Modelling the feasibility of bovine tuberculosis eradication in Argentina

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Summary

The ability of countries to control and eradicate bovine tuberculosis (TB) has been jeopardised by various epidemiological and ecological features of the disease. The authors have used epidemiological modelling to develop an analytical framework to assess the likely success of a national TB eradication programme in Argentina. Study results suggest that the current control programme is financially feasible in the long term. However, considering that the costs of the TB eradication programme in Argentina are entirely borne by the producer, the initial investment required and the long-term horizon needed to gain revenue may prevent producers from endorsing the programme. Regionalised programmes that allow differential control strategies to be implemented in specific regions may increase the likelihood of success. This methodological approach could be extended to design and evaluate control and eradication programmes for TB and other infectious diseases in other regions of the world.

Keywords

Argentina – Bovine tuberculosis – Epidemiology – Modelling – *Mycobacterium bovis* – Tuberculosis.

Introduction

Bovine tuberculosis (TB) is a chronic disease of cattle caused by infection with *Mycobacterium bovis*. During the last century, many countries initiated campaigns to control and eradicate the disease at national and regional levels, because of the risk of zoonotic infection and the economic impact that TB has on infected regions (2, 4, 9). These campaigns were based on the application of test-and-cull strategies and restrictions on animal movements. Despite the success of control and eradication programmes implemented in various countries, which resulted in a drastic reduction of the incidence of bovine TB in certain regions, the disease is still prevalent in many areas of the world (4, 8, 9). Lack of success in eradicating TB is probably due to a combination of factors, including:

– the chronic nature and long incubation period of the disease

– the lack of sufficient financial and human resources to control the disease

– the absence of an effective vaccine

– the absence of protective natural immunity to the infection

– re-infection from wildlife reservoirs

– failure in the design and implementation of diagnostic tests and control schemes.

Bovine tuberculosis is endemic in Argentina and the impact of this disease upon public health has been generally acknowledged. For example, *M. bovis* was found to be

responsible for 2.3% of the human tuberculosis cases reported in the province of Santa Fe between 1977 and 2001, and 65% of these *M. bovis* human cases occurred in slaughterhouse or rural workers (7, 13). For this reason, a compulsory national TB control programme was designed and launched in 1999. The control programme is based on a test-and-cull policy, using the caudal fold tuberculin test (CFT) with *M. bovis* purified protein derivative (PPD). All cattle in the herd aged six months or more are tested at intervals of three to four months.

The financial costs of the TB control programme in Argentina are entirely borne by the producer. For that reason, cost-benefit analyses to estimate the economic benefits of eradicating bovine tuberculosis are needed to motivate producers and, ultimately, to predict the likelihood of success of this programme in Argentina. Experimental studies, such as interventions and clinical trials, are expensive and difficult to conduct under field conditions. Epidemiological modelling, in contrast, may be an affordable alternative to identify the nature and extent to which epidemiological factors influence the risk of disease and to assess the feasibility and expected impact of various control and eradication programmes.

Epidemiological modelling was used in this instance to evaluate the feasibility and effects of the TB control programme in Argentina. The analytical framework (Fig. 1) consisted of successive stages of assessment, each of which was aimed at quantifying, respectively:

– the trends in TB prevalence in Argentina

– the spatial variation in the risk of the disease

– the most likely value of critical parameters that affect the transmission of the disease at the intra-herd level

– the expected impact of different test-and-cull schemes, based on the use of alternative diagnostic tests

– the association between TB incidence and productivity losses

– the expected revenues that the producers will receive as a consequence of eradicating the disease.

Trends and spatial clustering were assessed before the implementation of the compulsory control programme in 1999. Results were used to identify those areas of the country at high risk of the disease. The simulation exercise and cost-benefit analysis were then conducted for these areas, using data collected between 1999 and 2003. The modelling framework developed is also applicable to the evaluation and design of control and eradication programmes for TB in other regions, as well as for other infectious animal diseases.

Assessing trends

Data on the identification of TB-like lesions in cattle slaughtered during a 30-year period (1969 to 1998) in

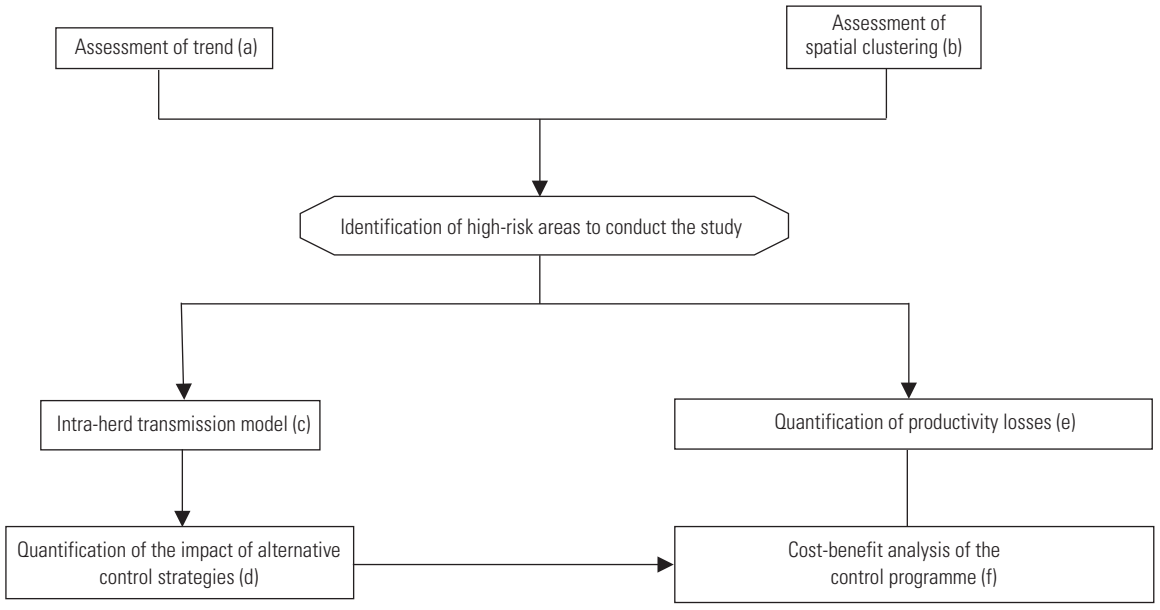

Fig. 1
Analytical framework of an epidemiological modelling study used to evaluate the bovine tuberculosis control programme implemented in Argentina

Argentina were provided by the Servicio Nacional de Sanidad Animal (SENASA). Data were collected from slaughterhouses which underwent federal inspection, accounting for approximately 60% of the total number of cattle annually slaughtered in Argentina during the period assessed. Tuberculosis-like lesions were detected by inspecting lungs, livers, and spleens, and through incising selected lymph nodes, according to national regulations (SENASA Ordinance Number 4238/68) (14) on the inspection of livestock products. The prevalence was estimated as the proportion of inspected cattle with TB-like lesions.

A significant ($P < 0.01$) decreasing linear trend in the annual prevalence of TB (1.7 cases per 1,000 cattle inspected per year) was estimated by using a simple weighted linear regression model, in which the yearly prevalence was the dependent variable, the year was the independent variable, and the number of cattle inspected per year was the weighting factor. The epidemic curve suggested three different stages of disease prevalence (Fig. 2). The first period (1969 to 1981) was characterised by a cyclical pattern of a decreasing trend ($P < 0.001$). The second period (1981 to 1987) was characterised by a stationary curve with no linear trend, associated with a period of social and economic disruption ($P = 0.39$). However, there was a significant decrease ($P < 0.001$) in the annual prevalence (2.4 cases per 1,000 cattle inspected per year) of the disease through the third period (1987 to 1998).

As no compulsory control programme was in place during the time the trend was assessed, the decreasing trend and the changes in the temporal patterns of the disease might have been due to changes in herd management practices that improved the health status of the animals. It should also be noted that, because data were not collected through random sampling of the population, the estimates here may not reflect the true prevalence of the disease in Argentina. Nevertheless, the decreasing trend observed before 1998, which resulted in estimates of <2% prevalence in that year, suggests that conditions were favourable for TB eradication and for the implementation of a mandatory control programme, which was launched in 1999.

Spatial clustering

A detailed description of the analysis assessing the spatial variation in the risk for TB is available elsewhere (12). In brief, from March 1995 to February 1997, data collected through the inspection of 9,472,396 cattle (47% of the total number of cattle slaughtered in Argentina over that period), at 126 slaughterhouses which underwent federal inspection, were used to assess the spatial distribution of TB in Argentina. Data included the origin (county) of shipments in which TB-like lesions were detected through routine inspection of organs and lymph nodes, as well as the proportion of cattle per shipment in which TB-like lesions were detected. Spatial clustering was assessed using the Bernoulli model of the spatial scan statistic (5, 6). The null hypothesis was that the proportion of cases (cattle with TB-like lesions) and controls (cattle with no TB-like lesions) per county was homogeneously distributed throughout Argentina. A spatial scanning window of up to 50% of the country was employed. A Monte Carlo simulation was used to identify windows in which the proportion of cases was

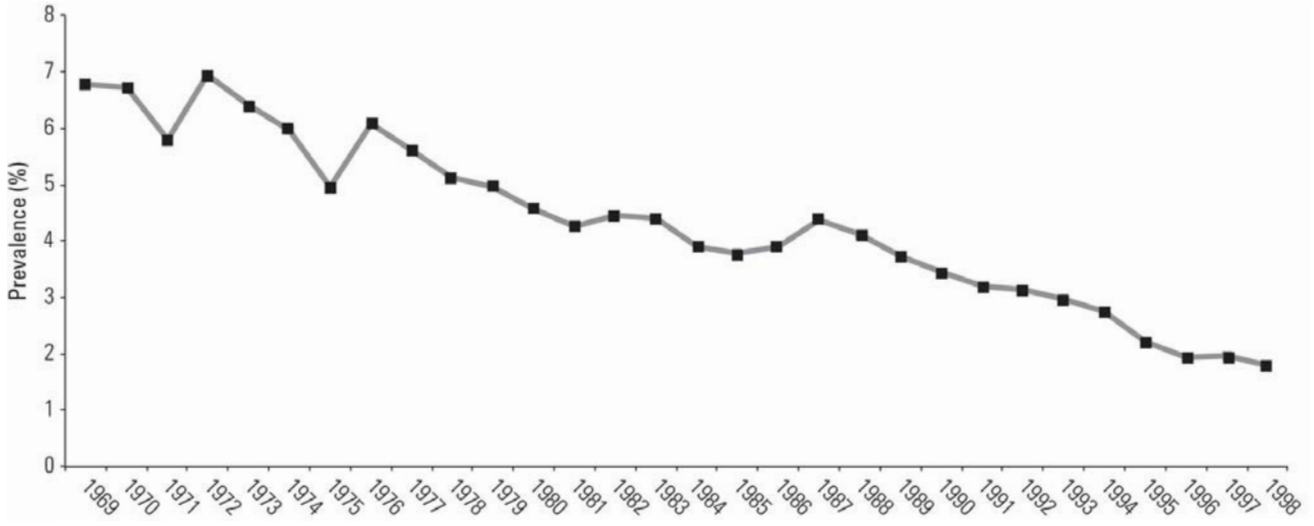

Fig. 2
Prevalence of bovine tuberculosis-like lesions found in cattle slaughtered under federal inspection in Argentina between 1968 and 1998

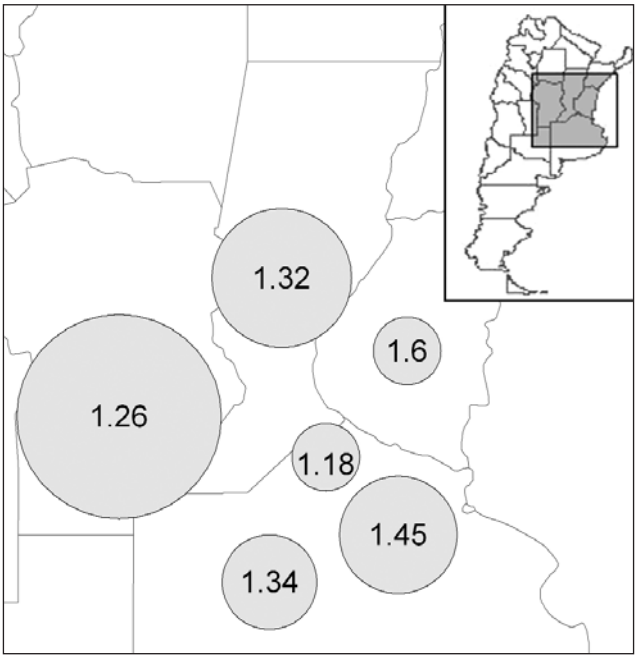

Fig. 3
Spatial clusters of bovine tuberculosis-like lesions, identified using a scan-based algorithm and data collected from slaughterhouses under federal inspection, in Argentina between 1995 and 1997
Numbers indicate the observed-to-expected ratio of tuberculosis cases within the clusters (12)

significantly higher than expected. Six significant clusters were detected, all of which overlapped areas of dairy cattle production (Fig. 3).

The most probable cluster ($P < 0.01$) included five counties within the provinces of Santa Fe and Cordoba, in which 4,382 and 5,793 TB cases were expected and observed, respectively (observed-to-expected ratio = 1.32). The results suggested that TB was clustered in Argentina, which supports the rationale behind the implementation of regionalised programmes for risk management and for controlling and eradicating the disease. The results also suggested that cows from dairying regions of Argentina were at significantly higher risk of TB than expected, under the null hypothesis of homogeneous risk distribution. The primary cluster included dairying districts in the Santa Fe and Cordoba provinces.

Intra-herd transmission model

As a result of these findings, the intra-herd transmission of TB in dairy herds in the province of Santa Fe was modelled, using a stochastic modification of the Reed-Frost model (11).

The number of cases at time t + 1 (C_{t+1}) was computed as a function of the cumulative number of cases (CC_t) and susceptible (CS_t) cattle at time t and the probability of effective contact as: $C_{t+1} = CS_t [1 - (1 - p)^{CCt}]$. This is a modified Reed-Frost formulation previously used to model TB and brucellosis transmission (1, 15). Thus, $CS_{t+1} = S_t + R_s - D_s$ and $CC_{t+1} = CC_t + C_{t+1} + R_i - D_i$, where R_s and R_i are the number of susceptible and infected replacement cattle, and D_s and D_i are the number of susceptible and infected culled cattle, respectively.

The transitions from the states of susceptible to infected and from infected to infectious were modelled using two stochastic parameters, which the authors refer to as the transmission coefficient (β) and the incubation period (α), respectively.

The value of β, which is the average number of individuals that become newly infected from an infectious individual per unit of time (3), was estimated using the results of CFT tests, applied over a period of approximately ten years, in three dairy herds in south Santa Fe Province. For each round of application (herd test) of the CFT, the number of cattle in the herd (N) was computed, as well as the number of infected cattle (I), the number of new cases (C), and the number of susceptible cattle (S = N – I – C). Since not all infected cattle (I) are infectious (Ia), the value of Ia was approximated, using a uniform distribution with minimum and maximum values of 1 and I, respectively. This corresponded to extreme scenarios in which only one or all of the infected cattle were infectious. Subsequently, β was estimated as the exponent of ln (Ca) – ln (SIa/N), where Ca is an adjustment of the value of C to represent the number of new cases that would be detected if cattle were tested at exactly one-year intervals. The median value of β($M\beta$) was computed, using the values of β estimated for the three herds throughout the period under study (~ 10 years), and incorporated into the Reed-Frost model, assuming a Poisson distribution with $\mu = M\beta$. Finally, the model was run assuming 12 different distributions of α and the theoretical distribution of α that best fitted the incidence of TB observed in the three herds throughout the ten-year period was selected for the model.

The value of $M\beta$ ($M\beta$ = 2.2 infective contacts per year) did not differ significantly ($P > 0.05$) among the herds, and the distribution for α that best fitted the incidence of TB was obtained, assuming that α was Poisson distributed with μ = 24 months. The results suggest that the latency and transmission rate of TB in the dairy herds of Santa Fe correspond to average values of 24 months and 2.2 infective contacts per year, respectively.

Quantification of the impact of selected control activities

The modification of the Reed-Frost model was used to estimate the number of herd tests needed, and the number of cows that must be culled, to eradicate TB in three different scenarios of:

– an initial high prevalence (22%)

– medium prevalence (11%)

– low prevalence (5%) (10).

The model was used to simulate the spread of the disease over a five-year period in a standard dairy operation in the province of Santa Fe, with an average production of 5,000 litres per lactation and 200 cows in milk. The impact of three different strategies was assessed, namely:

– using CFT alone

– using a single cervical test (SCT) during the first herd test and CFT thereafter

– using the γ-interferon test (γ-IFN); to be highly sensitive on the first herd test and highly specific thereafter.

Sensitivity and specificity were assumed to be 0.81 and 0.98 for the CFT; 0.95 and 0.80 for the SCT; 0.97 and 0.90 for the highly sensitive γ-IFN, and 0.80 and 0.99 for the highly specific γ-IFN, respectively. Additional model variables included:

– the time between consecutive herd tests (three months)

– immediate culling of cattle that tested positive

– a constant replacement rate (with TB-free cattle) of 2%.

The simulation results were highly variable, which is consistent with the difficulty in predicting the effects of differing control strategies within individual herds. The median number of tests required to eradicate the disease was similar for the three strategies and scenarios assessed. However, use of the γ-IFN consistently resulted in the lowest number of culled animals, followed by the CFT, whereas the SCT was the least efficient technique (Table I).

Quantification of productivity losses

The association between TB and the productive and reproductive performances of cattle was assessed in a dairy herd located in the province of Santa Fe. The herd was selected because of the availability of high-quality records and data, the herd history of TB (the bovine TB prevalence was >20% during the study period), regular PPD testing of the cows for *M. bovis* infection, the retention of cows that tested positive by the PPD test within the herd, and the cooperation of the dairy producer. Five hundred and thirty-five cows born in the herd between April 1981 and May 1997 were included in the study. Data collected between January 1993 and August 1999, as part of the herd and veterinary records, included, for each study cow:

– the results of all PPD tests performed (positive, negative)

– the number of days in lactation

– the number of days in milk per lactation

– milk produced (litres of milk per day)

Table I

Median number of herd tests, mean number of culled cattle, initial investment and net present value needed to eradicate bovine tuberculosis in scenarios of low (5%), medium (11%) and high (22%) prevalence in Argentina from a single hypothetical herd, using three different tests: the caudal fold test, the single cervical test and the γ-interferon test (10)

Initial investment and net present value are in thousands of Argentine pesos. The data were collected in March 2003

Scenario	Test	Median number of herd tests	Mean number of culled cattle	Initial investment	NPV
Low prevalence	CFT	7	91	40.9	3.5
	SCT	5	103	95.8	–51.3
	γ-IFN	3	52	70.4	–11.3
Medium prevalence	CFT	11	169	51.1	65.3
	SCT	11	187	77.2	26.5
	γ-IFN	11	116	62.3	24.5
High prevalence	CFT	12	274	80.9	168.2
	SCT	12	297	108.3	136.2
	γ-IFN	12	219	92.9	129.7

NPV: net present value
CFT: caudal fold test
SCT: single cervical test
γ-IFN: γ-interferon test

– the number of days on which the cow was not pregnant
– the number of days on which the cow was in calf
– the date of calving
– the type of calving (normal, abortion)
– the date of culling from the herd.

No significant ($P > 0.05$) differences were found between cows that tested positive by the PPD test and those that tested negative, in:

– the risk of culling
– days in milk
– the risk of abortion
– age at first calving.

For cows that tested positive, a reduction in daily milk production occurred only during the lactation period in which the cow first tested positive. Cows testing positive by PPD were more likely (odds ratio 45.0; 95% confidence interval [CI], $P < 0.01$) to abort for a second time than cows that continued to test negative during the study period. On average, cows that tested positive by PPD were not pregnant for 17 days more than cows that tested negative ($P < 0.0001$).

Cost-benefit analysis

Estimates of the following four factors were used to conduct a cost-benefit analysis of eradicating TB at the herd level in Argentina:

– the number of tests required to control TB
– the number of cattle that must be culled
– the productivity losses expected from the disease
– the financial benefits expected from eradicating the disease.

The benefits of eradication included a 2% increase in the value of milk ($0.4 per litre) after eradication and a 10% increase in milk production, weighted by the prevalence of TB in the herd when the simulation began.

The costs of eradication included testing ($2 per animal tested for CFT and SCT, and $22 for γ-IFN) and the difference between the value of culled and replacement cows ($1,200 per cow).

The differences between the costs and benefits of eradication were estimated yearly, and the net present value (NPV) of each control strategy and scenario was estimated, using a time horizon of 20 years. The real interest rate (6%) was estimated as the difference between the interest rate (49%) and the inflation rate (43%). All values were obtained in the field in March 2003 and expressed in Argentine pesos ($). The highest NPV and lowest initial investment for each of the three scenarios were obtained using the CFT (Table I).

The initial investment required was over $40,000 in all the assessed scenarios and strategies. The SCT and γ-IFN were not financially feasible in the low-prevalence scenario (with losses of $51,300 and $11,300, respectively). The highest benefits were estimated in the high-prevalence scenario, using the CFT test ($168,000). The initial investment required to control TB during the first year of testing was high. In the high-prevalence scenario, this initial investment was $80,900, which was more than 20% of the annual income from milk production in the simulated herd ($400,000). Since, in Argentina, producers are responsible for the entire replacement cost of the animals, it is possible that producers may not be able to afford the required initial investment until the benefits have been realised.

Discussion

The authors now describe the design and application of an epidemiological modelling framework to evaluate the feasibility of a mandatory control programme for TB in Argentina. This modelling framework could also be extended and modified to use as an example in designing and evaluating control programmes for other infectious diseases in other regions of the world.

The methodological approach consisted of successive analytical stages modelling different features of TB epidemiology and economics. First, it was estimated that there was a decreasing trend in the prevalence of the disease before the mandatory control programme was implemented, suggesting that conditions were favourable for eradicating the disease. In the second stage, those areas at highest risk of the disease were identified and an association between TB risk and dairy herd areas was suggested. Consequently, an epidemiological model was developed to set parameters for intra-herd transmission of the disease in dairy areas in those regions estimated to be at the highest risk of TB. The model was also used to simulate the effects of various control strategies and the expected benefits of TB control to the producers. The results suggested that, although the γ-IFN may be the most efficient diagnostic technique, in terms of the number of tests performed and cattle to be culled, the highest revenue came from using the CFT, probably as a result of its lower cost. Since, in Argentina, the cost of the control programme is entirely met by producers, the results of this modelling exercise suggest that the CFT may be more appropriate than the γ-IFN for controlling TB in this country.

These results also suggested that regionalisation may play an important role in controlling and eradicating TB. Zoning is a regionalisation strategy recognised by the World Organisation for Animal Health (OIE), which aims to identify those geographical regions that include groups of herds at similar risk for a given disease (16). Areas at high risk of the disease may be selectively targeted, as part of a national surveillance and control programme, to try to limit its economic and social impact. In turn, identifying areas at low risk of the disease may indicate where epidemiological and ecological conditions are most favourable for the implementation of eradication strategies. Moreover, the nature and extent to which management practices influence disease risk may be quantified, to aid in implementing regional control programmes. Multiple regression models, for example, can be used to identify factors and conditions that increase or decrease the risk of the disease locally. This information could ultimately help to guide producers to use management practices that contribute to reducing the incidence and prevalence of the disease.

Since, as stated above, the cost of the TB eradication programme in Argentina is entirely met by the producer, the initial investment needed to implement the control plan and the time horizon necessary to obtain the revenues from this initial investment are important components of the evaluation. The time period necessary to obtain these revenues (20 years) is probably too long, particularly in view of the fact that unstable social and economic conditions discourage long-term investment in developing countries. Social and economic instability certainly affects the willingness of producers to commit to the long-term efforts required to control chronic diseases, such as TB. This is compounded by the large financial resources required during the initial stages of implementation of a control programme in the herd. The results presented here suggest that the current test-and-cull programme, using CFT, is probably the most efficient way of controlling TB in Argentina. However, producers may well decide that a programme funded entirely by them is not feasible and support from external sources, such as the government or the dairy industry, may be necessary to control the disease on a national scale.

Simulation modelling has certain limitations that may have affected the results presented here. For example, uncertainty about the true value of certain epidemiological conditions (such as the association between disease status and productive and reproductive performance, and the biological variation expected for certain parameters, such as the latency period and transmission rate) led to the use of inflated distributions in the model. This increased the uncertainty of the results. Moreover, the analytical approach presented here was used to evaluate the feasibility of the programme *post facto*. Modelling exercises like the one presented here would be most beneficial if they were applied *before* the design and implementation of the control programme, so that control measures could be modified according to the model's results.

In conclusion, the authors used epidemiological modelling to develop an analytical framework to evaluate the feasibility of the TB control programme in Argentina. The results stressed the need for implementing regionalised programmes and for exploring the possibility of financial incentives to encourage producers to implement and adhere to the eradication programme in their herds. This analytical approach could be extended to help in designing and evaluating eradication programmes for TB and other livestock diseases in other countries.

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Utilisation de modèles pour déterminer la possibilité d'éradiquer la tuberculose bovine en Argentine

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Résumé
Les efforts déployés par les pays pour contrôler et éradiquer la tuberculose bovine se heurtent à des difficultés inhérentes aux caractéristiques épidémiologiques et écologiques de la maladie. Les auteurs ont recouru à la modélisation épidémiologique pour élaborer un cadre analytique visant à évaluer la possibilité de mettre au point un programme national d'éradication de la tuberculose bovine en Argentine. Les résultats de l'étude confirment la viabilité économique à long terme du programme de prophylaxie actuellement en vigueur. Toutefois, les coûts du programme d'éradication de la tuberculose bovine en Argentine étant entièrement pris en charge par les producteurs, le montant de l'investissement initial et le fait que le retour sur investissement ne se produit qu'à un horizon lointain sont souvent dissuasifs pour les éleveurs. La régionalisation des programmes avec des stratégies de prophylaxie différenciées suivant les régions pourrait améliorer les perspectives de succès. Cette approche méthodologique pourrait être utilisée pour concevoir et évaluer des programmes de prophylaxie et d'éradication de la tuberculose bovine ou d'autres maladies infectieuses dans d'autres régions du monde.

Mots-clés
Argentine – Épidémiologie – Modélisation – *Mycobacterium bovis* – Tuberculose – Tuberculose bovine.

Modelos para evaluar la viabilidad de erradicar la tuberculosis bovina en Argentina

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Resumen
La tuberculosis bovina (TB) presenta una serie de características epidemiológicas y ecológicas que han mermado la capacidad de los países para controlarla y erradicarla. Los autores, sirviéndose de modelos epidemiológicos, han creado un sistema analítico para evaluar las posibilidades de éxito de un programa nacional de erradicación de la TB en Argentina. Los resultados del estudio indican que el actual programa de lucha es económicamente viable a largo plazo. Sin embargo, teniendo en cuenta que son los propios productores quienes asumen íntegramente los costos del programa argentino de erradicación de la TB, la inversión inicial requerida y los largos plazos necesarios para rentabilizarla pueden disuadir a los productores de adherirse al programa. Quizá las probabilidades de éxito aumenten con programas por regiones, que permitan la aplicación de estrategias de lucha diferenciadas en ciertas zonas. Cabría extender a otras regiones del mundo este planteamiento metodológico para concebir y evaluar programas de control y erradicación de la TB y otras enfermedades infecciosas.

Palabras clave
Argentina – Elaboración de modelos – Epidemiología – *Mycobacterium bovis* – Tuberculosis – Tuberculosis bovina.

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Notes / Apuntes

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