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A model of animal–human brucellosis transmission in Mongolia

J. Zinsstag [a,*], F. Roth [a], D. Orkhon [b], G. Chimed-Ochir [c], M. Nansalmaa [d], J. Kolar [e], P. Vounatsou [a]

[a] *Swiss Tropical Institute, P.O. Box, CH-4002, Basle, Switzerland*
[b] *Ministry of Public Health, Olympic Street 2, Ulaan Baatar 11, Mongolia*
[c] *Infectious Disease Research Centre, P.O. Box 48, Ulaan Baatar, Mongolia*
[d] *Mongolian Academy of Sciences, Post Office 20A, P.O. Box 8, Ulaan Baatar 210620, Mongolia*
[e] *Podbelohorska 38, CR-150 00 Praha, Czech Republic*

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Abstract

We developed a dynamic model of livestock-to-human brucellosis transmission in Mongolia. The compartmental model considers transmission within sheep and cattle populations and the transmission to humans as additive components. The model was fitted to demographic and seroprevalence data (Rose Bengal test) from livestock and annually reported new human brucellosis cases in Mongolia for 1991–1999 prior to the onset of a mass livestock-vaccination campaign (S19 *Brucella abortus* for cattle and Rev1 *Brucella melitensis* for sheep and goat). The vaccination effect was fitted to livestock- and human-brucellosis data from the first 3 years of the vaccination campaign (2000–2002). Parameters were optimized on the basis of the goodness-of-fit (assessed by the deviance). The simultaneously fitted sheep–human and cattle–human contact rates show that 90% of human brucellosis was small-ruminant derived. Average effective reproductive ratios for the year 1999 were 1.2 for sheep and 1.7 for cattle.

Keywords: *Brucella* spp.; Animal–human transmission model; Livestock vaccination; Sheep; Cattle; Public health; Mongolia

* Corresponding author. Tel.: +41 61 284 81 39; fax: +41 61 284 81 05.
E-mail address: jakob.zinsstag@unibas.ch (J. Zinsstag).

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1. Introduction

Brucellosis is one of the world's major zoonoses (Boschiroli et al., 2001). Human brucellosis commonly is caused by exposure to infected livestock and livestock products (mostly raw milk and milk products). The clinically most-important causative bacteria in humans are in decreasing order of severity of illness: *Brucella melitensis* (small ruminants), *Brucella abortus* (cattle), *Brucella suis* (pigs) and *Brucella canis* (dogs). There is no recorded transmission of the infection between humans (Krauss et al., 1996) but humans can very rarely infect animals (Parnas et al., 1966). In humans, mortality is negligible, but the illness can last for several years (Madkour, 2001). In animals, brucellosis mainly affects reproduction and fertility, reduces survival of newborns (Sewell and Brocklesby, 1990) and reduces milk yield. Mortality of adult animals is insignificant (Sewell and Brocklesby, 1990).

Control strategies available to prevent human infection are pasteurisation of milk, livestock vaccination and the elimination of infected animals. In Mongolia, after numerous surveys in the 1960s, the World Health Organization (WHO) came to the conclusion that livestock vaccination was the only effective way to control brucellosis. The production of livestock vaccines successfully was established in the early 1970s and a country-wide mass-vaccination program of livestock planned for 11 years started in1975 under difficult field conditions. The vaccination of livestock successfully reduced human incidence of brucellosis to less than one case per 10,000 per year (Kolar, 1977). The vaccination program was interrupted in the early 1980s due to the end of WHO assistance and democratic reform followed by the shift away from dependence on the former Soviet Union in 1990; human brucellosis re-emerged. Based on a request of the Mongolian Government to WHO to provide assistance again in brucellosis control and to resurrect the vaccination program and recommendations made to the WHO and the Mongolian government (Garin-Bastuji, 1999), a whole-herd vaccination strategy covering 10 years was developed (Mikolon, 1999) to start in 2000.

Available models of brucellosis transmission consider only transmission between single livestock species and no transmission to humans, although brucellosis is transmitted to humans from both small ruminants (sheep and goat) and cattle (Roe, 1977; Carpenter et al., 1987; Dalrymple, 1993; Gonzalez-Guzman and Naulin, 1994). Our main objective was to develop a dynamic model of livestock-to-human brucellosis transmission to estimate demographic (birth rate, mortality) and transmission parameters (contact rates) between livestock and livestock to humans as an underlying basis for a cost-effectiveness analysis of a nation-wide mass-vaccination programme for livestock, which is reported elsewhere (Roth et al., 2003). Minor objectives were: (1) to fit vaccination parameters to data on the first 3 years of the national brucellosis livestock-vaccination campaign in Mongolia and (2) to simulate the brucellosis epidemic with and without specified interventions.

2. Materials and methods

2.1. Data collection

Livestock demographic data were provided by the Mongolian Statistical Office (Mongolian Statistical Yearbook, 1999). Animal brucellosis-seroprevalence survey data

(Rose Bengal; RBT) were provided at the provincial level for cattle and sheep for the years 1990–1999 by the Ministry of Agriculture for the model fit without intervention (Appendix A). The RBT is a simple and inexpensive test to detect antibodies against *Brucella* spp. in serum of many species. For the diagnosis of *B. melitensis* in sheep its sensitivity and specificity were recently estimated at 95 and 100% against culture (Ferreira et al., 2003). However, other authors point out that sensitivity and specificity vary in different settings and depending on investigators (Maichomo et al., 1998; Ostanello et al., 1999; MacMillan, 1997). The seroprevalence in cattle and sheep varied between 0.5 and 3%. (S.E. $\leq$ 0.045% in cattle and $\leq$0.035% in sheep). Data on the ongoing mass-vaccination campaign were provided from 2000 to 2002 (Appendix A). The quality of the available official national demographic and seroprevalence data presented could not be checked, but ongoing studies on brucellosis in livestock indicate that the reported seroprevalence is underestimated (A. Mikolon, personal communication). Our analysis is thus rather conservative with regard to the importance of brucellosis and was restricted to seroprevalences provided by the RBT. Baseline disease data on reported cumulative incidence of human brucellosis listed by province (Mongolian: Aimag), for 1990–1999, were provided by the Infectious Disease Research Institute (IDRI) in Ulaan Baatar. The human-brucellosis data are comprised of annually reported human cases that were diagnosed clinically and in general confirmed by two of the following tests (RBT, Huddelson or Wright). These tests were not standardized between the different Mongolian provinces. However, Mongolian physicians have long-standing experience with diagnosing clinical brucellosis and we see no reason to suspect that accuracy of clinical diagnosis would have changed in the decade of data we used. Brucella cultivation from human patients rarely is attempted.

2.2. Model

2.2.1. General considerations

We developed a deterministic model with stochastic parameter specification of animal-to-human brucellosis transmission in steps of 1 year (t) (Table 1 and Fig. 1), which is adapted to the availability of data for validation. Because only data on seropositive animals were available, we used (instead of ''infectious'' and ''recovered'' compartments), only one ''seropositive'' compartment. We considered transmission between sheep, between cattle, and from both livestock species to humans. We omitted the transmission between goats and from goats to humans due to the lack of data. We neither account for brucellosis in yaks and camels, nor for transmission between cattle and small ruminants for the same reason. Sheep total-population data are only available for the years 1995–1999. We reconstructed the total population for the years 1990–1994 by linear regression on the years 1995–1999 in analogy to the almost-linear growth of the cattle population. A posteriori, the sheep-brucellosis component was refitted to data on sheep population and brucellosis prevalence found after extensive archive studies in Ulaan Baatar for the years 1984–1999 (F. Roth, personal communication). Brucellosis affects mostly fertility and milk production. In the model, we consider a seroprevalence-dependent effect on sheep and cattle birth rates (Bernues et al., 1997) (see Section 2.3, Fig. 1, Table 1, Appendix B), e.g.

Table 1
List of fitted parameters to brucellosis transmission between sheep, cattle and humans and from sheep to human and cattle to humans with their 95% confidence limits and units (Figs. 2 and 3)

Parameter (symbol and description)	Estimate	95% confidence limits	Unit (remarks)	Distributions used in the sensitivity analyses
Sheep				
α_s Sheep birth rate	0.811	n.e., 0.83	$Year^{-1}$	Triangular (0.81, 0.826, 0.818)
β_s Sheep contact rate	$1.56\,e^{-7}$	n.e., $1.60\,e^{-7}$	$(Sheep * year)^{-1}$	Triangular ($1.69\,e^{-7}$, $1.5743\,e^{-7}$, $1.53422\,e^{-7}$)
β_{sh} Sheep-to-human contact rate	$1.127\,e^{-8}$	$1.124\,e^{-8}$, $1.127\,e^{-8}$	$(Sheep * year)^{-1}$	Triangular ($1.12\,e^{-8}$, $1.1279\,e^{-8}$, $1.12738\,e^{-8}$)
γ_s Proportion of infectious seropositive sheep	Uniform (0.2, 0.8)	–	Straight proportion	–
ε_s Immunity-loss parameter of seropositive sheep	0	–	$Year^{-1}$	Uniform (0, 0.022)
μ_s Mortality rate of sheep	0.78	0.774, 0.786	$Year^{-1}$	Triangular (0.81, 0.826, 0.818)
δ_s Snow-storm extra mortality in sheep	0.106	–	$Year^{-1}$	–
Cattle				
α_c Cattle birth rate	0.273	n.e., n.e.	$Year^{-1}$	Uniform (0.256, 0.285)
β_c Cattle contact rate	$3.49\,e^{-7}$	n.e., n.e.	$(Cattle * year)^{-1}$	Triangular ($3\,e^{-7}$, $3.49\,e^{-7}$, $4\,e^{-7}$)
β_{ch} Cattle-to-human contact rate	$2.11\,e^{-9}$	$2.09\,e^{-9}$, $2.13\,e^{-9}$	$(Cattle * year)^{-1}$	Triangular ($2.09\,e^{-7}$, $2.14\,e^{-7}$, $2.11\,e^{-7}$)
γ_c Proportion of infectious seropositive cattle	Uniform (0.1, 0.85)	–	Straight proportion	–
ε_c Cattle immunity-loss constant	0	–	$Year^{-1}$	–
μ_c Cattle mortality rate	0.226	n.e., n.e.	$Year^{-1}$	Uniform (0.256, 0.285)
δ_c Snow-storm extra mortality in cattle	0.221	–	$Year^{-1}$	–
Humans				
α_h Human birth rate	0.018	0.012, 0.023	$Year^{-1}$	Triangular (0.012, 0.023, 0.0181)
μ_h Human mortality rate	0.003	0.0001, 0.02	$Year^{-1}$	Triangular (0.0001, 0.02, 0.0031)

Parameter (symbol and description)		Assumption	Unit	
λ	End of registry constant	0.5 (definition)	$Year^{-1}$	–
κ	Registry	1	$Year^{-1}$	–
η	Prevalence dependent decrease of birth rate in sheep and cattle	Uniform (0.15, 0.5)	Straight proportion	–
t	Time	Steps of 1	Year	–

Distributions listed were used in the sensitivity analyses without interventions (Figs. 2–4) and with brucellosis mass vaccination (Fig. 5). n.e.: not estimated by the fitting algorithm; *: multiplication.

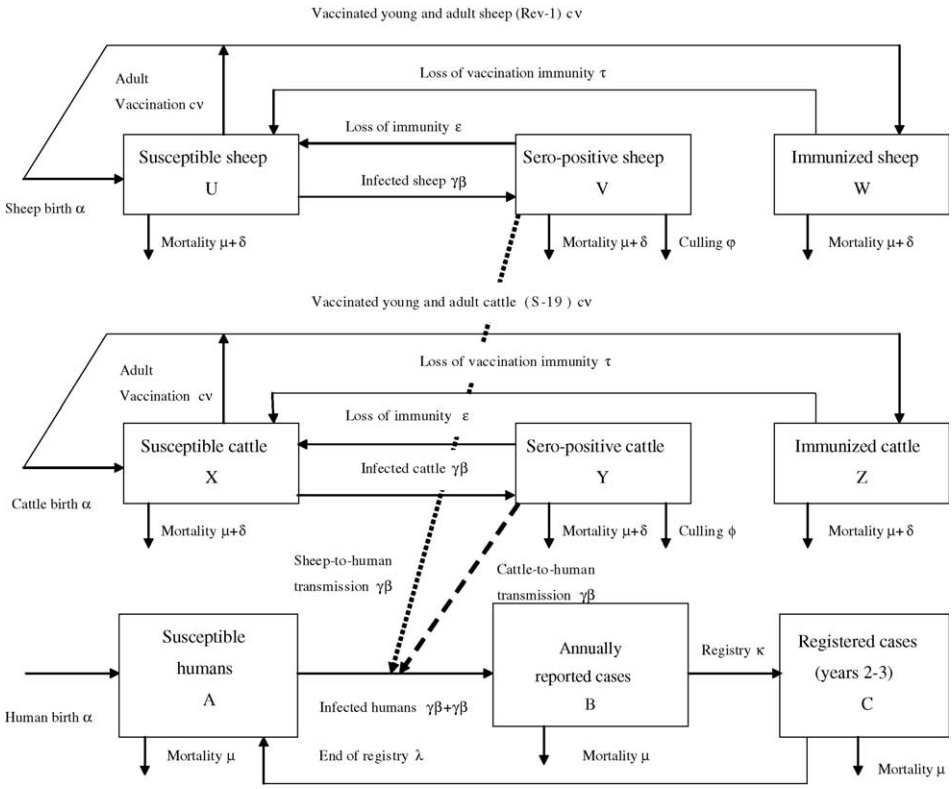

Fig. 1. Model for joint human–animal brucellosis transmission in Mongolia modified after Roth et al. (2003), with permission from the Bulletin of the World Health Organization.

for cattle

$$\alpha_{c(\text{effective})} = \alpha_{c(\text{baseline})}\left(1 - \left(\eta\left(\frac{Y}{(X+Y+Z)}\right)\right)\right) \tag{1}$$

where η is the prevalence-dependent reduction of birth rates α_c (including abortions) among the seropositive (expressed as uniform probability distribution, Table 1), X the number of susceptible, Y the number of seropositive and Z is the number of vaccine-protected cattle. The incidence (Fig. 1, infected sheep and cattle) is calculated by the product of γ_c (γ_s) (proportion of infectious), expressed as uniform probability distribution (see Table 1), the β (contact rate), the number of susceptible X (or U) and the number of seropositive Y (or V). Thus, the incidence in cattle is

$$\text{incidence}_{\text{cattle}} = \gamma_c \beta_c XY \tag{2}$$

2.3. Compartments and flows between compartments

Compartment U (Fig. 1) is the susceptible-sheep population (national sheep population of Mongolia minus V). Compartment V is the brucellosis-seropositive population. The size of V is obtained by multiplying the national sheep population with the prevalence estimated in annual surveys. Compartment W is the brucellosis-vaccinated sheep (Rev1). Compartment X is the susceptible-cattle population (national cattle population of Mongolia minus Y). Compartment Y is the brucellosis-seropositive cattle population. Its size is obtained by multiplying the national cattle population with the prevalence estimated in annual surveys. Compartment Z is the brucellosis-vaccinated cattle (S19 vaccine).

Compartment A represents the whole Mongolian human population, because precise estimates of the population at risk are not available. In Mongolia, reported Brucellosis patients are officially registered for 3 years. Compartment B represents the annually newly registered brucellosis patients and compartment C the registered patients between years 2 and 3 of state registration, after which they are considered no longer as registered brucellosis patients. Thus, the annual rate of flow (κ) from B to C (Fig. 1, registry) by definition = 1 and the end-of-registry constant = 0.5, i.e. inverse of the duration of registration in compartment (C). In this way, the model takes Mongolian health policy into account.

The descriptions of flows (Fig. 1) are as follows: flows into the susceptible-sheep compartment (U) are *sheep birth*, *loss of immunity* and *loss of vaccination immunity*: *sheep birth* (unit: sheep/year) = $\alpha_s(U + V + W)(1 - (\eta(V/(U + V + W))))(1 - c_{ys}\nu_{Rev1})$, where α_s is the birth rate of sheep (Table 1), multiplied by the sum of all compartments ($U + V + W$). This term is again multiplied by a seroprevalence—($U/U + V + W$) dependent decrease of sheep birth rate ($1 - \eta$) (Bernues et al., 1997). For the simulation of intervention, the whole term is multiplied by 1 minus the proportion of vaccination protected sheep ($c_{ys}\nu_{Rev1}$) (Table 2), where c_{ys} is the vaccination coverage of newborn sheep and ν_{Rev1} is the proportion of reduction of transmission of Rev1 vaccine (see below). The *loss of immunity of sheep* (unit: sheep/year) is considered by the term $\varepsilon_s V$, where ε_s is an immunity-loss parameter (Table 1) multiplied with compartment V (seropositive sheep). *Loss of vaccination immunity in sheep* (Rev1) (unit: sheep/year) = $\tau_{Rev1}W$, where τ_{Rev1} is a vaccination-immunity-loss parameter multiplied with compartment W (immunized sheep). Flows out of compartment U are *mortality* of susceptible sheep, *infected sheep* and *vaccinated young and adult sheep* (*Rev1*): *mortality* (unit: sheep/year) of susceptible sheep = $-(\mu_s U + \delta_s U)$, where μ_s is the mortality rate of sheep and δ_s is the extra mortality rate of sheep due to the snow-storm disasters (see below). *Infected sheep* (=incidence in sheep) (unit: sheep/year) is = $-\gamma_s\beta_s UV$ in analogy to Eq. (2) (see above). *Vaccinated young and adult sheep* (*Rev1*) (unit: sheep/year) is composed of the proportion of protected young sheep as fraction $-c_{ys}\nu_{Rev1}$ of *sheep birth*, and adult sheep vaccination = $-c_{as}\nu_{Rev1}U/3$, where c_{as} is the coverage of adult-sheep vaccination and ν_{Rev1} is the efficacy of Rev1 vaccine. The division by three of the adult vaccination accounts for two rounds of adult vaccination in 6 years. Flows into compartment U appear as positive terms and flows out of compartment U as negative terms in the differential Eq. (A.1) dU/dt in Appendix B. All other differential equations are constructed in the same way.

Flows going into the compartment of seropositive sheep V are *infected sheep* as described above. Flows out of compartment V are *mortality* of seropositive sheep *loss of*

Table 2
Intervention-related parameters used in the model

Parameter (symbol and description)		Assumption	Unit (remarks)
Sheep			
ν_{Rev1}	Vaccine efficacy of Rev1	0.65	Straight proportion
τ_{Rev1}	Inverse duration of vaccination protection of Rev1	Uniform (0.2, 0.25)	$Year^{-1}$
c_{as}	Vaccination coverage adult sheep	Scenario no vaccination = 0 Scenario 5065 = 0.5 Scenario 8065 = 0.8 Scenario 80100 = 0.8	$Year^{-1}$
c_{ys}	Vaccination coverage young sheep	Scenario no vaccination = 0 Scenario 5065 = 0.5 Scenario 8065 = 0.8 Scenario 80100 = 0.8	$Year^{-1}$
φ_s	Proportion tested and slaughtered sheep	Scenarios with and without vaccination = 0 Scenario test and slaughter 40% = 0.4	$Year^{-1}$
Cattle			
ν_{S19}	Vaccine efficacy of S19	0.65	Straight proportion
τ_{S19}	Inverse duration of vaccination protection of S19	Uniform (0.125, 0.142)	$Year^{-1}$
c_{ac}	Vaccination coverage adult cattle	Scenario no vaccination = 0 Scenario 5065 = 0.5 Scenario 8065 = 0.8 Scenario 80100 = 0.8	$Year^{-1}$
c_{yc}	Vaccination coverage young cattle	Scenario no vaccination = 0 Scenario 5065 = 0.5 Scenario 8065 = 0.8 Scenario 80100 = 0.8	$Year^{-1}$
φ_c	Proportion tested and slaughtered cattle	Scenarios with and without vaccination = 0 Scenario test and slaughter 40% = 0.4	$Year^{-1}$

immunity and *test and slaughter* of seropositive sheep. *Mortality* of seropositive sheep $V = -(\mu_s V + \delta_s V)$ is analogous to the mortality of susceptible sheep (see above) but for the compartment *V*. *Test and slaughter* (unit: sheep/year) of seropositive sheep = $-\varphi_s V$, where φ_s is the proportion of tested and slaughtered sheep multiplied with *V*. The *loss of immunity* is already described above but appears as negative term $-\varepsilon_s V$ in the differential equation (A.2) (dV/dt) in Appendix B. Flows going into the compartment of immunized sheep *W* are *vaccinated young and adult sheep* (*Rev1*): adult-sheep vaccination = $(c_{as}\nu_{Rev1}U)/3$ (see above) and young-sheep vaccination = $(c_{ys}\nu_{Rev1})(\alpha_s(U + V + W)(1-(\eta(V/(U + V + W)))))$. The latter term expresses the fraction of newborn sheep being protected from transmission (see above: sheep birth). Flows going out of compartment *W* are *mortality* of immunized sheep and *loss of vaccination immunity* of sheep. *Mortality* of immunized sheep *W* is $-(\mu_s W + \delta_s W)$ in analogy to the mortality of susceptible and seropositive sheep but

multiplied with W. The *loss of vaccination immunity* (unit: sheep/year) of sheep = $-\tau_{\mathrm{Rev1}}W$ is analogous to the description above but as a negative term. Adult- and young-sheep vaccination appear as positive terms in differential equation (A.3) (dW/dt) in Appendix B, whereas mortality of immunized sheep and the loss of vaccination immunity of sheep are negative terms.

Flows into the cattle compartments are analogous to those for sheep. Vaccinations of newborn cattle are accounted by multiplying the whole term with $(1 - (c_{\mathrm{yc}}\nu_{\mathrm{S19}}))$ where c_{yc} (Table 2) is the vaccination coverage of young cattle and ν_{S19} is the proportion of reduction of transmission resulting from the S19 vaccine (see below).

Flows into compartment A (susceptible humans) are *human birth* and *end of registry*. *Human birth* (unit: humans/year) = $\alpha_{\mathrm{h}}(A + B + C)$ where α_{h} is the human birth rate multiplied by the sum of all human compartments. *End of registry* (unit: humans/year) = λC, where λ is the end-of-registry (i.e. end of any one person's inclusion in the registry) constant multiplied with compartment C (registered cases in years 2–3). Flows out of A are *infected humans* and *mortality* of susceptible humans. *Infected humans* (unit: humans/year) (animal-to-human transmission) = $-((\gamma_{\mathrm{c}}\beta_{\mathrm{ch}}AY) + (\gamma_{\mathrm{s}}\beta_{\mathrm{sh}}AV))$ is described below. *Mortality* (unit: humans/year) of susceptible humans is = $\mu_{\mathrm{h}}A$, where μ_{h} is the mortality rate of humans multiplied with compartment A. (Changes of compartment A are expressed in Eq. (A.7) (dA/dt) in Appendix B.) Flows into compartment B are *infected humans* = $((\gamma_{\mathrm{c}}\beta_{\mathrm{ch}}AY) + (\gamma_{\mathrm{s}}\beta_{\mathrm{sh}}AV))$, which take a positive sign for this compartment. Flows out of B are *mortality* and *registry*. *Mortality* (unit: humans/year) of annually reported cases = $\mu_{\mathrm{h}}B$ in analogy for compartment A. *Registry* (unit: humans/year) = $-\kappa B$, with the registry constant $\kappa = 1$ as outlined above. Eq. (A.8) (dB/dt) considers changes of annually reported cases. Finally, flows into compartment C are *registry* cases and flows out of C are *end of registry* and *mortality* of registered cases (years 2–3). *Registry* = κB and *end of registry* (unit: humans/year) = $-\lambda C$, where λ is the end of registry parameter multiplied with C. *Mortality* of registered cases = $-\mu_{\mathrm{h}}C$ in the same way as for compartments A and B. (Eq. (A.9), (dC/dt) specifies changes among the registered cases.)

2.4. Fitting the transmission model

The fitting of the model to the data was done with Vensim™ systems-analysis software (Ventana Systems Inc., 60 Jacob Gates Road, Harvard, MA, USA; www.vensim.com) using the Powell nonlinear maximum-likelihood optimization algorithm (Press et al., 1991). Parameters were optimized on the basis of the goodness-of-fit, which is called "payoff" in Vensim software. The payoff compares the log likelihood of the current model with the log likelihood of a perfect model (having as many parameters as data points). The best model is the one with smallest payoff. In the first step, mortality and birth rates were optimized for the susceptible sheep (U), cattle (X) and humans (A) (Fig. 1). Birth rates were expressed proportionally to the total populations; mortality parameters in livestock included natural mortality and off take. In the second step, the transmissions within sheep and within cattle were fitted by fixing the demographic parameters. To fit the transmission process, the proportions of infected V and Y were expressed as uniform probability distributions and their boundaries were varied to identify the best fit (in terms of the deviance) of contact rates for the transmission between sheep and between cattle and the

loss of immunity. The transmission to humans is expressed as additive contributions of transmission from sheep and cattle to humans (Fig. 1, sheep-to-human transmission; cattle-to-human transmission):

$$(\gamma_{\text{sheep}}\beta_{\text{sheep}}AV) + (\gamma_{\text{cattle}}\beta_{\text{cattle}}AY) \quad (3)$$

where A is the susceptible human population. The effective reproductive ratio and threshold vaccination coverage were estimated according to Scott and Smith (1994), using the confidence limits of the proportions of infectious animals obtained during the fitting process. Long-term properties were investigated by keeping the animal populations stable from year 1999 onwards (in keeping with the limited carrying capacity of Mongolian pasture).

2.5. Fitting of the vaccination interventions

In the year 2000, the Mongolian authorities started the mass vaccination of their ruminants. However, the onset of the vaccination campaign coincided with consecutive snow-storm disasters in the winters 1999–2002 and the loss of >7 million animals. (A concurrent outbreak of foot-and-mouth disease in 2001 was not taken separately into account because of the lack of disease-specific data.) These massive demographic changes had to be considered for the fitting and validation of the vaccination campaign. Thus, the demographic change of the snow-storm disasters were fitted as an extra mortality from 1999 to 2002. The estimated mortality rates of cattle δ_c and sheep δ_s due to the snow-storm are 22 and 10% per year, respectively. The extra snow-storm mortalities were used for the fitting process of the vaccination campaign but not for the simulations of the different vaccination scenarios (see below). For the fitting of the vaccination campaign, the vaccination efficacy and vaccination coverage (see below) were optimized against the reported seroprevalence of brucellosis in sheep and cattle and the reported cases of human brucellosis.

2.6. Simulation of vaccination and test-and-slaughter scenarios

The current practice in Mongolia (since 1990) consists of low-level surveillance, with occasionally required testing of livestock herds followed by voluntary slaughter of seropositive animals without compensation. The present vaccination strategy (since 2000) aims to vaccinate all adult animals twice within 6 years (1/3 of the total adult population per year). All animals born during the 10 years of the plan will be vaccinated once (at <1 year of age). The reported efficacy in reducing transmission was measured as the prevented fraction $(1 - R)$, where R is the relative risk of disease in those who received the intervention compared to those who do not (Smith and Morrow, 1991). The vaccines used in cattle (Strain B19, *B. abortus*) and small ruminants (Rev1, *B. melitensis*) should reduce transmission by at least 65% (Nicoletti, 1977). These efficacies include also potential losses due to cold-chain deficiency (Mikolon, personal communication). Vaccine-coverage scenarios were set to 50 and 80% (same scenarios for sheep and cattle). The proportion of protection (PP) is computed as the product of the reduction of transmission $\nu_{(\text{Rev1;S19})}$ of the respective vaccine and the vaccination coverage $c_{(\text{ys;as;yc;ac})}$ (Eq. (4)). The proportion of protection of vaccinated young

and adult sheep and young and adult cattle were the product of vaccine-related reduction of transmission and vaccination coverage.

$$\mathrm{PP} = c\nu \tag{4}$$

Three different vaccination scenarios were considered assuming PP of 32% ($\nu = 65\%$; $c = 50\%$); 52% ($\nu = 65\%$; $c = 80\%$) and 80% ($\nu = 100\%$; $c = 80\%$), respectively. For Rev1, we considered an annual loss of vaccination immunity as a random function (uniform (0.2, 0.25); inverses of the duration of vaccination immunity of 4–5 years, WHO, 1998) and for S19, an annual loss of vaccination immunity as a random function (uniform (0.125, 0.142); inverses of duration of vaccination immunity of 7–8 years, AFSSA, 2001). The FAO (J. Otte) suggested including the testing and slaughtering of seropositive animals as a separate intervention. For the simulation, the current capacity of livestock RBT of the Mongolian veterinary laboratories was doubled to consider the proportion φ_c for cattle and φ_s for sheep of 40% of animals being tested and the seropositive animals removed.

2.7. Sensitivity analyses

Sensitivity analyses were done for the fitting of the model without interventions and for the intervention scenarios of 52% PP. For this we used multivariate Monte Carlo sensitivity simulation (MVSS) in Vensim™ with 200 simulations over the range of parameters specified in Table 1 (first column on the right). Monte Carlo multivariate sensitivity works by sampling a set of numbers from within bounded domains. To perform one multivariate test, the distribution for each parameter specified is sampled, and the resulting values used in a simulation. All simulations then are summarized by calculating mean values and 95% confidence limits.

3. Results

3.1. Parameter optimization without interventions

The model fitted the susceptible livestock and human populations very well (in Figs. 2a and 3, the observed and fitted values for cattle and humans overlie). The fits to the seropositive sheep and cattle and annually reported human brucellosis cases are presented in Figs. 2b and 3. In Table 1, the fitted parameters with their 95% confidence limits are presented. For sheep and cattle, the unknown proportions infectious were estimated by variation of their boundaries in a uniform distribution. The boundaries with the best payoff were then used in the model. For sheep, best payoff was obtained for a proportion of infectious ranging between 0.2 and 0.8 and for cattle between 0.1 and 0.85. The simultaneously fitted sheep–human and cattle–human contact rates show a contribution of small ruminant-derived human brucellosis of >90% indicating a dominance of *B. melitensis* in human brucellosis. Average effective reproductive ratios for the year 1999 indicated a slow-growing epidemic. The proportion of protection (Eq. (4)) needed to interrupt transmission was 0.46 for sheep and 0.66 for cattle. Long-term properties of the model (assuming stable sheep and cattle populations) predict a peak of seropositive

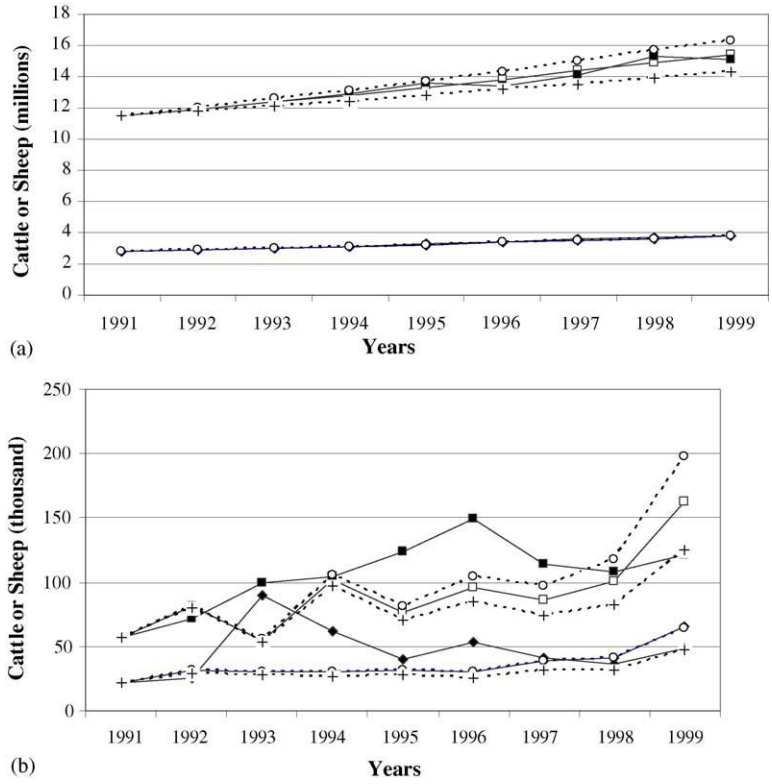

Fig. 2. (a and b) Fit of the model to livestock total population (a) and seropositive (b) data: filled squares, reported sheep population; empty squares, fitted sheep population (95% upper confidence limit, empty circles; and dashed line and 95% lower confidence limit, crosses with dashed line); filled diamonds, reported cattle population; empty diamonds, fitted cattle population (95% upper confidence limit, empty circles; and dashed line and 95% lower confidence limit, crosses with dashed line).

animals between 2020 and 2030 in sheep and between 2030 and 2040 in cattle. In humans, the growth rate between 1991 and 1999 was maintained and human brucellosis would peak, in parallel to that in sheep between 2020 and 2030.

3.2. Fit of vaccination interventions

After fitting the transmission model to the period from 1990 to 1999 (Figs. 2 and 3), during which no vaccination intervention happened, we used the estimated parameters to fit the model to the starting period of the national livestock brucellosis-vaccination campaign from 2000 to 2002. For sheep and cattle, the fitted vaccination campaign follows the trends of the observed seroprevalences. In a simultaneous fit, the fitted coverages are 0.97 (95% CI 0.57, 1) for young sheep (c_{ys}), 1 (not estimated, 1) for adult sheep (c_{as}),1 (95% CI 0.43, 1) for young cattle (c_{yc}), 1 (0.45, 1) and for adult cattle (c_{ac}) (Table 2). The vaccine efficacies are 0.63 (0.45, 0.84) for Rev1 (ν_{Rev1}) and 1 (0.72, 1) for S19 (ν_{S19}). The number of

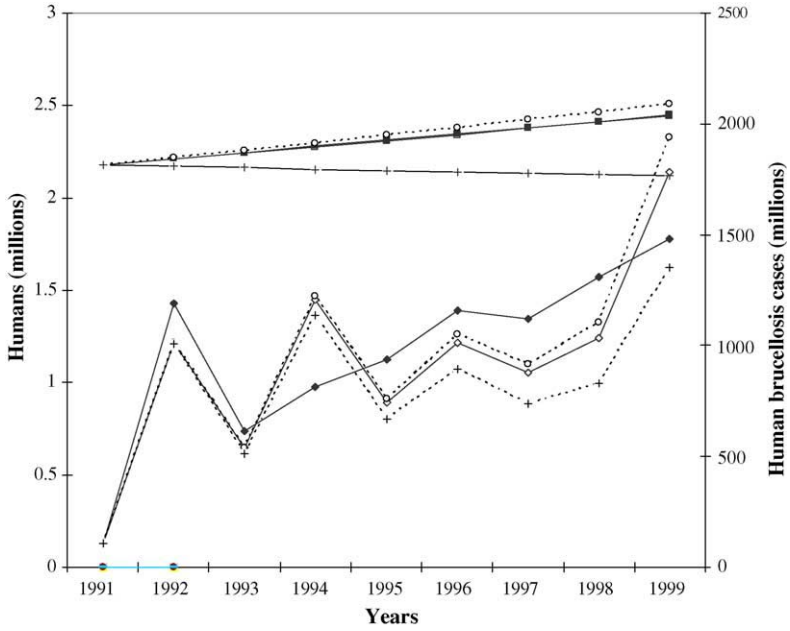

Fig. 3. Fit of the model to human total population and human brucellosis patient data: filled squares, reported susceptible human population; empty squares, fitted susceptible human population (95% upper confidence limit, empty circles; and dashed line and 95% lower confidence limit, crosses with dashed line); filled diamonds, reported human brucellosis cases (compartment *B*); empty diamonds, fitted, human brucellosis cases (95% upper confidence limit; empty circles and dashed line and 95% lower confidence limit, crosses with dashed line).

predicted vaccinated animals overshoots in the first year the reported number and fits better in the consecutive years (data not shown).

3.3. Simulation of specified interventions

3.3.1. Vaccination

A sensitivity analyses with and without the intervention scenario of 52% PP are presented in Figs. 4 and 5. In sheep, the reported seroprevalences for the years 2000–2002 agree best with a trend between the scenarios of 52 and 80% protection (Fig. 6a). In cattle, the simulated vaccination scenarios follow the reported trend for the years 2000–2002 but at a higher level (Fig. 6b).

3.4. Test and slaughter

The simulation of the RBT of 40% of the sheep and the removal of the seropositives predicts a decrease comparable to that in the vaccination scenarios. The test-and-slaughter intervention appeared more effective to reduce brucellosis prevalence in cattle than the vaccination scenarios. However, neither the vaccination nor test-and-slaughter intervention scenarios in cattle lead to elimination by 10 years.

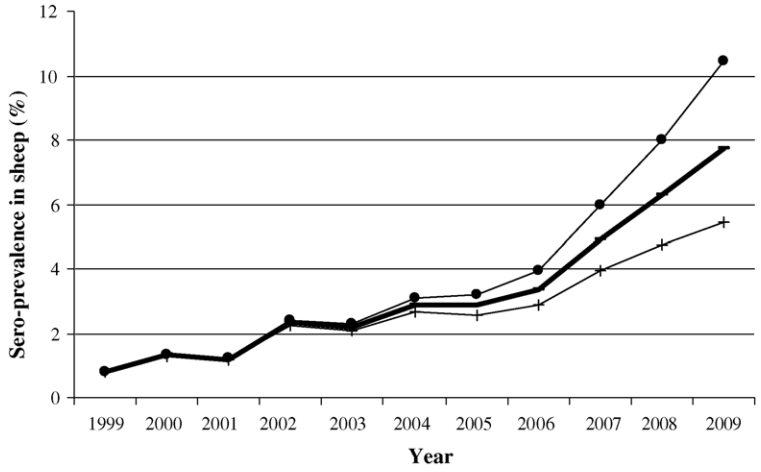

Fig. 4. Sensitivity analysis of the prediction of the brucellosis seroprevalence in sheep without intervention. Bold line: mean; filled circles: upper 95% confidence limit; crosses: lower 95% confidence limit.

4. Discussion

4.1. Model

To our knowledge, this reported model is the first comprehensive dynamic assessment of livestock-to-human brucellosis transmission fitted to a period of transmission with and without intervention. The model conception was adapted to the available data (only

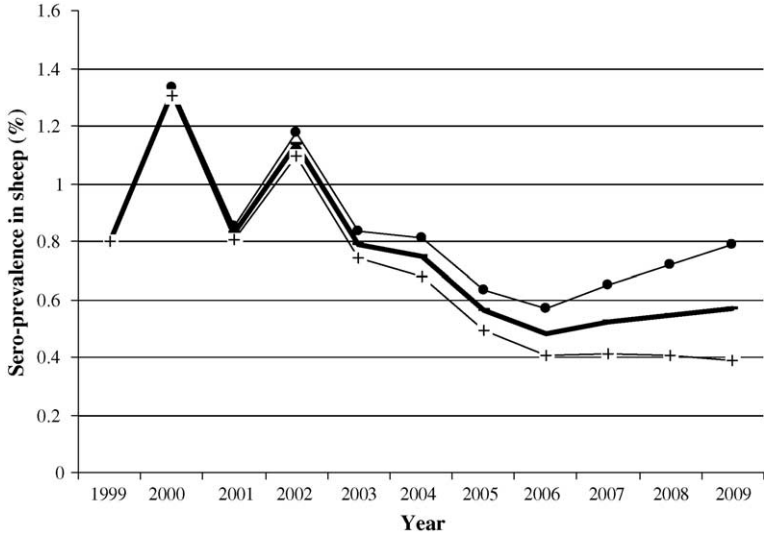

Fig. 5. Sensitivity analysis of the prediction of the brucellosis seroprevalence in sheep with the scenario of 52% PP using Rev1. Bold line: mean; filled circles: upper 95% confidence limit; crosses: lower 95% confidence limit.

seroprevalence data), the needs of economic assessment (Roth et al., 2003) and the consideration of the Mongolian brucellosis patient registry policy to adapt the analysis to the needs and decision pathways of the Mongolian authorities (Habicht et al., 1999). A more general model, without considering Mongolian registration policy, would need to include the duration of untreated human brucellosis and the loss of human post-infection immunity.

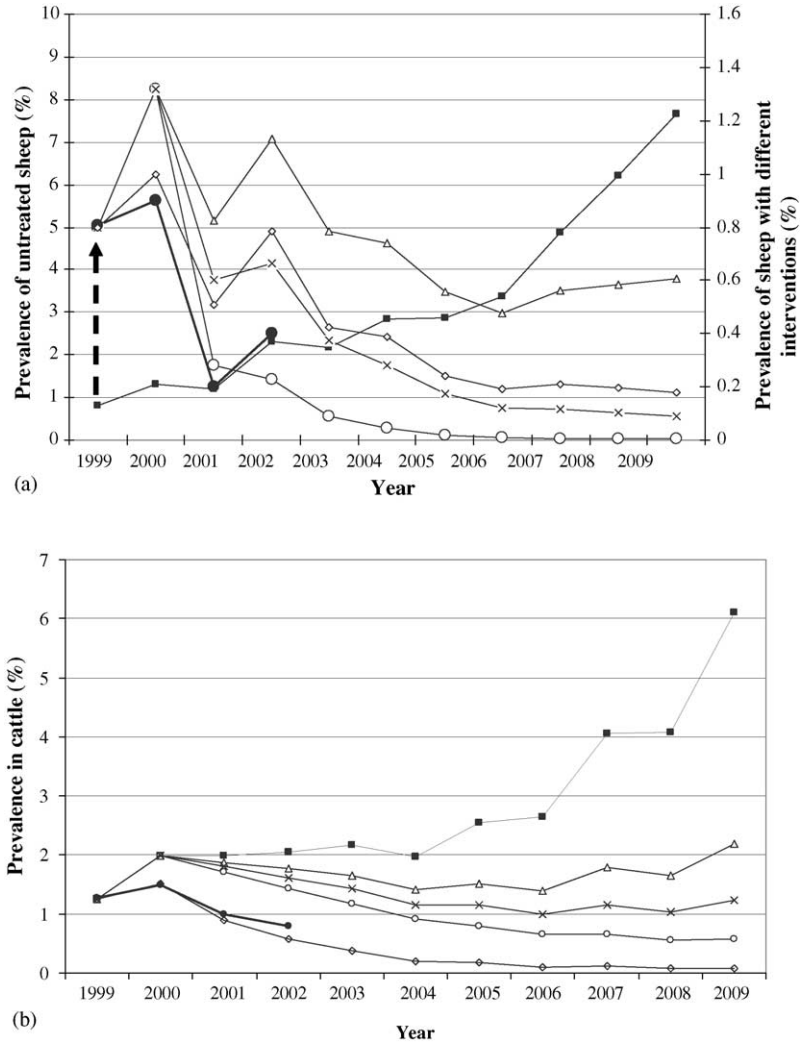

Fig. 6. (a–c) Effect of livestock brucellosis vaccination and test and slaughter of 40% of the sheep and cattle population (a and b) on human annual cumulative brucellosis incidence (c) (filled squares, control scenario; filled circles, reported vaccination; empty triangles, 32% proportion of protection; crosses, 52% proportion of protection; empty circles, 80% proportion of protection, empty diamonds, 40% test and slaughter; prevalences and cumulative incidences are given as straight proportions).

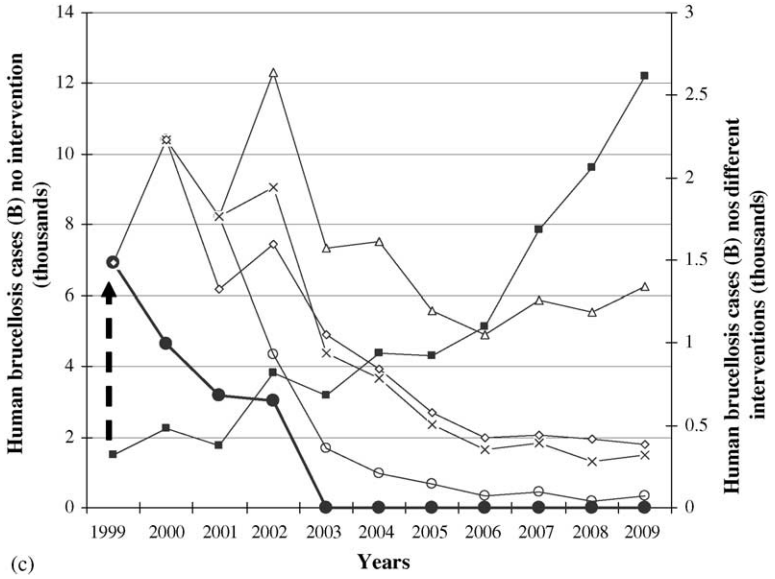

Fig. 6. (*Continued*).

The fit to the data seems satisfactory but the model captures only the large trends of the diseased compartments of livestock and humans (and not the smaller modulations). An estimation of the susceptible-sheep population for the missing years was done by linear backward extrapolation in analogy to the almost-linear growth trend of the cattle population (see Fig. 2a). A posteriori, the sheep-brucellosis component was refitted to a more complete data set and the contact rate β_s was 3% lower ($1.519\ e^{-7}$ against $1.56\ e^{-7}$) to the previous estimate based on the linear backward extrapolation of the susceptible sheep population. The proportions of infectious sheep and cattle might in fact range in more-narrow bands. Bürki and Sackmann (personal communication) estimate it between 50 and 60%, but the presented range yielded the best fit and is in line with Parnas et al. (1966) who estimated the range of shedders between 22 and 60%. That most human-brucellosis cases found in our model were small ruminant derived is in line with recent isolations of Brucella strains from human patients in Mongolia. All isolated strains ($n = 8$) were *B. melitensis* (Nansalmaa, personal communication).

The estimated threshold coverage of the vaccination must be corrected for the efficacy of the vaccines. The efficacy of Rev1 is considered to be 0.95 (AFSSA) and for S19 to be 0.7 (Nicoletti, 1977; WHO, 1998). This would need a corrected coverage of approximately 50% for sheep and 95% for cattle. The considerations on vaccine efficacy are also in line with observations by Denes (1997) in Mongolia. Our model shows higher numbers of vaccinated animals and a lower reduction of seroprevalence in livestock compared to the reported data. Nicoletti (personal communication, 2002) considers that the vaccine efficacy in mass vaccinations is actually much higher than that obtained in vaccine trials, due to the herd effect. This could explain partially the strong reduction of sheep and cattle prevalence obtained by the reported number of vaccinated animals. The long-term predictions have to be considered with caution, especially due to the recent massive demographic changes in the livestock

populations. The population should recover certainly from the consecutive snow-storm disasters; however, a comprehensive assessment of the effective carrying capacity of Mongolian pasture should inform policy on a sustainable regulation of livestock density.

4.2. Interventions

In general, the model mechanism is able to fit and simulate plausibly the different interventions. But, the long time-step causes oscillations and a lag period of the effect on human disease. The model predicts a decrease of seroprevalence in livestock by the vaccination campaign. After 10 years, the intervention strategies should be reviewed to consider that brucellosis might remain only in certain areas. In cattle, a test-and-slaughter policy should be considered at the end of the mass-vaccination campaign, if compensation could be offered for slaughtered animals. The model can produce estimates of the numbers of animals for which compensation is needed. The vaccination campaign seems more effective to reduce prevalence in sheep than in cattle. This work confirms the control strategy already chosen in the 1970s WHO brucellosis-control project, which effectively reduced human brucellosis through livestock mass vaccination (Kolar, 1977) and contributes a quantitative framework of analysis.

4.3. Limitations of the model

We did not consider geographical differences of the disease prevalence, age dependence, nor could we include goats (which might play an important role in the transmission to humans). The model could become smoother by reducing time steps to half-year or quarter-year intervals. This probably also would reduce the overestimation of the vaccinated animals in our model. We should bear in mind that the quality of the demographic and seroprevalence data are unknown, but the overestimation of the vaccinated animals and the provided coverage figures would indicate that the actual animal numbers are smaller than reported. The model could be used to assess other zoonoses and food-borne diseases. Improvements of the model should include spatial effects and might be formulated using Bayesian Markov Chain Monte Carlo methodology (Marshall et al., 2003)

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Appendix A

Data set to which the model was fitted in Vensim™ without vaccination intervention (years = 1991–1999) and to which the effect of the vaccination was fitted (years = 1999–2002).

Year	Sheep			Cattle			Humans	
	Number susceptible (*U*)	Number seropositive (*V*)	Seroprevalence (%)	Number susceptible (*X*)	Number seropositive (*Y*)	Seroprevalence (%)	Number susceptible (*A*)	Number of annually reported cases (*B*)
1991	11,468,330	57,630	0.50	2,765,217	22,044	0.80	2,179,560	108
1992	11,937,672	72,058	0.60	2,897,395	25,078	0.87	2,212,870	1,192
1993	12,393,552	99,948	0.81	2,968,915	90,140	3.04	2,246,180	616
1994	12,873,452	103,818	0.81	3,147,373	61,746	1.96	2,279,490	814
1995	13,595,133	123,467	0.91	3,276,856	40,242	1.23	2,312,800	937
1996	13,411,433	149,167	1.11	3,422,561	53,338	1.56	2,347,100	1,158
1997	14,105,744	113,756	0.81	3,571,865	41,033	1.15	2,379,600	1,122
1998	15,344,730	108,170	0.70	3,715,283	36,416	0.98	2,413,000	1,308
1999	15,069,770	121,530	0.81	3,776,780	48,018	1.27	2,446,400	1,482
2000[a]	13,876,400	124,888	0.90	3,097,600	46,464	1.50	2,407,500	992
2001[a]	11,937,300	23,875	0.20	2,069,600	20,696	1.00	2,442,500	685
2002[a]	10,636,602	42,546	0.40	1,884,279	15,074	0.80	2,432,229	652

Sample sizes for the prevalence estimates ranged between 80,000 and 260,000 in cattle and 100,000 and 340,000 in sheep.

[a] For these 3 years, the number of susceptible sheep (*U*) and cattle (*X*) include vaccinated sheep (*W*) and cattle (*Z*), respectively.

Appendix B. Differential equations for the fitting and simulation of vaccination

$$\frac{dU}{dt} = \varepsilon_s V + \tau_{Rev1} W + \left(\alpha_s (U+V+W)\left(1 - \left(\eta\left(\frac{V}{(U+V+W)}\right)\right)\right)\right) \times (1 - (c_{ys}\nu_{Rev1})) - \mu_s U - \delta_s U - \gamma_s \beta_s UV - c_{as}\nu_{Rev1}\frac{U}{3} \quad (A.1)$$

$$\frac{dV}{dt} = \gamma_s \beta_s UV - \varepsilon_s V - \mu_s V - \delta_s V - \varphi_s V \quad (A.2)$$

$$\frac{dW}{dt} = c_{as}\nu_{Rev1}\frac{U}{3} + \left(\alpha_s (U+V+W)\left(1 - \left(\eta\left(\frac{V}{(U+V+W)}\right)\right)\right)\right) \times (c_{ys}\nu_{Rev1}) - \mu W - \delta_s W - \tau_{Rev1} W \quad (A.3)$$

$$\frac{dX}{dt} = \varepsilon_c Y + \tau_{S19} Z + \left(\alpha_c (X+Y+Z)\left(1 - \left(\eta\left(\frac{Y}{(X+Y+Z)}\right)\right)\right)\right) \times (1 - (c_{yc}\nu_{S19})) - \mu_c X - \delta_c X - \gamma_c \beta_c XY - c_{ac}\nu_{S19}\frac{X}{3} \quad (A.4)$$

$$\frac{dY}{dt} = \gamma_c \beta_c XY - \varepsilon_c Y - \mu_c Y - \delta_c Y - \varphi_c Y \quad (A.5)$$

$$\frac{dZ}{dt} = c_{ac}\nu_{S19}\frac{X}{3} + \left(\alpha_c (X+Y+Z)\left(1 - \left(\eta\left(\frac{Y}{(X+Y+Z)}\right)\right)\right)\right)(c_{yc}\nu_{S19}) - \mu_c Z - \delta_c Z - \tau_{S19} Z \quad (A.6)$$

$$\frac{dA}{dt} = \alpha_h (A+B+C) + \lambda C - ((\gamma_s \beta_{sh} AV) + (\gamma_c \beta_{ch} AY)) - \mu_h A \quad (A.7)$$

$$\frac{dB}{dt} = ((\gamma_s \beta_{sh} AV) + (\gamma_c \beta_{ch} AY)) - \mu_h B - \kappa B \quad (A.8)$$

$$\frac{dC}{dt} = \kappa B - \mu_h C - \lambda C \quad (A.9)$$

References

AFSSA, Maisons Alfort (2001). La brucellose animale, http://www.afssa.fr.

Bernues, A., Manrique, E., Maza, M.T., 1997. Economic evaluation of bovine brucellosis and tuberculosis eradication programmes in a mountain area of Spain. Prev. Vet. Med. 30 (2), 137–149.

Boschiroli, M.L., Foulogne, V., O'Callaghan, D., 2001. Brucellosis: a worldwide zoonosis. Curr. Opin. Microbiol. 4 (1), 58–64.

Carpenter, T.E., Berry, S.L., Glenn, J.S., 1987. Economics of *Brucella ovis* control in sheep: epidemiologic simulation model. J. Am. Vet. Med. Assoc. 190 (8), 977–982.

Dalrymple, M., 1993. Model for assessing the risk of introducing brucellosis into a brucellosis-free area. Rev. Sci. Tech. 12 (4), 1175–1186.

Denes, B., 1997. Serological findings obtained in cattle herds immunised with the *Brucella melitensis* Rev.1 and the *B. abortus* B19 vaccine in Mongolia. Acta Vet. Hung. 45 (1), 33–43.

Ferreira, A.C., Cardoso, R., Travassos Dias, I., Mariano, I., Beloc, A., Rolão Preto, I., Manteigas, A., Fonseca, A.P., Corrêa De Sá, M.I., 2003. Evaluation of a modified Rose Bengal test and an indirect enzyme-linked immunosorbent assay for the diagnosis of *Brucella melitensis* infection in sheep. Vet. Res. 34, 297–305.

Garin-Bastuji, B., 1999. Report of a Mission to Mongolia from 2 to 16 April 1999, on the Epidemiological Surveillance and Control of Communicable Diseases of Public Health Importance, Including Zoonoses. World Health Organization, Geneva, p. 5.

Gonzalez-Guzman, J., Naulin, R., 1994. Analysis of a model of bovine brucellosis using singular perturbations. J. Math. Biol. 33 (2), 211–223.

Habicht, J.P., Victora, C.G., Vaughan, J.P., 1999. Evaluation designs for adequacy, plausibility and probability of public health programme performance and impact. Int. J. Epidemiol. 28 (1), 10–18.

Kolar, J., 1977. Brucella Vaccines Production in Mongolia. World Health Organization, Assignment Report on WHO Project MOG BLG 001, SEA/Vaccine/89, 40 pp.

Krauss, H., Weber, A., Enders, B., Schiefer, H.G., Slenczka, W., Zahner, H., 1996. Zoonotic diseases, infection diseases transmitted from animals to human (Original title in German: Zoonosen, von Tier auf den Menschen übertragbare Infek-tionskrankheiten), second ed., Deutscher Ärzte-Verlag Köln, 400 pp.

MacMillan, A.P., 1997. Investigation of the performance of the Rose Bengal plate test in the diagnosis of Brucella melitensis infection in sheep and goats. World Anim. Rev. 89, 2.In: http://www.fao.org/ag/AGa/AGAP/FRG/FEEDback/War/W6437t/w6437t09.htm#TopOfPage.

Madkour, M.M., 2001. Madkour's Brucellosis. Springer Verlag, Heidelberg, Berlin, 306 pp.

Maichomo, M.W., McDermott, J.J., Arimi, S.M., Gathura, P.B., 1998. Assessment of the Rose-Bengal plate test for the diagnosis of human brucellosis in health facilities in Narok district, Kenya. East Afr. Med. J. 75, 219–222.

Marshall, E.C., Frigessi, A., Stenseth, N.C., Holden, M., Ageyev, V.S., Klassovskiy, N.L., 2003. Plague in Kazakhstan: A Bayesian Model for the Temporal Dynamics of a Vector-Transmitted Infectious Disease. Technical Report Deptartment of Epidemiology and Public Health, Imperial College, London, http://www.med.ic.ac.uk/divisions/60/biostat/plague.ps.

Mikolon, A., 1999. Report of the WHO Mission to Mongolia from 14 August to 3 November, World Health Organization, Geneva, p. 74.

Mongolian Statistical Yearbook, 1999. Mongolian Statistical Office, Ulaan Baatar, Mongolia.

Nicoletti, P., 1977. Adult vaccination. In: Crawford, R.P., Hidalgo, RJ. (Eds.), Bovine Brucellosis. Texas A&M University Press, College Station, TX, pp. 177–188.

Ostanello, F., Farina, L., Turilli, C., Serra, P., Cagnolati, V., Abdullah, M., Scagliarini, A., Prosperi, S., 1999. Reliability of results of the Rose Bengal test performed for export control in northern Somalia. Rev. Sci. Tech. Off. Int. Epiz. 18, 660–666.

Parnas, J., Krüger, W., Töppich, E. (Eds.), 1966. Die Brucellose des Menschen (Human Brucellosis), VEB VErlag Volk und Gesundheit, Berlin, 566 pp.

Press, W.H., Flannery, B.P., Teukolsky, S.A., Viatour, P., 1991. Numerical Recipes in C, Cambridge, p. 309.

Roe, R.T., 1977. The application of computer simulation to the planning of the public investment in the control of animal disease. Ph.D. Thesis. Faculty of Veterinary Sciences, University of Melbourne, Australia.

Roth, F., Zinsstag, J., Orkhon, D., Chimed-Ochir, G., Nansalmaa, M., Hutton, G., Cosivi, O., Carrin, G., Otte, J., 2003. Human health benefits from livestock vaccination for brucellosis: a case study. Bull. World Health Organ. 81, 867–876.

Scott, M.E., Smith, G., 1994. Parasitic and Infectious Diseases: Epidemiology and Ecology. Academic Press, NY, USA.

Sewell, M.M.H., Brocklesby, D.W., 1990. Animal Diseases in the Tropics, fourth ed. Baillière Tindall, London, 385 pp.

Smith, P.G., Morrow, R.H. (Eds.), 1991. Methods for Field Trials of Interventions Against Tropical Diseases. Oxford University Press, New York, 326 pp.

WHO, 1998. The Development of New/Improved Brucellosis Vaccines. World Health Organization, WHO/EMC/ZDI/98, p. 14.