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Modeling the Zoonotic Transmission Dynamics of Brucellosis: Implication of Animal Health Policies on Human Health

브루셀라증의 사람-동물 전파 모형을 이용한 동물 방역 정책이 사람 건강에 미치는 영향 평가

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Abstract

Modeling the Zoonotic Transmission Dynamics of Brucellosis: Implication of Animal Health Policies on Human Health

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Since 2002, cases of human brucellosis are continuously reported in the Republic of Korea. Although the association between human and bovine brucellosis was identified, the effectiveness of animal-level interventions for human health was not quantitatively analyzed in the Republic of Korea. In this study, with the reported cases from the human and animal health database, the mathematical model for the zoonotic transmission dynamics of brucellosis was developed, which reflects the coordinated surveillance systems for the two diseases. Basic reproduction number was estimated and key factors in the dynamics were identified through sensitivity analysis. Moreover, scenarios of possible interventions including animal vaccination

policy that had been suspended were analyzed. The model was fitted to yearly reported cases from 2006 to 2018 in the country.

Given the estimated basic reproduction number, brucellosis would be eradicated. However, the frequency of surveillance for bovine brucellosis was an influential and potential factor leading to epidemic. Modifying the combination of diagnostic tests would reduce the incidences of the diseases more efficiently. Interestingly, sensitivity analyses show that animal-level interventions, especially for surveillance of bovine brucellosis, have stronger impacts on the outbreaks of human brucellosis than human-level intervention. Extending the surveillance for bovine brucellosis is the most effective control policy for both human and bovine brucellosis. Moreover, animal vaccination can be one of the effective strategies. These results suggest that a One Health approach would reduce the burden of brucellosis efficiently in the Republic of Korea.

Further studies including cost-effectiveness analysis and optimal control strategies study can be conducted based on this study.

Keyword: Brucellosis, Mathematical model, Zoonosis, Animal-level intervention, One Health

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Chapter 1. Introduction

1.1. Brucellosis

Brucellosis is one of the neglected zoonotic diseases around the world [1]. The disease adversely affects reproducibility in animals (e.g., abortion, reproductive failures); health and economic damages in humans (e.g., human infection and slaughtering infected animals) [2]. Brucellosis is caused by *Brucella* species, four of which are related to zoonotic transmission: *Brucella melitensis*, *Brucella abortus*, *Brucella canis*, and *Brucella suis*. These variants are related to the host specificity, and severity of the disease in human. *B. melitensis* is common in sheep or goat, *B. abortus* in cattle, *B. canis* in dog, *B. suis* in pig. The most virulent variants for humans are *B. melitensis*; The next virulent variants are *B. suis, B. abortus* and *B. canis* in order. Considering the burden of disease and severity in humans, the main concerns in public health sectors are *B. melitensis* and *B. abortus* [2, 3].

Humans brucellosis usually occur through contacts with infected animals including contacts with body fluid, aborted fetus or aerosol, or ingestions of contaminated livestock products such as raw cheese and milk. In general, *B. melitensis* is transmitted to humans through livestock products and *B. abortus* through contacts with infected animals. However, few cases infected through between-human transmission were reported; sexual contact, organ transplantation, and breastfeeding [4]. Efficient interventions of human brucellosis

should include the control of animal brucellosis. Therefore, interventions of human brucellosis require transdisciplinary approach mainly with animal health sectors [5, 6].

The infection of *Brucella* is usually chronic in human and animal. The clinical symptoms of human brucellosis are usually mild, chronic and non-specific signs including fever, anorexia, sweating, headache, myalgia and fatigue. The symptoms last for weeks or months without antibiotic treatments. However, mortality of human brucellosis is very low, less than 1% [2]. Similar with the clinical characteristics of human brucellosis, animal brucellosis has non-pathognomonic symptoms such as abortion. Due to these clinical symptoms in humans and animals, diagnosis should include laboratory test. Thus, surveillance in human and animal brucellosis have challenges. In human brucellosis, at-risk population usually lived in agricultural regions where medical service is not enough. Even, the non-specific symptoms do not lead to the laboratory test. Similarly, animal brucellosis usually does not been reported since the laboratory test is not requested [7]. As bacterial isolation has low sensitivity, serial (an individual is considered to be positive when all test shows positive results) or parallel (an individual is considered to be positive if any of the test shows positive results) serological tests are usually conducted. The host infected with *Brucella* produces antibodies: immunoglobulin M (IgM), immunoglobulin G (IgG) and any others. Serological tests were developed to mainly detect the IgG which is a type of antibodies that are produced after 3 ~ 4 weeks after infection. IgM can be used as indicators of exposure because of the

characteristics of initial response to the infection. However, the antibody often induces the cross-reactions with other pathogens. Rose-Bengal test (RBT) mainly detect IgG but possible for IgM. Indirect enzyme-linked immunosorbent assay (iELISA) and competitive enzyme-linked immunosorbent assay (cELISA) detect IgG. Some other test such as standard tube agglutination test (STAT) mainly detects IgM, which is not recommended by *Office international des epizooties* (OIE). Even if incorporating the diverse approaches, there are still limitations of diagnostic performance [8-10]. For this clinical characteristics and limitations of diagnosis, reports of human and animal brucellosis are dependent of the surveillance systems and so usually underestimated [11].

In animal health sectors, interventions mainly rely on "test and slaughter" and vaccination [12]. "Test and slaughter" policy is firstly to do diagnose potentially infected cattle and if positive, the cattle are slaughtered.

Safe and efficient vaccine for brucellosis was only developed for cattle and sheep. There are three kinds of vaccine strains widely used: Rev 1, S19 and RB51 [13]. Former strain was developed for sheep. And the others were for cattle. Unlike other strains, RB51 strains does not induce the antibodies detected by serological tests.

In the past, animal vaccine was inoculated to humans. However, side effects including infection occurred. Since then, safe vaccines for human brucellosis were not developed until now [14].

Antibiotic treatments of animal brucellosis are not conducted due to economic burden, long-time treatment period and concerns for

antibiotic resistance [15]. Human brucellosis should be treated with effective antibiotics and proper length of time. Treatment of the disease should start as early as possible. The later the patient is treated, the greater the risk of complications and relapses increases [2].

1.2. Epidemiological characteristics of brucellosis in the Republic of Korea.

In the Republic of Korea, characteristics of human brucellosis cases usually include animal-contacts and agricultural-related occupation. Moreover, the cases have been caused by *B. abortus* [16-18]. Almost cases of animal brucellosis in the country are bovine brucellosis caused by *B. abortus*. Previous studies in the Republic of Korea showed the relationship between human and bovine brucellosis [19-21]. Therefore, control of human brucellosis has focused on the bovine brucellosis.

Bovine brucellosis is a Class 2 notifiable animal disease by the Act on the Prevention of Contagious Animal Diseases. The first case of bovine brucellosis in the Republic of Korea was reported in 1955 [22]. From then, this disease had the highest reports in 2006 and continuously been reported until now (Figure 1). Total 84,728 cases

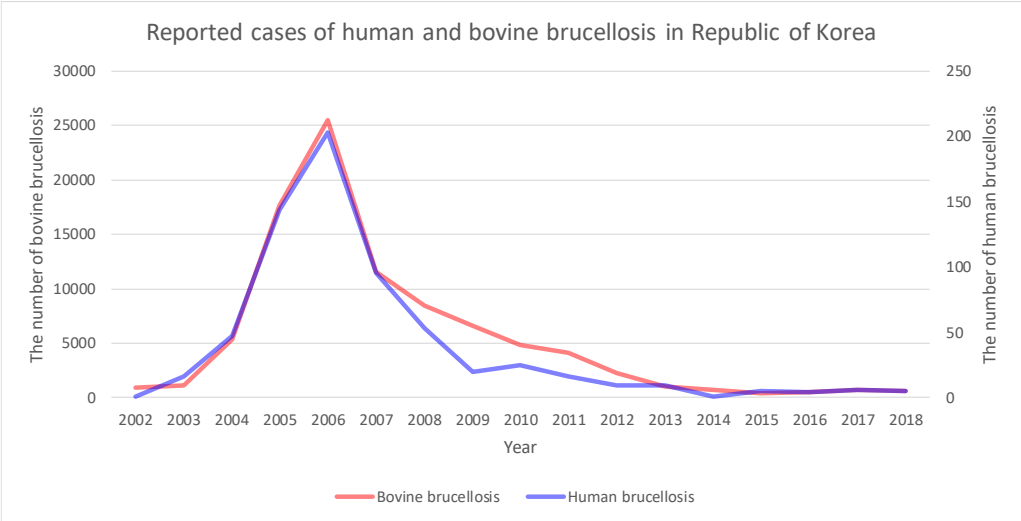

Figure 1. Reported cases of human and bovine brucellosis in Republic of Korea.

of bovine brucellosis were reported between 2005 and 2018.

For the purpose of eradicating the disease, "test and slaughter" policy have been conducted since 1960s [23]. The cattle that shows positive result in serological tests were slaughtered within 10 days [24]. However, since the policy was concentrated on the dairy cattle, the interventions for beef cattle were not enough. In 1999, vaccination policy for cattle with RB51 strain was launched. However, due to the unanticipated side effects including abortions, and premature death, the policy was stopped after 6 months from the starts [25, 26]. In 2004, intensive eradication program based on active surveillance for both beef and dairy cattle has been conducted. From then, the program has been expanded to increase the proportion of cattle to be tested once a year. From May 2004, all cattle should be tested before the trade. From March 2005, pre-slaughter test also conducted. In June 2006, the cattle in beef cattle farms with ≥ 10 heads were tested biannually. In 2008, all of the cattle was tested in a year [27]. However, due to the once-a-year frequency of surveillance, newly infections of bovine brucellosis occur during implementing the surveillance.

For diagnosis, serial approach have been organized: RBT for screening test and STAT for confirmatory test [24]. Adopting iELISA and cELISA (ELISAs) as a confirmatory test was suggested due to the limitations of STAT [28].

Human brucellosis was designated as a Korean National Notifiable Infectious Disease in 2000. Since the first case was reported in 2002 [17], the highest number of cases was reported in 2006. And the

cases continued to be reported until now (Figure 1). 595 cases of human brucellosis have been reported since 2005 [29]. The possibility of endemicity of human brucellosis in the country was discussed [30]. The surveillance systems for human brucellosis are coordinated with that of bovine brucellosis in the country. Once the infection of bovine brucellosis is reported, epidemiologically related person is screened and followed up [31].

Before the designation as notifiable diseases in 2000, human brucellosis was reported in some researches [32, 33]. This is the evidence of existence of human brucellosis in Korea before 2002. The reason is that it is easy for physician to misdiagnose the disease due to the non-specific clinical symptoms. Moreover, there were possibilities to be unable to detect the disease because healthcare services in high-risk regions such as rural area were usually scare [18].

1.3. Mathematical model for zoonotic brucellosis

Most previous studies focused on the modeling the between-animals transmission dynamics of brucellosis, rather than zoonotic transmission dynamics [34-38]. Some researches were conducted to understand the zoonotic dynamics of brucellosis [39-41]. Zinsstag, J. et al (2005) formulated the three species model including sheep, cattle and human for Mongolia. The authors estimated the demographic and epidemiological parameters such as births, death and contacts rate between animals, and between animals and humans as a basis for cost-effectiveness analysis of interventions. Moreover, the effects of the intervention methods such as vaccination, and "test and slaughter" were simulated with the model. Hou, Q. et al (2013) modeled the sheep-human transmission dynamics in Inner Mongolia, China. Unlike the previous researches, the model was formulated with the two kinds of transmission route; direct transmission from infected animals and indirect transmission from *Brucella* species in the environment. With the estimation of basic reproduction number, the authors revealed the limitations of vaccination and disinfection strategies and suggested the effective interventions to eradicate the brucellosis. Li, M. T. et al (2017) estimated the threshold values of interventions for each provincial level in China. However, all of these researches did not consider the dependency of reported data on the surveillance systems.

To the author's best knowledge, the previous researches in the Republic of Korea only focused on identifying the relationships

between human and bovine brucellosis in the microbiological, temporal and spatial aspects [19–21], but there were no researches for formulating the zoonotic transmission dynamics and quantifying the effects of interventions for human brucellosis as well as bovine brucellosis reflecting characteristics of the surveillance systems in the Republic of Korea. Moreover, due to the little evidence that basic reproduction number can be utilized outside the region where the metric was estimated [42, 43], the basic reproduction number estimated in other countries cannot be utilized in the Republic of Korea.

In this study, therefore, mathematical model for brucellosis was formulated to understand the zoonotic transmission dynamics with the data retrieved from both human and animal health database, reflecting the characteristics of surveillance for brucellosis. Using the model, the effects of animal and human–level interventions were analyzed to identify the key factors on the dynamics. Also, possible interventions scenarios including animal vaccination were also analyzed.

Chapter 2. Method

2.1. Case definition and Demography

Diagnostic process of human brucellosis is divided in 3 steps; suspected cases, probable cases and confirmed cases. Suspected case is defined as the person with clinical symptoms and epidemiological relationships such as occupational characteristics or contacts history with potentially infected animals. Probable case is the person who shows the positive results of serological diagnosis method including agglutination test and also meets the criteria of suspected case. The positive results of antigen or gene test including a direct polymerase chain reaction or bacterial culture lead to confirmed cases. The probable and confirmed cases were reported to the Korea Centers for Disease Control and Prevention (KCDC). Serological test was conducted at the provincial Public Health Laboratory and Antigen or gene test were performed at KCDC [44]. Bovine brucellosis was diagnosed with two serial steps; screening test and confirmation test. Only serological methods were used to detect this disease. RBT was used as screening test. If positive, STAT as confirmation was conducted. If the results were positive serially, the cattle were recognized as positive cases and reported to the Animal Health Integrated System of the Animal and Plant Quarantine Agency (KAHIS). Whole procedure was carried out at the provincial Veterinary Service Center [24].

Considering the occupational characteristics of human brucellosis, agriculture-related human populations were selected as at-risk

human populations. All cattle bred in the country were selected as at-risk cattle populations. Breed types of cattle were not stratified.

2.2. Data source

Reported data of human brucellosis were retrieved from the Infectious Disease Statistics System of the KCDC [29]. The data include only the number of reported cases of certain time period. Reported number in each year was used. Data for bovine brucellosis were obtained from KAHIS [45]. The data include reported date and administrative address, the number of infected cattle and the number of cattle bred in the confirmed farm. Total number of infected cattle per year used as reported cases.

Demography of at-risk human population was extracted from the database of the Survey of Agriculture, Forestry and Fisheries in Statistics Korea [46]. The survey is conducted on December of every year. Therefore, this data reflects the agriculture-related population of the end of a year. The number of cattle populations was retrieved from the Survey of Livestock Trend in Statistics Korea [47]. This database is surveyed quarterly in every year. The 4th quarter data of the survey in a year was used in this study.

2.3. Model description

In this study, a two-species continuous deterministic compartment model was formulated to characterize the transmission dynamics of brucellosis from 2005 to 2018 in the Republic of Korea. A schematic diagram of the model is shown in Figure 2 and parameters are described in Table 1. And initial values of the model are described in Table 2.

The model consists of two parts; cattle and human. Overall, infection is transmitted from cattle to cattle and human. The model classified the human population into susceptible, infected, and reported

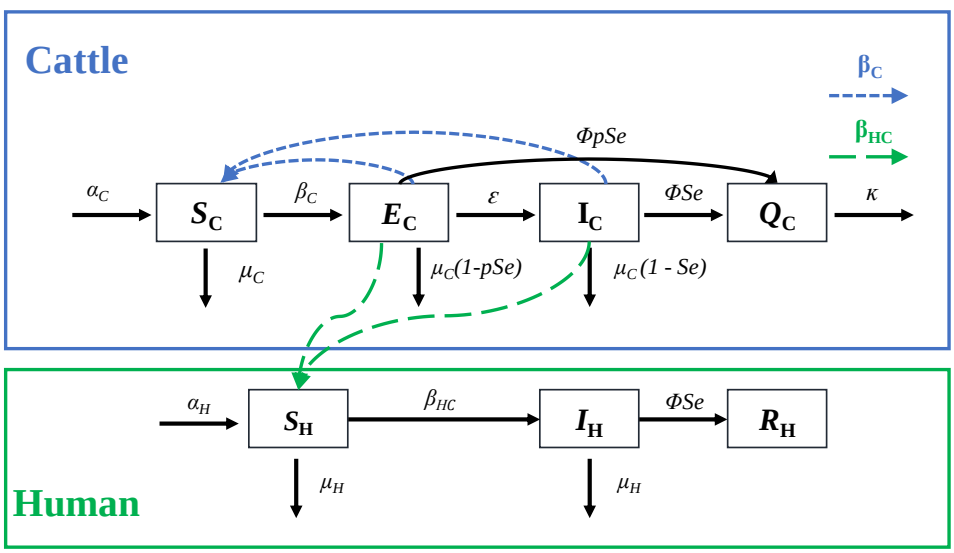

Figure 2. Flow chart on the zoonotic transmission dynamics of brucellosis (SEIQ-SIR model). Solid arrows represent transfer direction of population. Blue-colored dashed arrows represent the transmissions between cattle; Green-colored long dashed arrows represent transmissions from cattle to human.

Table 1. Description of parameters in SEIQ−SIR model.

Parameters	Value	Unit	Description	Source
α_C	967482.4	$year^{-1}$	Birth rate of cattle	Statistics Korea [46]
μ_C	0.277	$year^{-1}$	Natural elimination rate of cattle	Statistics Korea [46]
α_H	80943.43	$year^{-1}$	Birth rate of human	Statistics Korea [46, 48]
μ_H	0.035	$year^{-1}$	Mortality rate of human	Statistics Korea [46]
ε	13	$year^{-1}$	Transmission rate from exposed to infected compartment	Godfroid, J et al (2010) [8]
ϕ_1	0.92	$year^{-1}$	Quarantining rate of bovine brucellosis from 2006 to 2007	
ϕ_2	1.27	$year^{-1}$	Quarantining rate of bovine brucellosis from 2007 to 2008	Statistics Korea. [47, 49]
ϕ_3	1	$year^{-1}$	Quarantining rate of bovine brucellosis from 2008 to 2018	
Se	0.9	*none*	Sensitivity of diagnostic methods	Rahman, A. K. M. A. et al. (2019) [50]
κ	36.5	$year^{-1}$	Slaughtering rate of quarantined cattle	Ministry of Government Legislation. [24]
p	0.5	*none*	Reduced diagnostic performance for cattle in exposed compartment	Assumption
ω	0.1~0.9	*none*	Scaling factor for infectivity of the exposed cattle	–
β_C	–	*none*	Effective contact rate between cattle	Estimation
β_{HC}	–	*none*	Effective contact rate between human and cattle	Estimation

Table 2. Descriptions for initial values in SEIQ–SIR model.

Parameters	Value	Unit	Description	Source
$S_C(0)$	2267476	*individual*	Initial number of the susceptible cattle	Statistics Korea [47]
$E_C(0)$	2138	*individual*	Initial number of the exposed cattle	*
$I_C(0)$	27800	*individual*	Initial number of the infected cattle	*
$Q_C(0)$	0	*individual*	Initial number of quarantined cattle	–
$S_H(0)$	3433316	*individual*	Initial number of susceptible humans	Statistics Korea [46]
$I_H(0)$	258	*individual*	Initial number of susceptible humans	*

* $I_C(0)$ and $I_H(0)$ were estimated using maximum likelihood method. $E_C(0)$ was calculated as $E_C(0) = \frac{I_C(0)}{\varepsilon} \approx 2138$

compartments denoted by S_H, I_H, and R_H, respectively (SIR model), and the cattle population into susceptible, exposed, infected and the quarantined (reported) compartments denoted by S_C, E_C, I_C and Q_C, respectively (SEIQ model) (Figure 2)

Due to the lack of the death and birth rate data for at-risk human population, the parameters were calculated in this study. The average age of at-risk human population was 55.32 in 2013 [46]. Life expectancy of the birth cohort in 2013 was 28.6 years [48]. Thus, death rate of human was assumed as $\mu_H = \frac{1}{28.6} \approx 0.035 / \textit{year per capita}$. The number of at-risk human populations was continuously decreasing to 2,314,982. Therefore, birth rate was assumed as $\alpha_H = \frac{1}{28.6} \times 2314982 = 80943.43 / \textit{year}$. The average life-year of cattle in the Republic of Korea is 3.615 years. Thus, the natural elimination rate of cattle was assumed as $\mu_C = \frac{1}{3.615} \approx 0.277 / \textit{year per capita}$. During the study period, the cattle population increased to 3,187,921. Birth rate was assumed as $\alpha_C = \frac{1}{3.615} \times 3497449 = 967482.4 / \textit{year}$ [46].

According to the surveillance systems in the Republic of Korea, the model has some characteristics. The incubation period of human brucellosis is highly variable from two weeks to five weeks or longer, which is depending on the patient's condition [7]. Reported data of human brucellosis did not separate the period. Thus, exposed

compartment was not considered in the human model. However, E_C was defined as the period between being exposed to *Brucella* and when the seroconversion of IgG occurs. Seroconversion of IgG appear 3 and 4 weeks after the infection [8]. Time unit of this model is a year. Therefore, transmission rate from E_C to I_C ε was selected as 13 ($\varepsilon = \frac{53}{4} \approx 13 / \textit{year per capita}$). The frequency of surveillance for bovine brucellosis ϕ had been changed because of the modification of the surveillance policy. Thus, ϕ has time-varying values. From January 2006 to June 2006, only pre-trade and pre-slaughter test were conducted. After June 2006, cattle in beef cattle farms with ≥ 10 heads were tested biannually [27]. In 2006, 57% of cattle in the country was sold and slaughtered. Moreover, the proportion of the cattle reared in beef cattle farms ≥ 10 head among all cattle in the country was 63.5%. Thus, $\phi_1 = \frac{0.57 + 0.635 \times 2}{2} = 0.92 / \textit{year per capita}$. Since this policy was not changed until the end of 2007, ϕ_2 was $0.635 \times 2 = 1.27 / \textit{year per capita}$ from 2007 to 2008. After 2008, the policy was changed to test the all of cattle annually. Thus, ϕ_3 was $1 / \textit{year per capita}$ [47]. The cattle identified as bovine brucellosis were reported and quarantined timely after the diagnosis. Thus, the identified cattle in I_C and E_C are transmitted to the Q_C. And then, the cattle will be slaughtered within 10 days ($\kappa = 36.5 / \textit{year per capita}$) [24].

Given the epidemiological characteristics of brucellosis, some

assumptions have been made: (1) The cattle in E_C and I_C was both infectious. Scaling factor for the infectivity of cattle in E_C compared to the cattle in I_C (ω) was forced into the model to reflect the difference of infectivity; (2) sensitivity of diagnostic test for bovine brucellosis was incorporated in the cattle model ($Se = 0.9$) [50]. However, for human brucellosis, thanks to the epidemiological investigations and follow-up, sensitivity for diagnosing human brucellosis was not considered; (3) sensitivity of diagnostic test for the cattle in E_C reduce to 50% of the sensitivity of the current diagnostic tests ($p = 0.5$). This is because the current diagnostic test detect IgG and also possible for IgM but not completely; (4) Due to the mandatory pre-slaughtering test (test before the natural elimination) [27], cattle in E_C and I_C that show pseudo-negative results can be eliminated; (5) the risk of human-to-human and human-to-animal transmission is very low, and the case have not been reported in the Republic of Korea. Therefore, the human-to-human and human-to-animal transmission was ignored; (6) Deaths due to human brucellosis was ignored because of very low mortality rate; (7) Due to the clinical characteristic and limitations of surveillance system of both human and bovine brucellosis, there are cases that are not reported at the start of the study period. Therefore, the reported human and bovine brucellosis was underestimated. The initial values of infected cattle and human were estimated in the model; (8) To reflect the coordinated surveillance system between bovine and human brucellosis, the same frequency of surveillance

was modeled (ϕSe). Therefore, the SIRQ-SIR model was described as the following ODEs:

$$
\begin{cases}
\frac{dS_C}{dt} = \alpha_C - \frac{\beta_C S_C(\omega E_C + I_C)}{T_C} - \mu_C S_C \\
\frac{dE_C}{dt} = \frac{\beta_C S_C(\omega E_C + I_C)}{T_C} - \varepsilon E_C - \mu_C(1 - pSe)E_C - \phi pSeE_C \\
\frac{dI_C}{dt} = \varepsilon_C E_C - \mu_C(1 - Se)I_C - \phi SeI_C \\
\frac{dQ_C}{dt} = \phi pSeE_C + \phi SeI_C - \kappa Q_C \\
\frac{dS_H}{dt} = \alpha_H - \frac{\beta_{HC} S_H(\omega E_C + I_C)}{T_C} - \phi\mu_H S_H \\
\frac{dI_H}{dt} = \frac{\beta_{HC} S_H(\omega E_C + I_C)}{T_C} - \mu_H I_H - \phi SeI_H \\
\frac{dR_H}{dt} = \phi SeI_H - \mu_H R_H
\end{cases}
$$

$$T_C = S_C + E_C + I_C$$

2.4. Basic reproduction number

To get insight of infectious disease dynamics, the basic reproduction number $\boldsymbol{R_0}$ plays a vital role. $\boldsymbol{R_0}$ is defined as the expected number of secondary infections caused by one infected individual in totally susceptible population. The dynamics can be easily understood with this index. When $\boldsymbol{R_0} > 1$, the disease continuously spread, that is, epidemic occurs. While, if $\boldsymbol{R_0} < 1$, the disease will disappear [42].

$\boldsymbol{R_0}$ can be calculated with *next generation matrix* (NGM) method [51]. This method regards the infection dynamics as generation of the epidemiological offspring infected with disease through transmission. In this aspect, infection dynamics can be translated as the demographic process of infected individuals with consecutive generations. If infected offspring increase subsequently, epidemic occur, otherwise, the disease will die out in the long run [52].

For compartments model established with ordinary differential equations, NGM is a matrix that relates the rates of newly infection with each compartment in subsequent generations. According to the NGM method, the first step is to assume the disease-free equilibrium states (DFE) and linearize the non-linear ordinary differential equations (ODEs). The linearized equations include the subsystems describing the production of the new infection and changes in the states of already existing infected, which is called *infection sub-system*. The system can be divided into two matrices: transmission matrix F and transition matrix $-V$. F includes the rate of new infections in certain compartment. $-V$ includes all other rates such

as births, deaths and recovery. The elements of each matrix $e_{i,j}$ indicate the rate at which individuals in state j reproduce individuals in state i. The multiplicated matrix of F and V^{-1} is called NGM. Maximum eigenvalues (spectral radius) of the NGM $\rho(FV^{-1})$ is a basic reproduction number [52].

As the human part is independent of the cattle part in the model, only the basic reproduction number of bovine brucellosis was estimated and used as proxy for the risk of human brucellosis.

2.5. Scenario analyses

In this study, scenario analyses were conducted to show the possible reduction of the diseases. Firstly, percentage of reduction of the diseases were analyzed for each parameters including ϕ, Se, β_C, β_{HC}. The parameters were assumed at the possible level. Frequency of surveillance ϕ was assumed to be extended to test all of cattle biannually from June 2006. Thus, ϕ_1, ϕ_2 and ϕ_3 were assumed as 1.285, 2 and 2, respectively. Sensitivity of diagnostic test Se was assumed to be 0.95 using the sensitivity of serial combination of RBT and ELISAs.

The effective contact rate can be divided into two categories: probability of infection per contact, contact rate per capita. The policies that can impact on the β_C are usually related with the contact rate per capita. Contact rate per capita between cattle is related with livestock industry-related activities. Moreover, intervention policies only conducted to the Brucella-affected farms consisting of relatively small proportions of all farms. Thus, the effect of the polices such as movement restriction have limitations. β_C was assumed to be 80% of the estimated value. β_{HC} was assumed to be 50% of the estimated value in the model. This is because it was assumed that health education can reduce the probability of infection per contact to 50%.

Secondly, the impacts of animal vaccination policy were analyzed. Schematic diagram for vaccination-scenario model is shown in

Figure 3 and parameters are described in Table 3. Based on the SEIQ-SIR model, vaccinated compartment V_C was added in this model, that is, VSEIQ-SIR model.

Among the vaccine strains for bovine brucellosis, RB51 vaccine can be used because the antibodies induced by RB51 do not interfere with the serological test such as RBT and STAT [13]. Therefore, RB51 strain vaccine can be used with the current diagnosis methods in the Republic of Korea.

All of vaccinated cattle do not get effective immunization. Thus, efficacy of vaccination was modeled (Figure 3). The efficacy of RB51 is not significantly different from that of S19 strain vaccine [13].

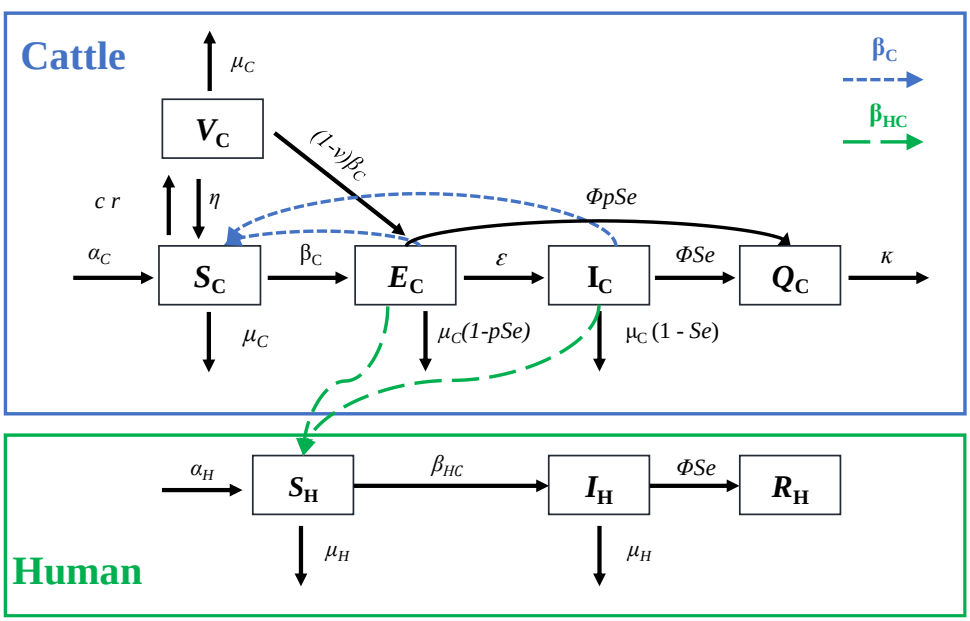

Figure 3. Flow chart on the zoonotic transmission dynamics of brucellosis. Solid arrows represent transfer direction of population. Blue-colored dashed arrows represent the transmissions between cattle; Green-colored long dashed arrows represent transmissions from cattle to human.

Thus, efficacy of RB51 was selected as 65% which is the efficacy of S19 strain used in Zinsstag et al (2005) [39]. Also, as immunization induced by vaccination do not persist for whole life, vaccinated cattle are flow back to S_C with certain rate η. According to the fact that boosting of the vaccination is recommended at the 4 or 5 years of age [53], waning rate of RB51 was assumed as 1/4.5. In the Republic of Korea, life span of cattle is about 3.6 years. Thus, boosting was not considered. Animal vaccination should be done by veterinarian. Thus, vaccination rate r is dependent on the workforce of veterinarian. Emergency vaccination intervention for foot and mouth disease that is known as rapidly transmitted disease usually are conducted within 1 month for all susceptible animals in the country. The rate was assumed based on the fact that brucellosis is usually not regard as rapidly transmitted disease. Thus, vaccination rate can be slower compared to the other livestock disease such as foot and mouth disease. Moreover, RB51 strain can be inoculated when the calf is 3 month-age. Thus, r was assumed as $\frac{1}{3} \approx 0.33 / \textit{year per capita}$

Table 3. Description of parameters in vaccination-scenario model.

Parameters	Value	Unit	Description	Source
c	0 ~ 100%	none	Coverage of the vaccination	-
r	0.33	$year^{-1}$	Vaccination rate	Dorneles et al (2015) [13]
v	0.65	none	Efficacy of the vaccination in cattle	Dorneles et al (2015) Zinsstag et al (2005) [13, 39]
η	0.22	$year^{-1}$	Waning rate of vaccine	Dorneles et al (2015) [13]

The ODEs of vaccination−scenario model were expressed as:

$$
\begin{cases}
\dfrac{dV_C}{dt} = crS_C - \dfrac{\beta_C V_C(1-v)(\omega E_C + I_C)}{T_C} - \mu_C V_C - \eta V_C \\
\dfrac{dS_C}{dt} = \alpha_C - \dfrac{\beta_C S_C(\omega E_C + I_C)}{T_C} - \mu_C S_C - crS_C + \eta V_C \\
\dfrac{dE_C}{dt} = \dfrac{\beta_C S_C(\omega E_C + I_C)}{T_C} + \dfrac{\beta_C V_C(1-v)(\omega E_C + I_C)}{T_C} - \varepsilon E_C - \mu_C(1-pSe)E_C - \phi pSeE_C \\
\dfrac{dI_C}{dt} = \varepsilon_C E_C - \mu_C(1-Se)I_C - \phi SeI_C \\
\dfrac{dQ_C}{dt} = \phi pSeE_C + \phi SeI_C - \kappa Q_C \\
\dfrac{dS_H}{dt} = \alpha_H - \dfrac{\beta_{HC} S_H(\omega E_C + I_C)}{T_C} - \mu_H S_H \\
\dfrac{dI_H}{dt} = \dfrac{\beta_{HC} S_H(\omega E_C + I_C)}{T_C} - \mu_H I_H - \phi SeI_H \\
\dfrac{dR_H}{dt} = \phi SeI_H - \mu_H R_H
\end{cases}
$$

$$T_C = V_C + S_C + E_C + I_C$$

The cumulative incidences of human and bovine brucellosis were calculated according to the vaccination coverages ranged from 0% to 100% and vaccination timings. The results were plotted as contour density maps.

2.6. Analysis

Because of the uncertainty of ω, the model was firstly fitted to the reported data with ω values from 0.1 to 0.9. The best fitted model was selected based on the likelihood and used to further analysis.

Reported data are cumulative reported cases during a year. Considering that the cattle diagnosed as bovine brucellosis are slaughtered within 10 days after the date of diagnosis, fitting Q_C to the data is different from empirical situation. Thus, auxiliary equations were formulated to show the sum of newly reported cases during a year. The equations can be expressed as:

$$\frac{dW_C}{dt} = \phi pSeE_C + \phi SeI_C$$

$$y_{C,t} \sim Poisson(W_{C,t} - W_{C,t-1})$$

$$\frac{dW_H}{dt} = \phi SeI_H$$

$$y_{H,t} \sim Poisson(W_{H,t} - W_{H,t-1})$$

where W_C and W_H are cumulative reported cases of bovine and human brucellosis until the year t, respectively; $y_{C,t}$ and $y_{H,t}$ are the reported number of cases during a year t for bovine and human brucellosis, respectively. Differences of cumulative reported cases between serial times were modeled as Poisson distribution because the distribution describe the cumulative cases in a certain time.

Parameters were estimated to maximize the likelihood using Subplex algorithm [54].

After the estimating the parameters, the time series for the empirical reported data and the fitted curves was plotted. Moreoever, to understand the relationship between report and incidences pattern, the time series of the fitted curves and estimated incidences curve was also plotted. The incidences of brucellosis were calculated through the auxiliary equations expressed as:

$$\frac{dX_C}{dt} = \frac{\beta_C S_C(\omega E_C + I_C)}{T_C} + \underbrace{\frac{\beta_C V_C(1-v)(\omega E_C + I_C)}{T_C}}_{(1)}$$

$$x_C(t) = X_C(t) - X_C(t-1)$$

$$\frac{dX_H}{dt} = \frac{\beta_{HC} S_H(\omega E_C + I_C)}{T_C}$$

$$x_H(t) = X_H(t) - X_H(t-1)$$

where $X_C(t)$ and $X_H(t)$ are the cumulative incidences of brucellosis until the year t for bovine and human brucellosis, respectively; (1) of $\frac{dX_C}{dt}$ was only estimated for vaccination scenarios; $x_C(t)$ and $x_H(t)$ are the incidences of brucellosis during in the year t for bovine and human brucellosis, respectively.

The relationships between $\boldsymbol{R}_0$ and epidemiological parameters were plotted to enhance the understanding of dynamics. To quantify the impacts of the parameters, sensitivity analyses were conducted on each parameter within ±10 % changes with the cumulative incidences

of the two diseases, whose results were plotted in tornado diagrams. Lastly, scenarios analyses were conducted for parameters and vaccination.

All analyses were conducted using *POMP2* [55] and *subplex* [54] packages in R software 3.5.3 [56].

Chapter 3. Results

3.1. Fitting results

The estimated values of parameters were listed in Table 4. The model with $\omega = 0.1$ was the most appropriately fitted to the data. Figure 4. shows the graphical results of the empirical data and the best fitted model. Estimated β_C and β_{HC} are 6.029×10^{-1} and 2.515×10^{-3}, respectively. In Figure 4, red dashed lines are the empirical reported cases and black solid lines are fitted reported curves.

Time series plot of incidences of bovine and human brucellosis are shown in Figure 5, whose red lines are incidences curves and black lines are fitted reported curves. Similar with the time series of reported cases, incidence of bovine and human brucellosis continuously decreased. Also, the difference between reported cases and incidence was diminished.

Table 4. Results of parameters estimation in the model according to ω

Parameters	Value				
ω	0.1	0.3	0.5	0.7	0.9
β_C	6.029×10^{-1}	5.976×10^{-1}	5.922×10^{-1}	5.870×10^{-1}	5.819×10^{-1}
β_{HC}	2.515×10^{-3}	2.490×10^{-3}	2.472×10^{-3}	2.448×10^{-3}	2.427×10^{-3}
Likelihood	−1393.192	−1393.338	−1393.504	−1393.640	−1393.840

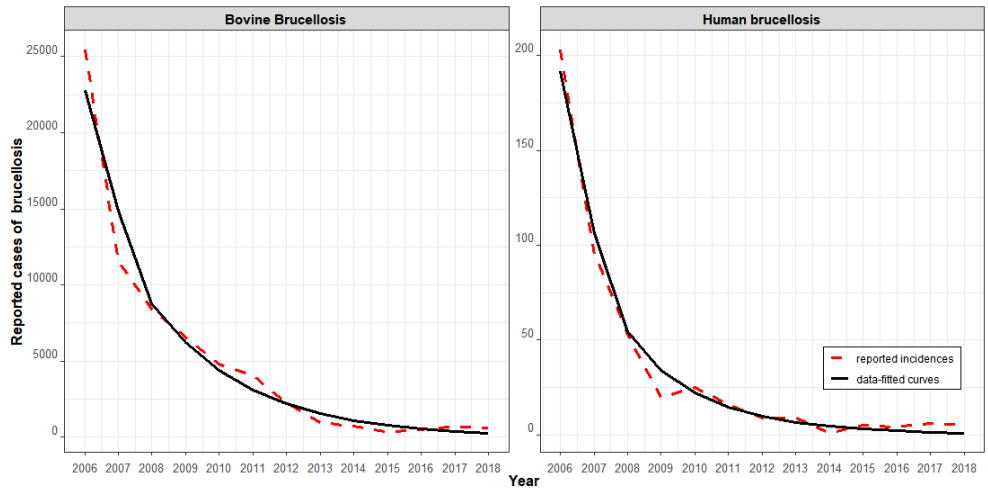

Figure 4. Reported cases of brucellosis (red dashed lines) and its fitted curves (black solid lines).

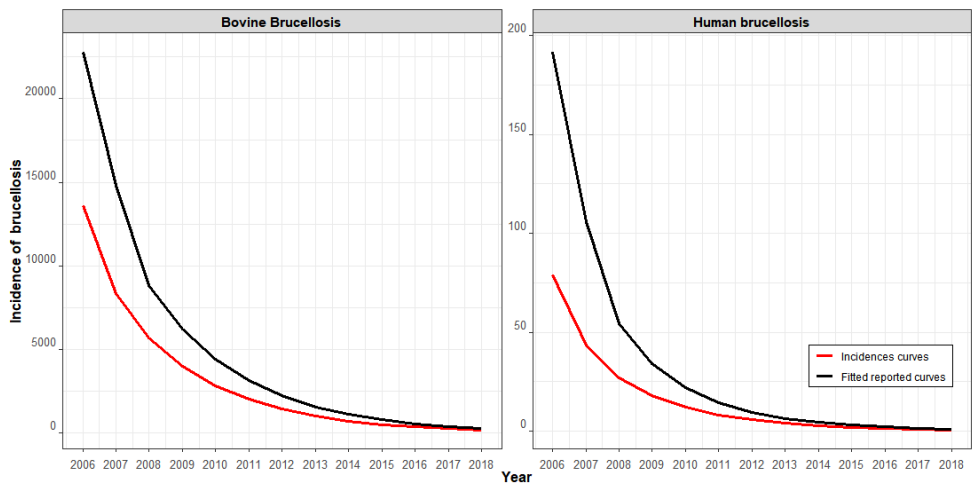

Figure 5. Incidences curves (red line) and fitted reported curves (black line).

3.2. Estimation of basic reproduction number

At the DFE, the condition was satisfied like below:

$$(T_C, S_C, E_C, I_C, Q_C) = (S_C, S_C, 0, 0, 0)$$

With the assumption of DFE, the *infection sub−system* was linearized, expressed as:

$$\begin{cases} \frac{dE_C}{dt} = \beta_C(\omega E_C + I_C) - \varepsilon E_C - \mu_C(1 - pSe)E_C - \phi pSeE_C \\ \frac{dI_C}{dt} = \varepsilon_C E_C - \mu_C(1 - Se)I_C - \phi SeI_C \\ \frac{dQ_C}{dt} = \phi pSeE_C + \phi SeI_C - \kappa Q_C \end{cases}$$

Therefore, transmission matrix F and transition matrix $-V$ of *infection sub−system* were expressed as:

$$F = \begin{pmatrix} \omega\beta_C & \beta_C & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

and

$$-V = \begin{pmatrix} -\varepsilon - \mu_C(1 - pSe) - \phi pSe & 0 & 0 \\ \varepsilon & -\phi Se - \mu_C(1 - Se) & 0 \\ \phi pSe & \phi Se & -\kappa \end{pmatrix}$$

Spectral radius of NGM $\rho(FV^{-1})$ is a basic reproduction number which is expressed as:

$$R_0 = \underbrace{\frac{\omega\beta_C}{\varepsilon + \mu_C(1-pSe) + \phi pSe}}_{R_E} + \underbrace{\frac{\varepsilon\beta_C}{\left[\varepsilon + \mu_C(1-pSe) + \phi pSe\right]\left[\phi Se + \mu_C(1-Se)\right]}}_{R_I}$$

The basic reproduction number can be divided into two components: infection from exposed compartment $\boldsymbol{R}_{\mathrm{E}}$, and from infected compartment $\boldsymbol{R}_{\mathrm{I}}$. In the study period, ϕ was time-varing parameter. Thus, average basic reproduction number $\overline{\boldsymbol{R}}_0$ was estimated with $\bar{\phi} = \frac{\phi_1 \times 1 + \phi_2 \times 1 + \phi_3 \times 13}{1+1+13} \approx 1.013 / \textit{year per capita}$, expressed as:

$$\overline{R_0} = \underbrace{\frac{\omega\beta_C}{\varepsilon + \mu_C(1-pSe) + \bar{\phi} pSe}}_{\overline{R_E}} + \underbrace{\frac{\varepsilon\beta_C}{\left[\varepsilon + \mu_C(1-pSe) + \bar{\phi} pSe\right]\left[\bar{\phi} Se + \mu_C(1-Se)\right]}}_{\overline{R_I}}$$

Through these steps, $\overline{\boldsymbol{R}}_0$ was estimated as 0.618. The contribution of $\overline{\boldsymbol{R}}_{\mathrm{E}}$ to $\overline{\boldsymbol{R}}_0$ can be expressed as:

$$\frac{\overline{R_E}}{\overline{R_0}} = \frac{\dfrac{\omega\beta_C}{\varepsilon + \mu_C(1-pSe) + \bar{\phi}pSe}}{\dfrac{\omega\beta_C}{\varepsilon + \mu_C(1-pSe) + \bar{\phi}pSe} + \dfrac{\varepsilon\beta_C}{\left[\varepsilon + \mu_C(1-pSe) + \bar{\phi}pSe\right]\left[\bar{\phi}Se + \mu_C(1-Se)\right]}}$$

$$= \frac{\omega}{\omega + \dfrac{\varepsilon}{\bar{\phi}Se + \mu_C(1-Se)}}$$

$$= \frac{\omega\left[\bar{\phi}Se + \mu_C(1-Se)\right]}{\varepsilon + \omega\left[\bar{\phi}Se + \mu_C(1-Se)\right]}$$

Therefore, p did not affect the contribution of $\bar{R}_E$ to $\bar{R}_0$. The contributions of $\bar{R}_E$ and $\bar{R}_I$ to $\bar{R}_0$ were plotted in Figure 6. $\bar{R}_E$ and $\bar{R}_I$ contribute to $\bar{R}_0$ for 1.116 % and 98.884 %, respectively.

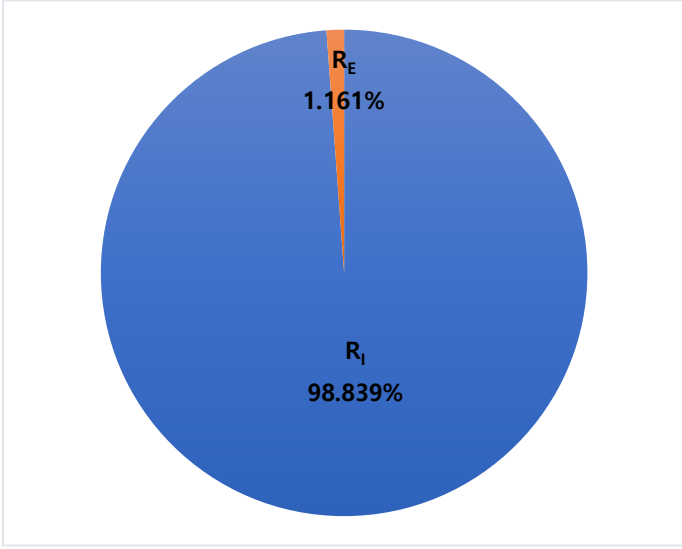

Figure 6. The contribution of E_C and I_C to average basic reproduction number $\bar{R}_0$. The percentage is displayed with a pie chart.

The relationship $\overline{R}_0$ between the parameters is plotted in Figure 7. As Se decreases, the change of $\overline{R}_0$ is exponentially increase. Even more, $\overline{R}_0$ is highly exponentially affected by ϕ, especially for low frequency. If β_C increases, $\overline{R}_0$ increases. However, as p increases, $\overline{R}_0$ decreases. Moreover, p seems that the parameter cannot lead the $\overline{R}_0$ to 1. It can be identified in the Table 5. As expected, p cannot lead $\overline{R}_0$ to 1. Also, threshold values of other parameters were shown; the value of Se was 0.453; ϕ for 0.614; β_C for 0.854.

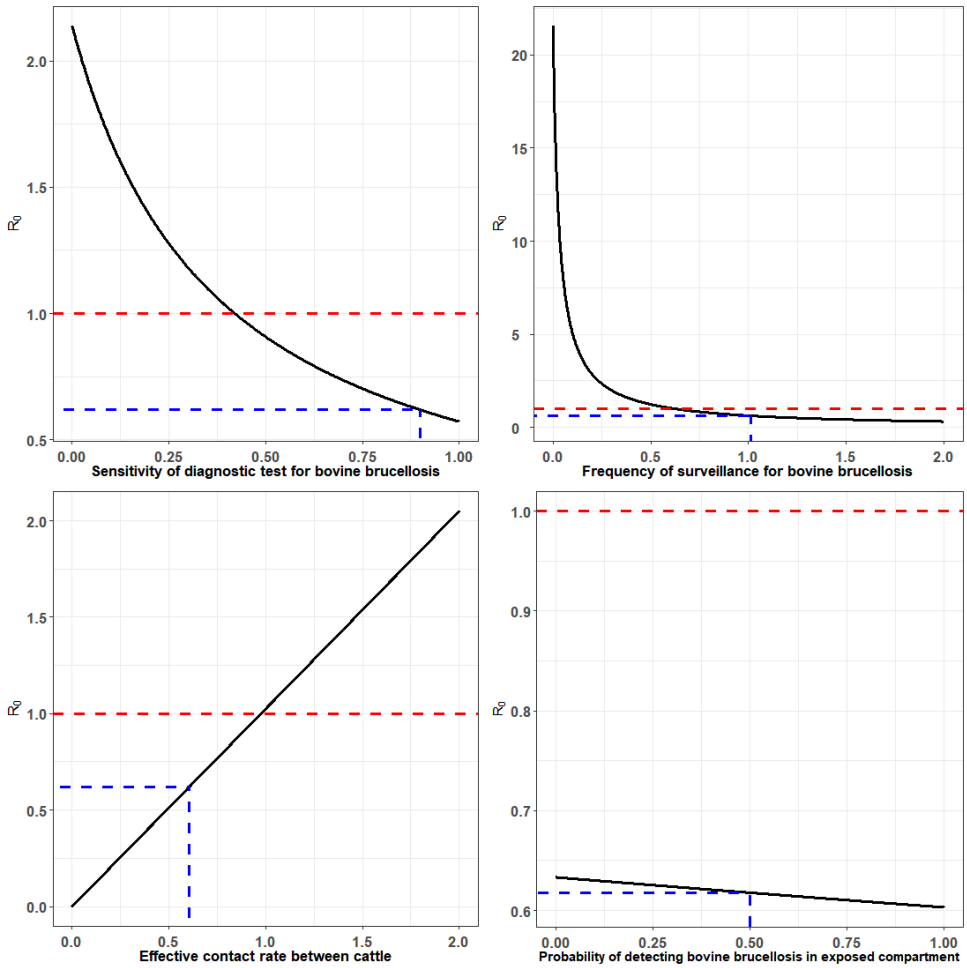

Figure 7. Plot of the relationships between basic reproduction number and epidemiological parameters: Se (top−left), ϕ (top−right), β_C (botom−left) and p (bottom−right) Blue dashed lines denote the value of

Table 5. Threshold values of parameters for $\bar{R}_0$>1

Parameters	Threshold values
Se	0.453
ϕ	0.614
β_C	0.854
p	Not available

3.3. Sensitive analysis

Figure 8. shows quantitative effects of parameters on the cumulative incidences of bovine brucellosis: effective contact rate between cattle, frequency of surveillance for bovine brucellosis, sensitivity of diagnostic test and effective contact rate between human and cattle. Effective contact rate between cattle and frequency of surveillance for bovine brucellosis were the most influential parameters. As expected, effective contact rate between human and cattle cannot impact the incidences of bovine brucellosis.

Tornado diagram for human brucellosis shows that the most influential parameters were frequency of surveillance for bovine brucellosis (Figure 9). Compared to the results of sensitivity analyses for bovine brucellosis, effective contact rate between cattle were less sensitive to the incidences of human brucellosis. Effective contact rate between human and cattle had the lowest impact on both human and bovine brucellosis. However, the frequency of surveillance was an influential factor for both diseases.

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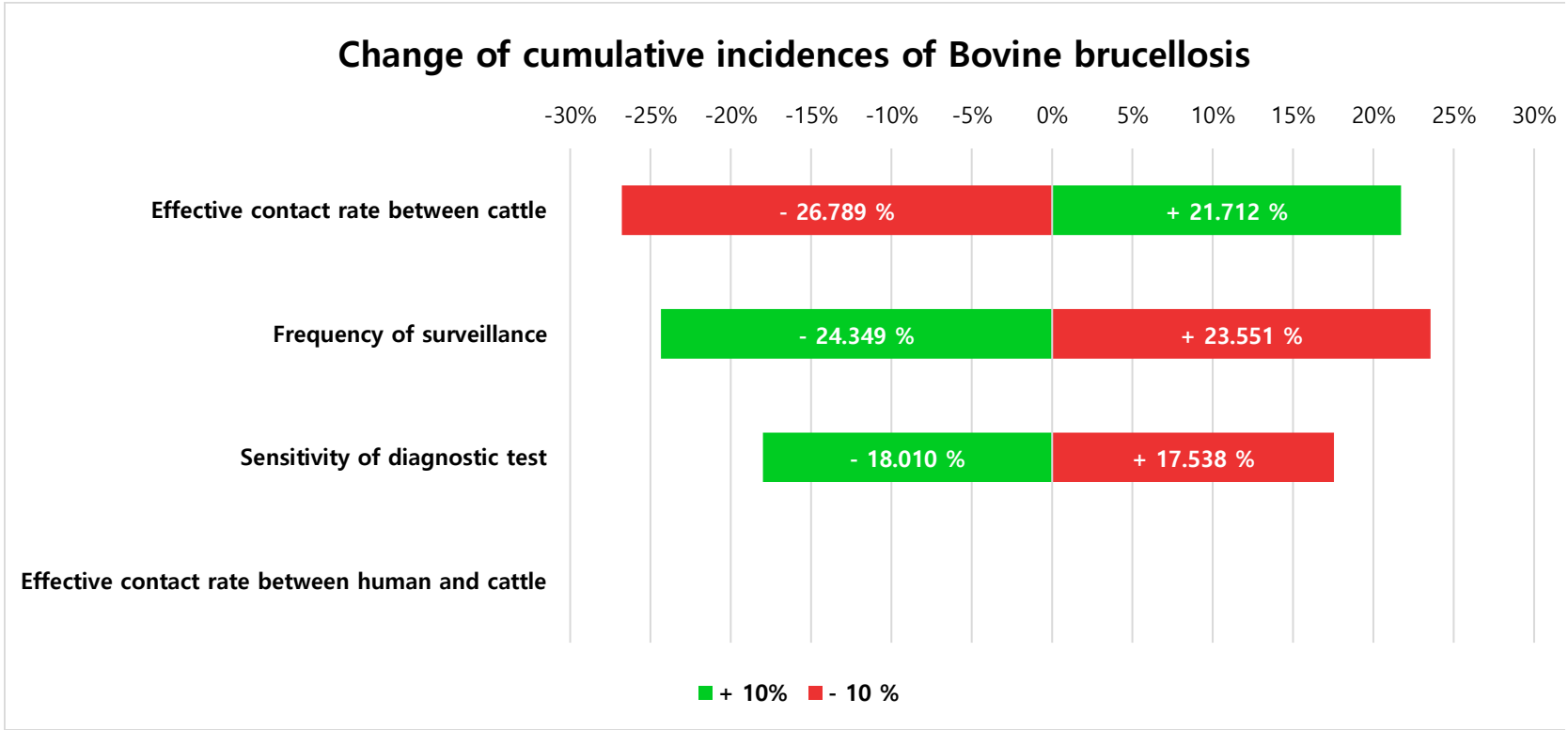

Figure 8. Tornado diagram of change of cumulative incidences of bovine brucellosis according to the changes of parameters within ±10 %

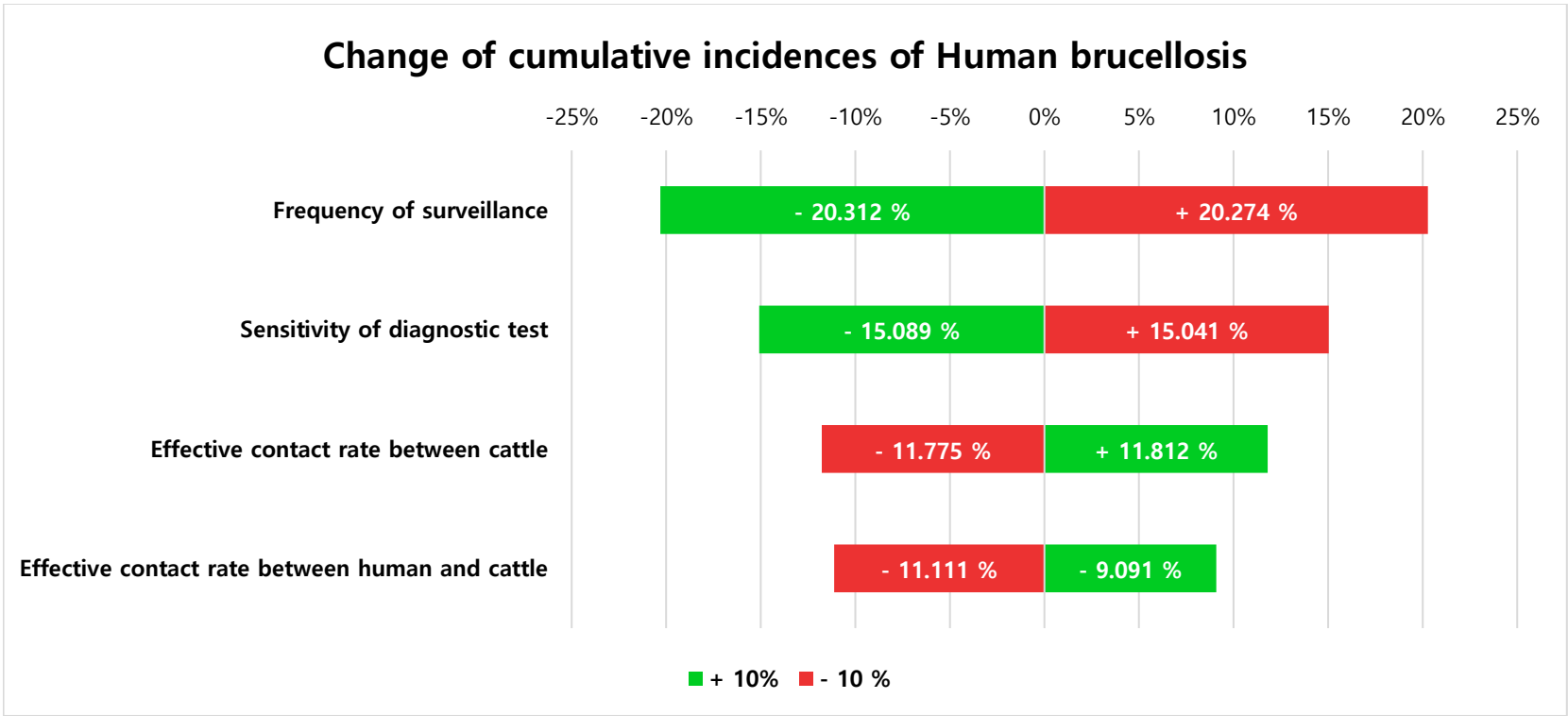

Figure 9. Tornado diagram of change of cumulative incidences of human brucellosis according to the changes of parameters within ±10 %

3.4. Scenario analyses

The results of scenario analyses for parameters were shown in Table 6. Frequency of surveillance shows the most dramatic reduction of the both diseases (59.308% for bovine brucellosis and 53.526% for human brucellosis). However, sensitivity of diagnostic test shows the least reduction of cumulative incidence (9.071% for bovine brucellosis and 7.744% for human brucellosis). Effective contact rate between cattle shows 37.651% for bovine brucellosis and 19.005% for human brucellosis at 80% level of estimated value, respectively. 49.920% of human brucellosis incidences were reduced when effective contact rate between human and cattle was changed at and 50%. Incidences of bovine brucellosis was not affected.

Figure 10. shows the reduced percentages of cumulative incidences of brucellosis according to the animal vaccination scenarios. Both cumulative incidences of bovine and human brucellosis were significantly decrease when vaccination policy with more earlier timing and higher coverage was implemented. If the timing was delayed, vaccination coverage should be higher to reduce the

Table 6. Results of scenario analyses for each parameter.

Parameters	Value	Percentage of reduction of cumulative incidence	
		Bovine brucellosis	Human brucellosis
Se	0.95	9.071%	7.744%
ϕ	2	59.308%	53.526%
β_C	80%	37.651%	19.005%
β_{HC}	50%	0.000%	49.920%

cumulative incidence to early−timing level. Even, if the vaccination policy has been implemented since 2009, the reduction percentage of brucellosis cannot be reached to the level when the policy has been implemented since 2006 with about 8 percentage coverage, whose reduced percentages were 15 % and 6 % for bovine and human brucellosis, respectively. Similarly, after 2012, the reduction of bovine and human brucellosis cases cannot be reached to 5% and 2 % each no matter how highly the vaccination was covered. Moreover, the higher the coverage is, the lesser the change of reduction of cumulative incidences is. For example, in 2006, the vaccination coverage increased from 0 % to 10%, the reduction percentage greatly increases. However, if the vaccination coverage increases from 40% to 50%, the reduction percentage is relatively small.

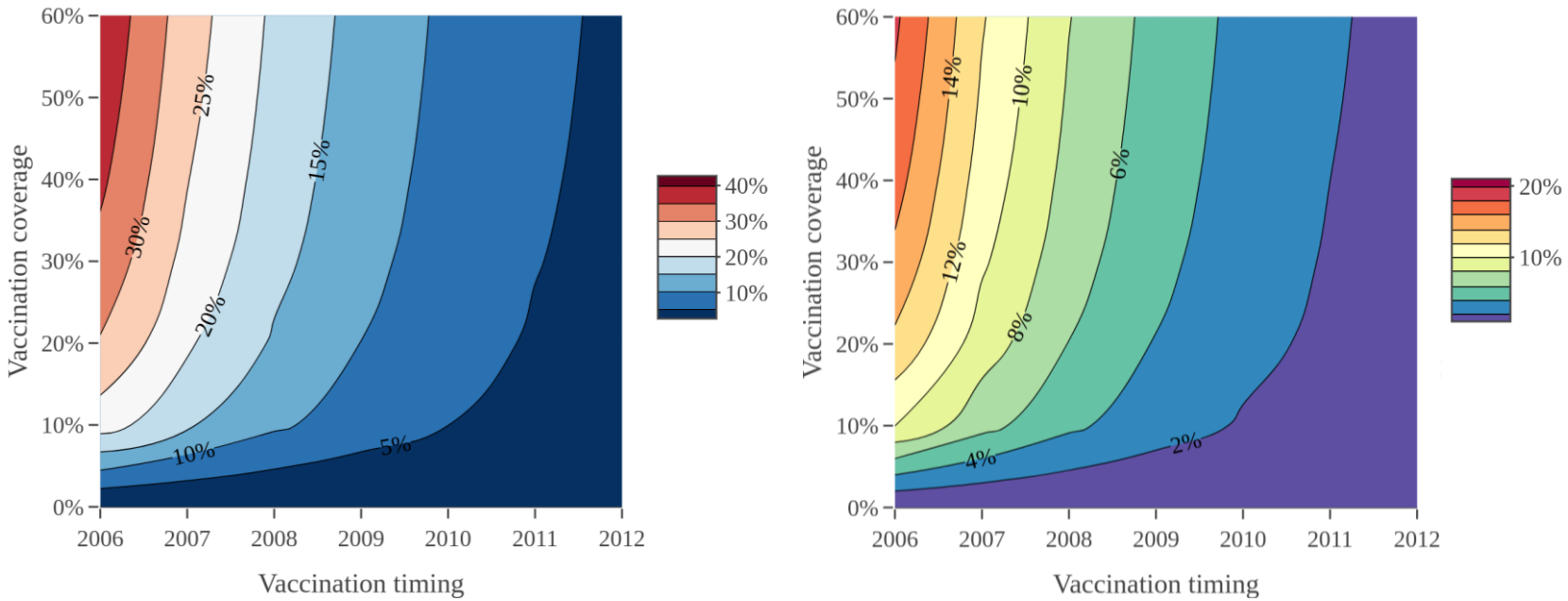

Figure 10. Contour maps of reduced percetages of cumulative incidence of bovine (left) and human brucellosis (right) as a function of vaccination timings and coverages

Chapter 4. Discussion

Mathematical model is useful for understanding the transmission dynamics of infectious diseases, which is crucial to build the control strategies, especially for zoonosis that have multiple host and cross-species transmission dynamics [57].

Effective control of zoonosis requires transdisciplinary approaches [58], that is, "One Health" strategies defined as "a collaborative, multisectoral, and transdisciplinary approach — working at the local, regional, national, and global levels — with the goal of achieving optimal health outcomes recognizing the interconnection between people, animals, plants, and their shared environment." by the Centers for Disease Control and Prevention [59]. Therefore, it is helpful to understand the within-species and between-species transmission dynamics. However, the majority of modeling studies for zoonosis usually considered the transmission in a single species [57].

In the Republic of Korea, human and bovine brucellosis has been continuously reported. As eradication of animal brucellosis needs a lot of resources and decades of times as other countries have shown [12], control for human brucellosis, of course, has obstacles. Considering that spillover to humans is not frequent cases [2], recent reported cases of human brucellosis reflect the prevalence of bovine brucellosis and potential risk for human infection in Republic of Korea [29].

In this study, the zoonotic transmission dynamics of brucellosis was

modeled reflecting the coordinated surveillance systems with animal and human health sectors in Republic of Korea. To improve the understanding of the dynamics, the relationships between $\bar{R}_0$ and epidemiological parameters were identified. Moreover, sensitivity analyses were conducted for the purpose of quantitively identifying their impacts. Additionally, animal vaccination scenarios were analyzed.

In the Republic of Korea, once the cattle infected with the bovine brucellosis is identified, the cattle would be reported, quarantined and slaughtered. Thus, the reports of the disease impacts on the transmission dynamics of the disease. In this study, it is assumed that the incidences of brucellosis were under-reported at the start of the study period. However, in the fitted model, the number of reported cases is higher than that of incidences cases over the study period. This seems to be because the frequency of surveillance during the study period was higher than threshold value of frequency of surveillance for $\bar{R}_0>1$. If the frequency of surveillance was the same as the threshold value, that is, $\bar{R}_0=1$, the number of reported cases would be same as or lower than that of incidences; for example, once a cattle infects another cattle (the first infection), a cattle would be slaughtered before the second infection occurs. If the report and quarantine occured right after the first infection, the number of the reported cases was the same as that of incidence cases. However, practically, the infected cattle were usually identified between the time when the first infection and the second infection occur. This made time-lag between incidence and report, which contributes to

the difference between the number of incidence and report at the same time point. Moreover, if the surveillance do not cover all of the cattle, the difference would be much higher. In the study period, the frequency of surveillance was firstly over the threshold value in 2006. As extensive eradication program included the biannual test for the cattle in beef cattle farms with ≥ 10 heads, the frequency of brucellosis was increased to near 1 per year. These changes of surveillance lead to the rapid report and slaughter of cattle that were infected at the start of the study period and newly infected, which makes higher-reports and lower-incidences.

Likewise, for human brucellosis, as the frequency of surveillance increases, the infected cattle were rapidly slaughtered. Moreover, due to the coordinated surveillance for two diseases, the number of reported cases increased. These may lead to the high number of reported cases than the incidence of the disease.

Given the estimated $\overline{R}_0$, brucellosis seems to be eradicated. Also, since the combinations of diagnostic test used in the country or recommend by OIE have a higher sensitivity than the threshold value of Se for epidemic, change or addition of diagnostic tests seems not to worsen the epidemiological situations. However, reduction of frequency of surveillance for bovine brucellosis can lead to a significant change. And the threshold value for frequency of surveillance is not that different from the current value. Therefore, when rebuilding the policy for the surveillance, threshold value should be considered. Similarly, for effective contact rate between cattle, current policies such as pre-trade test or movement

restriction for cattle reared in the affected farm could affect the contact rate between cattle. Although the effect of the policies on the contact rate between cattle do not estimated quantitively, changing these policies also can leads to the further spread of the diseases.

Sensitivity analysis is crucial in identifying key parameters and finding effective control strategies. Remarkably, the results of sensitivity analysis suggest that animal-level interventions are more sensitive to both of human and bovine brucellosis outbreaks than human-level intervention. For frequency of surveillance, increased frequency of surveillance would rapidly "test and slaughter" the infected cattle. This can lower the newly infected cases and also shortens the period during which infected cattle can spread the disease to cattle and human. This leads to a great reduction of incidence of bovine and human brucellosis and also rapid detection of human cases. Since the duration before treatment for human brucellosis affects the complications and relapse [2], early detection of human brucellosis can lead to relieve the burden of human brucellosis.

Reducing the effective contact rate between cattle impacts on the incidence of bovine brucellosis, but relatively small impacts on the incidence of human brucellosis compared to results of frequency of surveillance. This is because the reducing the effective contact rate between cattle lower new infections, not infectious duration. For these reasons, the cumulative incidence of bovine brucellosis may be greatly affected due to the direct effects of change of the contact rate, however, the cumulative incidence of human brucellosis was affected

weakly.

In the Republic of Korea, serial diagnostic tests for bovine brucellosis include RBT and STAT in order [24]. However, the latter is not recommended by the OIE due to the cross-reactions with other pathogens. On the other hand, ELISAs recommended by the OIE mainly detects the IgG [10], whose characteristics reduce the false-positive results. Moreover, sensitivities of ELISAs are higher than that of STAT [8]. The problem is that the cattle in E_C that produce IgM cannot be detected because the serial combination test with RBT and ELISAs only detect IgG. Despite this, it may not occur further problems. Our results show $\overline{R}_{\mathrm{E}}$ contributed to very small part of $\overline{R}_0$, which implies that the cattle in E_C did not play a crucial role in the transmission dynamics. Moreover, the contribution level of $\overline{R}_{\mathrm{E}}$ to $\overline{R}_0$ was not affected by the sensitivity that diagnosis test can detect the cattle in E_C. In the aspect of diagnostic process, when STAT is conducted, it takes time to identify the results for about 2 days and needs to have diagnostic experience [8]. ELISAs have its advantages at this respect; less time to diagnose and less requirements for experience [8]. Thus, a new combination of diagnostic tests would lower the burden of diagnosticians. Taken together, serial combination test with RBT and ELISAs could reduce the burden of bovine and human brucellosis more efficiently.

Although effective contact rate between human and cattle has the least sensitive to the incidence of human brucellosis, human-level intervention should be included for the effective control strategies.

The effective contact rate can be divided into two parts: contact rate per capita and probability of infection per contact. In the Republic of Korea, while the populations related with agriculture is declining, the number of cattle is growing, which increases contact rate between human and cattle [46, 47]. In this aspect, without the safe and efficient vaccines for human, reducing the probability of infection is a key factor in human-level intervention. Previous studies revealed the positive effect of health education for at-risk human populations [60]. Especially, personal protective equipment (PPE) shows the protective effects on the infections [61, 62]. However, previous studies showed that many of at-risk human population inappropriately used PPE such as protective glasses and apron [61, 63, 64]. Even more, they felt inconvenient to wear PPE in the condition they worked [65, 66]. The combined animal and human health programs educating and working with stakeholders such as community engagement approach can be one of the effective solutions, which can also affect the occurrence of bovine brucellosis [67].

Scenario analyses show the possible impact of policy for controlling the brucellosis. Based on the results of scenario analyses, extension of surveillance can be the most effective strategy on both human and bovine brucellosis in the country. Reducing the effective contact rate between human and cattle can effectively reduce the cumulative incidence of human brucellosis but not for bovine brucellosis. Changing the combination of diagnostic test has the least impact on the incidences. This is because the current combination of diagnostic

test has also high sensitivity comparted to the new combination. Although reducing the effective contact rate between cattle is the best policy for preventing the bovine brucellosis among the scenarios, this is not the case for human brucellosis.

Previous studies show effects of animal vaccination on human brucellosis [60, 68]. In Greece, animal vaccination led to the significant decline of incidence of human brucellosis [60]. Moreover, animal vaccination was cost-saving and cost-effective for the animal health and human health [68]. In this study, animal vaccination scenarios show the possible reduction of incidence of bovine and human brucellosis. "test and slaughter" policy impose economic burden both on the government and farmers because of compensation for slaughtered cattle at 80% of running price [27]. This approach can also reduce the economic damage. Although the animal vaccination policy was not launched again after the termination of the policy due to the unexpected side effects, this result shows the possibility of reduction of the diseases burden and also give insights for vaccine coverage and timing.

This study shows influential impact of frequency of surveillance on the transmission dynamics. In the Republic of Korea, the surveillance systems for bovine and human brucellosis is coordinated but unidirectional: only from animal health sectors to human health sectors [31]. Furthermore, database for the two diseases are isolated [29, 45]. With the bidirectional coordinated surveillance and information system that is shared across the sectors, the frequency of surveillance could be higher, therefore, the burden of the diseases

may be more easily relieved [69].

The findings in this study need to be interpreted with cautions because of some limitations. First, cattle populations were not stratified by breed types. Biosecurity, breeding environment and contact patterns may be different from each breed types. Thus, the assumption of homogenous populations may bias the results. However, beef cattle constitute the major part of cattle population in the country [47]. And, the reported cases of bovine brucellosis were mainly from beef cattle [45]. Therefore, these results can be applied to the empirical situations despite this limitation. Second, the cost-effectiveness and the achievable upper-bound level of performance for each policy were not included in the analyses. Therefore, it is difficult to identify whether animal-level and/or human-level interventions are optimal control strategies for zoonotic brucellosis. Further studies incorporating these limitations can be examined based on this study.

Chapter 5. Conclusion

To the author's best knowledge, this is the first study for modeling the zoonotic transmission dynamics of brucellosis in the Republic of Korea. In this study, brucellosis in the Republic of Korea seems to be eradicated. However, the frequency of surveillance for bovine brucellosis was an influential factor that can lead to epidemic. Interestingly, animal-level interventions especially active surveillance was more sensitive to the incidence of human brucellosis than human-level intervention. Furthermore, RBT and ELISAs serial test can effectively reduce the burden of the brucellosis in the Republic of Korea. Extending the surveillance for bovine brucellosis is the most effective control policy for both human and bovine brucellosis. Moreover, animal vaccination can be one of the effective strategies.

In the Republic of Korea, human brucellosis is continuously reported, which shows the prevalence of the bovine brucellosis and the potential risk for human brucellosis. These results are expected to aid policymakers to build and implement "One Health" strategies for zoonotic brucellosis.

Bibliography

1. World Health Organization. *Neglected Zoonotic Diseases.* 2015 [cited 2018 Jun 29]; Available from: http://www.who.int/neglected_diseases/zoonoses/infections_more/en/.

2. Corbel, M.J., *Brucellosis in humans and animals*. 2006: World Health Organization.

3. Pappas, G., et al., *The new global map of human brucellosis.* The Lancet Infectious Diseases, 2006. **6**(2): p. 91-99.

4. Tuon, F.F., R.B. Gondolfo, and N. Cerchiari, *Human-to-human transmission of Brucella - a systematic review.* Trop Med Int Health, 2017. **22**(5): p. 539-546.

5. Fosgate, G.T., et al., *Time-space clustering of human brucellosis, California, 1973-1992.* Emerg Infect Dis, 2002. **8**(7): p. 672-8.

6. Zinsstag, J., et al., *Human benefits of animal interventions for zoonosis control.* Emerg Infect Dis, 2007. **13**(4): p. 527-31.

7. Corbel, M.J., *Brucellosis: an overview.* Emerg Infect Dis, 1997. **3**(2): p. 213-21.

8. Godfroid, J., K. Nielsen, and C. Saegerman, *Diagnosis of Brucellosis in Livestock and Wildlife.* Croatian Medical Journal, 2010. **51**(4): p. 296-305.

9. Nielsen, K., *Diagnosis of brucellosis by serology.* Veterinary microbiology, 2002. **90**(1-4): p. 447-459.

10. World Organisation for Animal Health. *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals 2018*. 2018 [cited 2019 10 April]; Available from: http://www.oie.int/en/standard-setting/terrestrial-manual/access-online/.

11. Dean, A.S., et al., *Global Burden of Human Brucellosis: A Systematic Review of Disease Frequency.* PLOS Neglected Tropical Diseases, 2012. **6**(10): p. e1865.

12. Zhang, N., et al., *Animal brucellosis control or eradication programs worldwide: A systematic review of experiences and lessons learned.* Prev Vet Med, 2018. **160**: p. 105-115.

13. Dorneles, E.M., N. Sriranganathan, and A.P. Lage, *Recent advances in Brucella abortus vaccines.* Vet Res, 2015. **46**: p. 76.

14. Perkins, S.D., S.J. Smither, and H.S. Atkins, *Towards a Brucella vaccine for humans.* FEMS Microbiol Rev, 2010. **34**(3): p. 379-94.

15. Monath, T.P., *Vaccines against diseases transmitted from animals to humans: a one health paradigm.* Vaccine, 2013. **31**(46): p. 5321-38.

16. Park, M.Y., et al., *A sporadic outbreak of human brucellosis in Korea.* J Korean Med Sci, 2005. **20**(6): p. 941-6.

17. Park, M.S., et al., *The first case of human brucellosis in Korea.* Infection and Chemotherapy, 2003. **35**(6): p. 461-466.

18. Lim, H.S., et al., *Brucellosis: an overview.* Korean Journal of Epidemiology, 2005. **27**(1): p. 26-36.

19. Lim, J.S., et al., *Spatial analysis to assess the relationship between human and bovine brucellosis in South Korea, 2005-2010.* Sci Rep, 2019. **9**(1): p. 6657.

20. Lee, H.S., et al., *Time series analysis of human and bovine brucellosis in South Korea from 2005 to 2010.* Prev Vet Med, 2013. **110**(2): p. 190-7.

21. Her, M., et al., *A genetic comparison of Brucella abortus isolates from animals and humans by using an MLVA assay.* J Microbiol Biotechnol, 2010. **20**(12): p. 1750-1755.

22. Park, D. and C. Lee, *Brucellosis of cattle in Korea.* J Kor Vet Med Assoc, 1959. **3**: p. 1-12.

23. Wee, S.H., H.M. Nam, and C.H. Kim, *Emergence of brucellosis in cattle in the Republic of Korea.* Veterinary Record, 2008. **162**(17): p. 556-557.

24. Ministry of Government Legislation. *Control and prevention measures standard operation protocol of brucellosis and tuberculosis.* [cited 2019 2 March]; Available from: http://www.law.go.kr/LSW/eng/engLsSc.do?menuId=2&query=ACT%20ON%20THE%20PREVENTION%20OF%20CONTAGIOUS%20ANIMAL%20DISEASES#liBgcolor0.

25. Yoon, H., et al., *Epidemiology of brucellosis among cattle in Korea from 2001 to 2011.* Journal of Veterinary Science, 2014. **15**(4).

26. Lim, H.-S., *Brucellosis.* J Korean Med Assoc, 2004. **47**(11): p. 1048-1055.

27. Yoon, H., et al., *Impact of bovine brucellosis eradication programs in the Republic of Korea.* Prev Vet Med, 2010. **95**(3-4): p. 288-91.

28. Sung, S.-R., et al., *Evaluation on diagnostic efficiency of the standard tube agglutination test for bovine brucellosis.* Korean Journal of Veterinary Service, 2012. **35**(4): p. 269-273.

29. Korea Centers for Disease Control and Prevention. *Infectious Disease Statistics System* 2018 [cited 2018 May 6th]; Available from: http://www.cdc.go.kr/npt/.

30. Kim, E.K., et al., *Is Human Brucellosis Endemics in Korea?* Yonsei Med J, 2017. **58**(1): p. 259-260.

31. Korea Centers for Disease Control and Prevention. *Guidelines for human brucellosis*. 2007 [cited 2019 1 Mar]; Available from: http://www.cdc.go.kr/CDC/cms/content/mobile/71/138471_view.html.

32. Yeom, J.S., et al., *Seroepidemiologic study of brucellosis in Cheju Island.* Korean Journal of Infectious Diseases, 1998. **30**(2): p. 165-172.

33. Lee, K., et al., *Seroprevalence of Brucellosis among Risk Population in Gyeongsangbuk-do, 2006.* J Prev Med Public Health, 2007. **40**(4): p. 285-290.

34. Hou, Q. and X.-D. Sun, *Modeling sheep brucellosis transmission with a multi-stage model in Changling County of Jilin Province, China.* Journal of Applied Mathematics and Computing, 2015. **51**(1-2): p. 227-244.

35. Zhang, J., et al., *Prediction and control of brucellosis transmission of dairy cattle in Zhejiang Province, China.* PLoS One, 2014. **9**(11): p. e108592.

36. Nie, J., et al., *Modeling the Transmission Dynamics of Dairy Cattle Brucellosis in Jilin Province, China.* Journal of Biological Systems, 2014. **22**(04): p. 533-554.

37. Lolika, P.O., et al., *Modeling and analyzing the effects of seasonality on brucellosis infection.* Chaos, Solitons & Fractals, 2017. **104**: p. 338-349.

38. Li, M.-T., et al., *Transmission dynamics of a multi-group brucellosis model with mixed cross infection in public farm.* Applied Mathematics and Computation, 2014. **237**: p. 582-594.

39. Zinsstag, J., et al., *A model of animal-human brucellosis transmission in Mongolia.* Prev Vet Med, 2005. **69**(1-2): p. 77-95.

40. Hou, Q., et al., *Modeling the transmission dynamics of sheep brucellosis in Inner Mongolia Autonomous Region, China.* Math Biosci, 2013. **242**(1): p. 51-8.

41. Li, M., et al., *Transmission dynamics and control for a brucellosis model in Hinggan League of Inner Mongolia, China.* Math Biosci Eng, 2014. **11**(5): p. 1115-37.

42. Ridenhour, B., J.M. Kowalik, and D.K. Shay, *Unraveling R0: considerations for public health applications.* Am J Public Health, 2014. **104**(2): p. e32-41.

43. Delamater, P.L., et al., *Complexity of the Basic Reproduction Number (R0).* Emerg Infect Dis, 2019. **25**(1): p. 1-4.

44. Korea Centers for Disease Control and Prevention. *Case definitions for national notifiable infectious diseases*. 2016 [cited 2019 1 April].

45. Animal and Plant Quarantine Agency. *Korea Animal Health Integrated System*. 2018 [cited 2018 Mar 6th]; Available from: http://www.kahis.go.kr.

46. Statistics Korea. *Census of Agriculture, Forestry and Fisheries*. 2018 [cited 2018 May 6th]; Available from: https://mdis.kostat.go.kr/index.do.

47. Statistics Korea. *Survey of Livestock Trend*. 2018 [cited 2019 2 Mar]; Available from: http://kosis.kr/publication/publicationThema.do?pubcode=SD.

48. Korean Statistical Information System. *Complete life table*. 2018 [cited 2019 3 Mar.]; Available from: http://kosis.kr/statHtml/statHtml.do?orgId=101&tblId=DT_1B42.

49. Animal and Plant Quarantine Agency. *Report of livestock slaughter* 2016 [cited 2019 1 Mar]; Available from: http://www.qia.go.kr/livestock/clean/listTcsjWebAction.do.

50. Rahman, A.K.M.A., et al., *Bayesian evaluation of three serological tests for the diagnosis of bovine brucellosis in Bangladesh.* Epidemiology and Infection, 2019. **147**.

51. Diekmann, O., J.A.P. Heesterbeek, and J.A.J. Metz, *On the definition and the computation of the basic reproduction ratio R 0 in models for infectious diseases in heterogeneous populations.* Journal of Mathematical Biology, 1990. **28**(4).

52. Diekmann, O., J.A. Heesterbeek, and M.G. Roberts, *The construction of next-generation matrices for compartmental epidemic models.* J R Soc Interface, 2010. **7**(47): p. 873-85.

53. Olsen, S.C. and W.S. Stoffregen, *Essential role of vaccines in brucellosis control and eradication programs for livestock.* Expert Review of Vaccines, 2005. **4**(6): p. 915-928.

54. King, A., *subplex: Unconstrained optimization using the subplex algorithm.* R package version, 2015: p. 1.1-6.

55. King, A.A., D. Nguyen, and E.L. Ionides, *Statistical inference for partially observed Markov processes via the R package pomp.* arXiv preprint arXiv:1509.00503, 2015.

56. Team R Core, *R: A language and environment for statistical computing.* 2013.

57. Lloyd-Smith, J.O., et al., *Epidemic dynamics at the human-animal interface.* Science, 2009. **326**(5958): p. 1362-7.

58. Ryu, S., et al., *One Health Perspectives on Emerging Public Health Threats.* J Prev Med Public Health, 2017. **50**(6): p. 411-414.

59. Centers for Disease Control and Prevention. *One Health*. 2018 November 5, 2018 [cited 2019 1 May]; Available from: https://www.cdc.gov/onehealth/index.html.

60. Jelastopulu, E., et al., *Incidence of human brucellosis in a rural area in Western Greece after the implementation of a vaccination programme against animal brucellosis.* BMC Public Health, 2008. **8**: p. 241.

61. Acharya, D., S.D. Hwang, and J.H. Park, *Seroreactivity and Risk Factors Associated with Human Brucellosis among Cattle Slaughterhouse Workers in South Korea.* Int J Environ Res Public Health, 2018. **15**(11).

62. Esmaeili, S., et al., *Seroprevalence of Brucellosis, Leptospirosis, and Q Fever among Butchers and Slaughterhouse Workers in South-Eastern Iran.* PLOS ONE, 2016. **11**(1): p. e0144953.

63. Korea Centers for Disease Control. *Current status of human brucellosis after national survey*. 2006 [cited 2019 30 April]; Available from: http://www.cdc.go.kr/CDC/cms/cmsFileDownload.jsp?fid=31&cid=12256&fieldName=attach1&index=1.

64. Korea Centers for Disease Control. *A survey on the status of zoonoses in a livestock farmers*. 2013 [cited 2019 30 April]; Available from: http://www.google.co.uk/url?sa=t&rct=j&q=&esrc=s&source=web&cd=2&ved=0ahUKEwiz_rmxotjbAhXGw7wKHfavDF0QFggoMAE&url=http%3A%2F%2Fwww.nih.go.kr%2FCDC%2Fcms%2FcmsFileDownload.jsp%3Ffid%3D3081%26cid%3D25365%26fieldName%3Dattach1%26index%3D1&usg=AOvVaw0GOxsmjKH1mQm3JzXf6oEi.

65. Choi, K.-B., et al., *Awareness of Major Zoonoses among Dairy Farmers in Gyeonggi Province.* Journal of agricultural medicine and community health, 2010. **35**(4): p. 339-349.

66. Lim, H.-S., S.-J. Yoo, and K. Lee, *Awareness of Zoonoses among Cattle Slaughterhouse Workers in Korea.* Journal of agricultural medicine and community health, 2009. **34**(1): p. 101-112.

67. Berrian, A.M., et al., *A community-based One Health education program for disease risk mitigation at the human-animal interface.* One Health, 2018. **5**: p. 9-20.

68. Roth, F., et al., *Human health benefits from livestock vaccination for brucellosis: case study.* Bull World Health Organ, 2003. **81**(12): p. 867-76.

69. Halliday, J., et al., *Bringing together emerging and endemic zoonoses surveillance: shared challenges and a common solution.* Philos Trans R Soc Lond B Biol Sci, 2012. **367**(1604): p. 2872-80.

국문초록

브루셀라증의 사람-동물 전파 모형을 이용한 동물 방역 정책이 사람 건강에 미치는 영향 평가

사람 브루셀라증은 동물에서 사람으로 전파되는 인수공통감염병으로 2002년 국내 첫 보고 이후, 현재까지 지속적으로 보고되고 있다. 기존 연구들을 통하여 소 브루셀라증과 사람 브루셀라증의 관련성이 확인되었지만, 동물 방역 정책이 사람 건강에 미치는 영향에 대해 정량적으로 분석한 연구는 부족한 실정이다. 따라서 본 연구에서는 사람 및 동물 감염병 데이터베이스로부터 추출한 전수감시자료를 바탕으로 브루셀라증의 사람-동물 전파 모형을 통해 동물 방역 정책이 사람 건강에 미치는 영향에 대해 확인해 보았다.

본 연구에서는 2006년부터 2018년까지의 보고된 사람 및 소 브루셀라증 자료를 이용했으며 진단법의 민감도 및 두 질병의 연계된 감시체계의 특성을 반영하였다.

추정된 기본감염재생산수는 브루셀라증이 근절될 것임을 보여주었다. 하지만 소 브루셀라증에 대한 감시체계 주기가 확산에 가장 큰 영향을 끼칠 수 있으며 재유행에 대한 잠재력 있는 요인으로 나타났다. 또한, 새로운 조합의 진단법은 브루셀라증 감시에 더 효과적일 것으로 보인다. 흥미롭게도, 사람 단계의 중재보다 동물 단계의 중재가 사람 브루셀라증 전파 동역학 (transmission dynamics)에 더 민감한 변수임을 확인할

수 있었다. 국내 사람 및 소 브루셀라증 근절을 위해서는 소 브루셀라증 감시체계 확대가 가장 효과적인 전략이 될 것이며 동물 백신 정책은 또한 동물은 물론 사람의 건강 향상에 효과적으로 기여할 수 있는 방법이 될 것으로 보인다. 본 연구결과는 원헬스 전략이 국내 브루셀라증에 대한 효과적인 중재 방법이 될 수 있음을 보여준다.

본 연구의 모델은 브루셀라증의 사람-동물 전파 특성을 반영한 국내 최초의 모델이며 비용-효용 분석 및 최적 관리 전략 연구에 대한 기초자료로 사용될 수 있을 것이다.

주요어: 브루셀라증, 감염병 수리모형, 인수공통감염병, 원헬스

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