination in controlling animal brucellosis.

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This study aimed to evaluate the effects of the implementation of small ruminant vaccination program in BiH on small ruminant brucellosis flock prevalence.

2. Materials and methods

2.1. Epidemiological model

The scenario tree model was used to describe the implementation of the vaccination program and the surveillance activities during 8 years (2009–2016) (as shown in Figure 1). Model outputs were proportions of true positive (TP), true negative (TN), false positive (FP), and false negative (FN) flocks after each year. Initial average flock prevalence (year 1) was considered at three levels (2%, 5%, and 10%). In consecutive years (from year 2 to 8), the initial flock prevalence rose from the fitted probability distribution of unidentified diseased flocks (FN) from previous year, multiplied by the stochastically represented basic reproductive number (Ro). This represented an estimate of annual among-flock spread rate (9). Average within flock prevalence was provided separately for vaccinated and unvaccinated flocks, indirectly accounting for the less than perfect vaccine efficacy. The model also included annual sampling of flocks and animals within flocks, followed by diagnostic testing of individual animal samples by two serological tests, i.e. Rose Bengal plate and Complement fixation, applied in series (as it is prescribed officially). Disease detection was represented by herd-level sensitivities and specificities of the applied testing protocol, which took into account the sampled flock size, within flock prevalence, and sensitivity and specificity of each test. Specificity of diagnostic tests was reduced by 5% for vaccinated flocks to represent the increased probability of false positive results of serologic test applied to vaccinated animals. Each of the 24 simulations (3 levels of initial flock prevalence, 8 years of implementation) was iterated 1000 times using @Risk. In each individual iteration, the value of input variables given as probability distribution was randomly selected, with consideration of

the set parameters/type of assigned distribution. Outputs of models were evaluated using the average, 5th, and 95th percentile of the resulting proportions for TP, TN, FP, and FN flocks.

Most of the model inputs (as shown in Table 1) were given as probability distribution, allowing stochastic simulation. Also, for describing inputs in the model, we used data from published experimental or observational studies for the purpose of science-based contribution to the validity of our model (8–16).

2.2. Questionnaire survey

Besides using official reports on vaccination implementation as data source, we conducted a questionnaire survey in 2013 on selected municipal veterinary organizations throughout the country. Participants were selected based on small ruminant identification data collected in 2009 (alongside mass vaccination), using criteria of having more than (>) 10,000 registered sheep and goats in a municipality. Through the survey, data were collected from 26 municipalities (out of 141) in BiH, which comprised 56.2% of the entire small ruminant population in the country. The applied questionnaire had 37 questions regarding domestic animal populations in a municipality and implementation of veterinary measures, number of small ruminants and flock size distribution, rearing and production characteristics, general health status of small ruminant population, implementation of the vaccination program, as well as surveillance measures for small ruminant brucellosis.

2.3. Small ruminant population data

Small ruminant identification data collected in 2009 were provided by the State Veterinary Office of BiH. These data included municipality of origin of animals/flocks, veterinary organization in charge of implementation of identification/vaccination, owner, animal species (sheep or goat), and number of animals in a flock. For the purpose of the study, small ruminant flocks were identified as animals of the same owner regardless of species (sheep
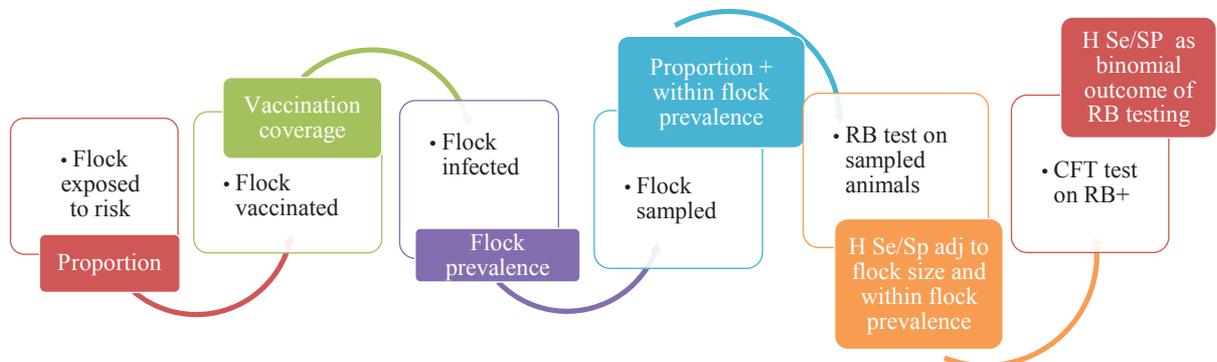

Figure 1. Scheme of the scenario tree model representing annual implementation of the vaccination program in BiH.

Table 1. Input parameters of the model simulating vaccination program.

Input variable of the model (source)	Variable type	Variable descriptions/parameters		
		Min	Expected average	Max
Start average flock prevalence	Fix for Y_0 $=R_0 \times FN_{(Y-1)}$ for $Y_{1,..8}$	0.020 0.050 0.100		
Proportion of flocks in high-prevalence areas (national database)	Fix	0.180		
Proportion of nomadic flocks (10)	Fix	0.600		
Sensitivity RB test (11)	β distribution	0.740	0.758	0.777
Sensitivity CFT test (11)	β distribution	0.789	0.806	0.823
Specificity RB (unvacc. flocks) (11)	β distribution	0.995	0.997	0.999
Specificity CFT (unvacc. flocks) (11)	β distribution	0.991	0.998	1
Avrg. within flock prev. (unvacc. flocks) (12)	Pert distribution	0.100	0.150	0.400
Sampling coverage (8)	Pert distribution	0.050	0.100	0.150
Averg. within flock prev. (vacc. flocks) (13)	Pert distribution	0.010	0.050	0.100
Vaccination coverage (8, survey results)	Pert distribution	0.500	0.700	0.850
Specificity RB (vacc. flocks) (14)	β distribution	0.945	0.947	0.949
Specificity CFT (vacc. flocks) (14)	β distribution	0.941	0.948	0.950
Ro (9)	Pert distribution	0	0.05	0.1
RR for flocks from high-prevalence areas (15)	Pert distribution	2.0	3.3	5.6
RR for nomadic flocks (10, 16)	Pert distribution	1.5	5.7	22

and goat flocks of the same owner were merged as a single data entry), while owner personal data were replaced by the numeric code. After removal of duplicate entries, the database contained 1,127,289 small ruminants and 23,683 small ruminant flocks. For the purpose of simulation modeling, only flocks with more than (>) 10 animals were considered, resulting in the final database containing 1,097,743 animals and 19,421 flocks. Study population was compared to the estimates on population size provided by the surveyed veterinary organizations where no significant differences were observed.

2.4. Consideration of risk factors
In our model, considered risk factors (high-prevalence areas and transhumance) influenced both the flock-level prevalence and within-flock prevalence. They were selected based on the observed effect on brucellosis occurrence and spread in many previously published studies (10,15,16). Their effect was incorporated through reported values of odds ratio (approximation of a relative risk), represented in the model by the Pert distribution (as shown in Table 2). Risk measure was transformed into differential risk for groups within population exposed to different combinations of considered risk factors in order to maintain the average risk for the population equal to 1 (formula below):

$$\sum_{l=1}^{L}(R_l * G_l) = 1 \tag{17}$$

where L is the number of groups in a population exposed to different risk factor combinations (four), Rl is the differential risk for group L, and Gl is the proportional size of the group.

Brucellosis prevalence (flock and within flock) for groups of flocks exposed to different risk factors were calculated according to the formula bellow:

$$P_l = \prod R_l * \bar{P} \tag{17}$$

where Pl is the adjusted prevalence (due to different levels of exposure), Rl is the differential risk for group L, and P is the average prevalence estimate for the entire population (as shown in Table 1).

2.5. Model assumptions
Our model was based on the following assumptions:
- Population size (number of animals and number of flocks) does not alter during the period of simulation,
- In identified diseased flocks (TP) and in noninfected flocks falsely identified as diseased (FP), all positive animals are detected, removed, and replaced,
- Other than changes of prevalence over the years, all other parameters influencing disease occurrence, spread, and detection remain the same,

Table 2. Relative and differential risk values for different exposure groups considered in the model.

Exposure group	Relative risk	Differential risk
Flocks from high-prevalence areas	Pert (2, 3.3, 5.6)	2.334
Flocks originating from other areas	1	0.707
Transhumance flocks	Pert (1.5, 5.7, 22)	1.492
Nontranshumance flocks	1	0.262

- Sampling of flocks and within flocks for the surveillance purposes is random,

- Brucellosis spread rate among flocks is constant through time and encompasses all means of disease transmission (direct and indirect contact),

- Vaccine efficacy is not incorporated directly; however, since the model allows disease presence in vaccinated flocks, as well as disease spread on vaccinated flocks, it is implied that vaccine efficacy is less than 100%.

2.6. Sensitivity analysis

According to the level of influence on model outputs (proportions of TP, FP, TN, and FN flocks), model inputs were ranked using @Risk. In addition, the applied software enabled determination of minimal and maximal percentage of influence, resulting from the variation of the individual input variable, compared to the estimated average value of output. Results were provided as the average influence over the simulation period, while the influencing inputs were ranked from highest to lowest.

3. Results

3.1. Results of the survey

Breeding of small ruminants is the most important type of animal husbandry in one third of the surveyed municipalities. Estimates of the population size by the interviewed veterinarians were not significantly different from the data for the same municipalities in national small ruminant registration. The most common veterinary interventions in small ruminants were vaccination against *B. melitensis*, treatment against infectious diseases followed by treatment of metabolic disorders. The most common infectious diseases in small ruminants were infestation by internal and external parasites, mastitis, pneumonia, brucellosis, contagious ecthyma, foot rot, and Q fever. Average vaccination coverage based on estimates by the interviewed municipal veterinarians was 70.22% (95% CI 47.6%–82.9%), while the testing coverage ranged from 1% to 10%.

3.2. Results of the model

Using the stochastic scenario tree model, we simulated changes in prevalence of small ruminant brucellosis based on field-verified data on implementation of the vaccination program in BiH in conjunction with diagnostic testing and removal of diseased animals. Our research showed that effect of the vaccination program in BiH reflected slow decrease of flock prevalence regardless of the initial average flock prevalence (as shown in Figure 2). Over the 8-year period, flock prevalence was reduced from the initial 2%, 5%, or 10% (year 0) to 1.45%, 3.63%, and 7.26%, respectively (year 8).

With higher initial prevalence, more significant reduction can be expected; however, the variability of an estimate is also higher. Our results show that reduced testing coverage during implementation of vaccination has significantly reduced the ability of the system to recognize and consequently remove the infected animals and flocks (as shown in Figure 3). In addition, based on our model estimates, a large proportion of small ruminant flocks identified as positive are in fact false positive flocks (healthy vaccinated flocks mistakenly identified as positive due to decreased ability of the applied diagnostic test to differentiate vaccinated and infected animals), more so for the lower initial average flock prevalence.

3.3. Sensitivity analysis results

Average estimates of the proportions of TP and FN flocks were mostly influenced by the variation of input variables, while the observed variation in estimates of the other two model outputs (TN and FP flocks) was less than ±1% for any input. Ranking of model inputs and level of influence on outputs (± percent of change) was almost identical regardless of the initial flock prevalence (see Table 3; data regarding TP and FN). Two most influential input variables (i.e. ranked either as first, second, or third for all model outputs) were sampling coverage and average flock prevalence (for years 1 to 8).

4. Discussion

Animal brucellosis eradication programs in developed countries were succesful examples; however, at the same time, they were characterized as expensive, time-consuming, and resource-demanding, so to use this experience in developing countries sound epidemiological intelligence for optimal decision making is required
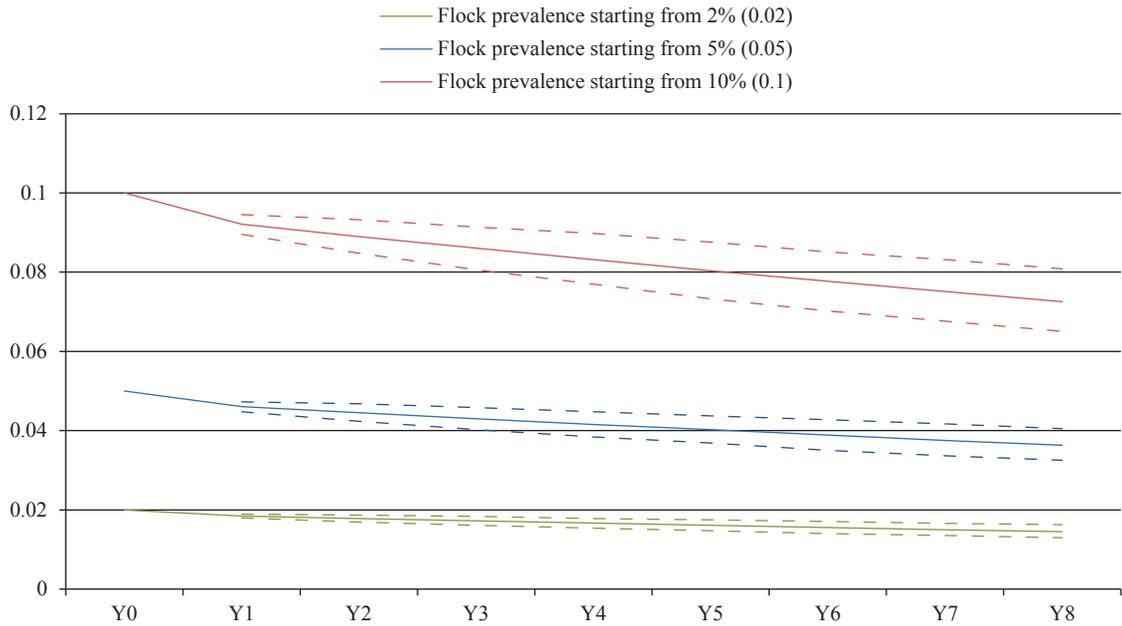
Figure 2. Average (full line), 5th and 95th percentile (doted lines below and above average estimate, respectively) of flock prevalence estimated by the model over 8 years for start prevalence of 2%, 5%, and 10%.
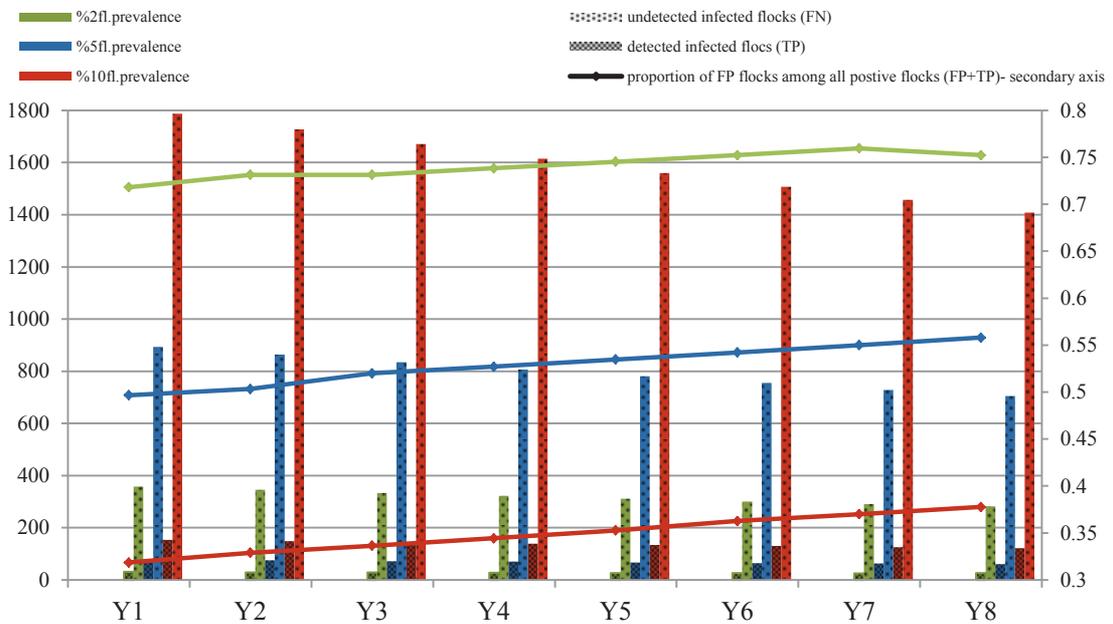

Figure 3. For 3 levels of initial flock prevalence (2%, 5%, and 10%), resulting annual estimates of the number of undetected infected flocks (FN) and number of detected infected flocks (TP), alongside the proportion of misclassified positive flocks (FP) among all positive flocks (TP+FP) on a secondary axis.

(2,5,9,18). This study confirmed that effectiveness of small ruminant vaccination program as applied in BiH changes depending on initial disease prevalence and its homogeneity thoughout population. The predicted humble flock prevalence reduction after 8 years of vaccination was additionally influenced by the reduced sampling coverage and increased misclassification error of the applied testing regime. Other modeling studies and empirical experiences from countries implementing Rev1 vaccination have initially showed good results regarding reduction of

Table 3. Ranking of the model inputs according to their influence on model outputs (proportion of detected infected flocks (TP) and proportion of undetected infected flocks (FN)) color-coded according to first column (rank of inputs on TP for 2% flock prevalence) and followed throughout the table.

Model inputs	Rank of influence on model outputs					
	2% flock prevalence		5% flock prevalence		10% flock prevalence	
	TP	FN	TP	FN	TP	FN
Sampling coverage	1	2	1	2	1	2
Flock prevalence	2	1	2	1	3	1
Within-flock prevalence (unvaccinated)	3	3	3	3	2	9
Sp. CFT in vaccinated flocks	4	4	6	4	6	3
Sp. RB test in vaccinated flocks	5	5	5	6	10	7
RR transhumance	6	6	4	5	4	4
Vaccination coverage	7	8	10	10	5	8
Se RB test	8	7	9	11	11	10
RR high-prevalence areas	9	10	8	7	7	5
Within flock prevalence (vaccinated)	10	11	7	8	8	6
Se CFT	11	9	11	9	9	11

human brucellosis; however, effects on occurrence of disease in animals may be variant depending on the initial prevalence, vaccination coverage and efficiency, dynamics of brucellosis spread, and implementation of control measures (2,3,18,19). Due to less than 100% vaccination coverage and efficacy, without more focused measures of active removal of diseased animals, brucellosis among small ruminant population continues to persist (9). Even though we were not able to fully assess its influence, precision of our predictions is also dependent on transmission dynamics of brucellosis (within and among flocks), on which few studies are available. Particularly since small ruminant brucellosis

in developing countries, such as BiH, goes hand in hand with extensive animal breeding, transhumance, lack of movement control, and scarcity of resources and suboptimal capacities of the national veterinary service (1,2,5). Hence, there is genuine probability that after vaccination ends, brucellosis of small ruminants will still remain an important issue in BiH. Considering the limitations, next steps would preferably be an integrated approach involving both human health and veterinary services, using one health- and/or commodity-based approach, to allow a better understanding of the disease, as well as a more cost-effective utilization of resources (1,3).

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