Ph.D. Thesis

Quantitative analyses for considerations on control measures of important animal and zoonotic infectious diseases

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Quantitative analyses for considerations on control measures of important animal and zoonotic infectious diseases

(重要家畜・人獣共通感染症制御方法の定量的検討方法に関する研究)

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Contents

ABBRIVIATIONS

BSE: Bovine Spongiform Encephalopathy

FMD: Foot-and-mouth disease

HPAI: High pathogenic avian influenza

KAP: Knowledge, attitudes and practice

RABV: Rabies virus

VD: Vietnamese Dong

WTP: Willingness-to-pay

Chapter 1. General introduction

1.1. Background

In recent years, Japan has experienced the occurrence of several infectious diseases. Foot-and-mouth disease (FMD) was confirmed in 2000, which was rapidly contained; however in 2010, FMD epidemic resulted in the deaths of 290,000 animals due to slaughtering of the infected and vaccinated animals for the disease control [15]. In 2001, first domestic Bovine Spongiform Encephalopathy (BSE) was detected in Japan, and caused huge socio-economical consequence. By the announcement of BSE outbreak, consumers were alerted by the risk and became anxious about eating beef and beef products, and as a result, sudden reduction in meat consumption severely affected to livestock industries [16,19]. Furthermore, several outbreaks of high pathogenic avian influenza (HPAI) occurred, and slaughtering large numbers of birds and halting movement of birds and eggs have caused large economic damages. Moreover, uncontrolled use of antimicrobial agents poses serious risk of multi-drug resistance, and the world started efforts of facilitating prudent use of antimicrobials agents. These infectious diseases are the great threat to livestock production, as well as public health, and frequencies of such disease emergence and re-emergence are increasing due to several factors such as globalization, global warming, and encroachment into wildlife territories [20]. In order to tackle with the risks of animal and zoonotic infectious disease, having effective control options in advance provides a compass to the livestock industries, authorities, and the public for better preparedness. Epidemiology is a set of diverse powerful tools to realize such evidence-based formulation of disease control measures.

1.2. Epidemiology

The epidemiology is defined as the study of a disease in the population at risk and of factors that determine its occurrence [46]. Many disease problems can be better dealt through population-based interventions rather than individual-based. However, veterinary epidemiology in Japan is far belated from the other countries. Epidemiology can quantify the nature of disease by measuring the distribution and frequency of the disease in relation to the population at risk [58]. The scopes of veterinary epidemiology are to detect the causes of the disease in the animal and human populations, to increase the livestock productivity and to improve animal and human health and welfare. The epidemiology is also used to predict the future outbreaks or to quantify the economic consequence of the infectious disease outbreaks [58].

In this thesis, a variety of epidemiological, mathematical and socio-economical techniques were applied to explore how veterinary epidemiology can contribute to the better decision making on the control of animal infectious and zoonotic diseases. Two important diseases, rabies, and FMD were studied to achieve this purpose.

1.3. Research objectives and thesis layout

In the Chapter 2, the risk of rabies spread once it is introduced into Japan was assessed using infectious disease modelling. Mathematical models can predict and understand the nature of infectious disease from various perspectives. For example, a mathematical model is applied to illustrate the course of infectious disease and its cause. Moreover, models can be developed to evaluate the efficacy of control measures against infectious diseases. On the other hand, mathematical models can cause serious social damage as seen in the FMD epidemic in the UK in 2001, when models were first used for policy making, which resulted in the application of pre-emptive culling without use of vaccination and extreme loss of animals [60]. In Japan, over 60 years elapsed since the elimination of rabies from the country, and decline of vaccination coverage has been argued to elevate the risk of causing large scale epidemic. On the other hand, most of the rabies free countries do not employ mandatory rabies vaccination. The chapter explored the risk of rabies spread under both current vaccination coverage and hypothetical discontinuation of rabies vaccination to provide the scientific evidence for the future discussion to review the current rabies control measures in Japan. The effectiveness of current rabies control and the influence of the behavior of dog owners and stray dogs on the risk were also examined.

In the Chapter 3, socio-economic characteristics associated with voluntary rabies control among the population in northern Vietnam was studied. While Chapter 2 demonstrates the significant value of mathematical modelling on the decision making, models cannot predict the acceptability and feasibility of disease control options. Rabies can be effectively prevented both in human and animals using pre-exposure vaccination. However, the practice of dog rabies vaccination is affected by limited resources and the decision of dog owners. The integrated approach based on One Health is necessary to detect the obstacle to rabies control. In this chapter, a socio-economic study was conducted in the rabies endemic region of Vietnam where human deaths are said to be increasing to provide an opportunity to discuss about rabies control measures among stakeholders in Vietnam and to help establish the effective control measures against rabies in Vietnam based on the evidence [50]. The factors associated with dog rabies vaccination, willingness-to-pay for dog rabies vaccination and tethering the dogs were revealed under the structure of knowledge, attitudes and practice.

In the Chapter 4, the risk factors on the hesitation to restart farming after FMD epidemic in Miyazaki Prefecture, Japan, were analyzed. Risk factor analysis is usually used to examine the relationship between exposure and the disease. While Chapter 2 and 3 showed the evidence to consider the control strategy to communicable disease among human and animal population, this chapter will cover the way to help vulnerable people in the disaster due to infectious disease which mostly affects animals. During the FMD epidemic in 2010, the lives of 290,000 animals were lost, and this caused heavy mental stress to the livestock farmers, as well as veterinarians and local civil [15]. However, little attention to the consequence of large outbreak with slaughtering such as FMD and HPAI to mental health is paid. Thus, it is important to make a best-bet decision to prevent and control infectious disease, but rapid recovery from the damages of epidemics is also very important to maintain food security and human welfare from the perspective of human health. In this chapter risk factor analysis was applied to identify the reasons of hesitating restarting livestock farming among the farmers who lost animals in the epidemic. Finally, Chapter 5 discussed the result chapters and integrated the findings to conclude this thesis. This thesis provides the way of consideration on infectious disease control based on the scientific evidences, understanding ecological and social systems.

Chapter 2. Risk assessment of rabies spread in Japan using a mathematical modelling

2.1. Introduction

Rabies is a fatal zoonotic disease and is caused by rabies virus (RABV) belonging to the genus *Lissavirus* in the family *Rhabdoviridae*. There are fourteen *lyssaviruses*, which are maintained among specific different species [20]. Every year 59,000 people are estimated to die of rabies transmitted by domestic dogs, mostly in Asia and Africa [13]. The main reservoir hosts for rabies are domestic dogs in low- and middle-income countries, but wild animals including foxes, raccoons, skunks, and raccoon dogs also maintain rabies in some parts of the world [53]. A cross-species transmission of rabies variants from a reservoir host normally maintaining original variant to another animal species occasionally occurs [20]. Historically, measures for controlling dog rabies have included dog population management, movement restriction, and vaccination [24]. Dog vaccination is the most effective control measure [21,60]. Today, rabies mostly circulates in countries where large-scale dog vaccinations have not been undertaken, and has emerged in unvaccinated dog populations in previously rabies-free areas [47,57].

Japan has been free from rabies since 1957 [27], following rigorous implementation of control measures under the Rabies Prevention Act, which was enacted in 1950. This act includes dog registration, capture of free-roaming dogs, mandatory dog vaccination, and quarantine of animals brought into the country. In Japan, free-roaming dogs can still be found, and local government employees capture them. Any person who wants to keep them can adopt captured and surrendered stray dogs. Dog vaccinations were performed twice per year until 1985, and dog vaccination coverage remained high until 1995 [32]. The long absence of rabies from Japan has weakened public interest in rabies control measures and based on reported numbers of vaccinated dogs and the estimated total dog population in Japan, including non-57 registered dogs, vaccination coverage has declined to less than 50% [18,33].

There is therefore growing concern about the elevated risk of rabies spreading following the introduction of a rabid dog into Japan—though the risk of such an introduction is considered to be very low [27]. Compared to the time when rabies was endemic in Japan, many more dog owners confine their dogs inside and the number of stray dogs has substantially reduced. Therefore, the current risk of rabies spreading in Japan has likely changed considerably compared to the historical risk. The aims of this study were to assess, using infectious disease modelling, 1) the risk of rabies spread in Japan in the event of a rabid dog being introduced, and 2) the efficacy of current contingency plans to prevent an outbreak.

2.2. Methods and Materials

2.2.1. Study site selection

Ibaraki and Hokkaido Prefectures were selected for this study (Figure 1). Ibaraki Prefecture was chosen because vaccination coverage is low (51.8%, Table 1), and more free-roaming dogs are captured annually in the prefecture than any other in Japan [33,35]. Hokkaido Prefecture was also chosen because of the frequency of visits to its ports by fishing vessels taking dogs on board from Russia, where rabies is endemic [27]. In Hokkaido Prefecture, estimated vaccination coverage is higher than in Ibaraki Prefecture (56.3%, Table 1), but many free-roaming dogs are captured annually [33,35].

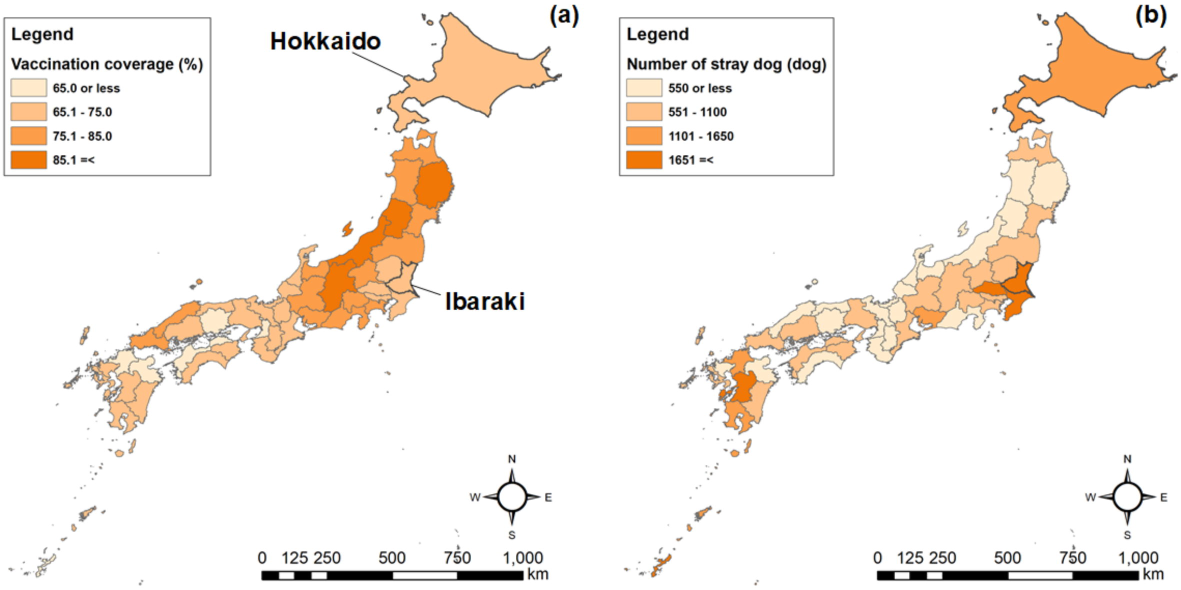

Figure 1. Hokkaido and Ibaraki Prefecture in Japan and potential high-risk characteristics of prefectures, specifically: a) the number of stray dogs and b) vaccination coverage

Table 1. Characteristics of Hokkaido and Ibaraki Prefectures as of 2013 (Prefectural data)

Items	Hokkaido	Ibaraki	Source
Area (km^2)	77,282	5,878	National Statistical Bureau
Human population	5,454,447	2,941,109	Hokkaido Prefecture Ibaraki Prefecture
Human population density (km^{-2})	70.6	500.4	Hokkaido Prefecture Ibaraki Prefecture National Statistical Bureau
Number of stray dogs	1,089	2,181	Hokkaido Prefecture Ibaraki Prefecture Ministry of the Environment
Estimated total dog population	352,662	232,683	Japan Pet Food Association
Density of dogs (dogs/km^2)	4.6	39.6	Japan Pet Food Association National Statistical Bureau
Vaccination coverage (%)	56.3	51.8	Japan Pet Food Association
Proportion of dogs registered (%)	80.8	79.0	Japan Pet Food Association
Areal proportion of plain fields	28.5	65.2	Forestry Agency

2.2.2. Data collection

Demographic and epidemiological data including numbers of registered dogs, vaccination coverage among registered dogs, and numbers of stray dogs captured per city/town/village (shi/cho/son) administrative unit in 2013 were collected from both prefectures. Numbers of captured stray dogs may not accurately reflect total numbers of stray dogs in an area, but was used as a best-estimate proxy. Vaccination coverage was calculated from the recorded number of vaccinated dogs and the estimated total dog population [18].

This study used historical data on rabies epidemics in Osaka Prefecture between 1914 and 1915, from Prefectural reports and newspapers, described elsewhere [26] . The 1914 dog population was collected from newspaper reports [26], and the human population from the 1920 census [34]. To estimate the public health impact of rabies, newspaper and public reports published in Tokyo and the surrounding prefectures between 1893 and 1954 were surveyed for descriptions of the numbers of persons bitten by individual rabid dogs.

2.2.3. The development of mathematical model

We used an individual-based model to simulate the spread of rabies on a 1-by-1 km grid representing the geography of the study prefectures, as adapted from a previous study [60]. Each cell included demographic and epidemiological information, such as the human and dog population densities and vaccination coverage within the city/township administrative unit. For every simulated case, the number of secondary cases was determined by drawing from a negative binomial distribution with mean equal to the basic reproductive number, R_0. Secondary cases are allocated to grid cells according to a dispersal kernel and become infectious after the serial interval, Ts, elapses. Estimation of R_0 and Ts (Table 2) from historical epidemics in Osaka Prefecture is described elsewhere [26]. All analyses were conducted using R, version 3.1.0 [49].

Table 2. Model parameters and distributions used in the default model (Ibaraki Prefecture with vaccination coverage at 0%)

Items	Parameters/distributions (unit)	Source
Reproduction number	Gamma distribution (shape = 24.6, rate = 9.87) (dog); R_0 = 2.42 (90%CI: 1.94 – 2.91)	[26]
Serial interval	Gamma (shape = 1.41, rate = 0.03) (day)	[26]
Dispersion kernel	Gamma (shape = 0.215, scale = 4.08) (km)	[14]
Mixing parameter (α)	0.5	Estimated
Adjusting parameter for dog population (δ)	0.73	Estimated
Adjusting parameter for dispersion kernel (ε)	1.13	Estimated
Parameter to model dog-to-human population ratio ζ/δ (ζ)	11.5	[33]
Walking time with dog per day	Beta (shape 1 = 0.01, shape 2 = 0.5) (hour)	[43]
Delay of initial action	30 days	Assumption
Probability of detection in outbreak investigation	Binomial (p = 0.5, n = N_{det}) (dog)	Assumption
The number of captured dogs per day	Poisson (lambda = 10) (dog)	Assumption
The number of vaccinated dogs per day	Poisson (lambda = 100) (dog)	Assumption

Table 2. Model parameters and distributions used in the default model (Ibaraki Prefecture with vaccination coverage at 0%) (Continued)

Items	Parameters/distributions (unit)	Source
Probability of releasing a rabid owned dog	50%	Assumption
Probability that a rabid stray dog selects a stray dog to bite	50%	Assumption

2.2.4. Initialization

The total number of dogs in each grid cell is denoted $dogs_i$ and cases cannot exceed this number. To calculate $dogs_i$, dogs were classified into: (a) dogs that are always kept indoors, (b) dogs that go outdoors only for walks, (c) dogs occasionally kept outdoors, (d) dogs always kept outdoors, and (e) stray dogs, according to published data [18]. Dogs were assigned within a cell according to these proportions, with the estimated number of dogs in a given administrative unit equally allocated across the cells within that unit. Dogs in category *a* were assumed to never have contact with a rabid dog, and were removed from $dogs_i$. The number of dogs outdoors in category b ($N_{Out,\,i}$) was modeled using a binomial distribution, with the probability of being outdoors at a given time P_W, calculated from published data on daily time spent walking [43]:

$N_{out,i} = binom(N, P_w)$ (Equation 1)

Stray dogs (e) in each administrative unit were allocated randomly to the cells within it. Thus, $dogs_i$ is described as:

$dogs_i = (N_{Out,i} + c_i + d_i + e_i)$ / area of administrative unit i (Equation 2)

Vaccinated animals were assumed to not develop rabies if bitten by a rabid dog. Stray dogs were assumed to all be unvaccinated.

2.2.5. Parameterization

Locations of secondary cases were assigned according to distances from primary cases assuming preferential movement towards areas of higher dog population density, such that the probability of secondary cases occurring in cell *i*, Pr_i was:

$$\Pr_i = \frac{\alpha \times dK_{OSi} + (1-\alpha)\delta dens_i}{\sum_{i=1}^{n}\{\alpha \times dK_{OSi} + (1-\alpha)\delta dens_i\}} \text{ (Equation 3)}$$

where: dK_{OSi} is the likelihood of the distance between primary and secondary cases, according to the dispersal kernel derived from the historical epidemic in Osaka [26]; $dens_i$ is the dog population density in cell *i*; the parameter α characterizes the influence of dog population density on secondary case locations, taking a value between 0 and 1; and δ is a tuning constant. dK_{OS} was modelled modifying a gamma distributed dispersal kernel reported from Tanzania [14]. The shape parameter of a gamma distribution represents numbers of events, and the scale parameter the time duration [6], or distance for a dispersal kernel. Thus dK_{OS} was modelled as:

$$dK_{OS} = gamma(v, \varepsilon w) \text{ (Equation 4)}$$

where ε adjusts the distance between primary and secondary cases in Tanzania [14] to the historical Osaka epidemic [26]. The distance between primary and secondary cases in Osaka Prefecture was calculated from the centroids of the administrative units where cases occurred, as exact locations were not available. Dog population data at the zone/township/village administrative unit were not available, but only the total dog population for Osaka Prefecture. A constant dog-to-human ratio was therefore assumed for all locations, and dogs allocated to each unit accordingly. The parameters α, ε and ζ were optimized using the optim() function of R package stats [51] to minimize the chi-square value:

$$x^2 = \sum_{j=1}^{n} \frac{(O_j - E_j)^2}{E_j} \quad \text{(Equation 5)}$$

where n is the total number of administrative units in Osaka Prefecture in 1914 and O_j the number of reported rabies cases in administrative unit, j. Expected rabies cases, E_j, in each administrative unit, with a particular parameter set were obtained from 1000 iterations of the simulation. Estimated parameters were validated by using the chi-square test to verify that there was no significant difference between the numbers of simulated and reported cases in each administrative unit [55].

Two other aspects relating to the behavior of rabid dogs and their owners was modeled. In Japan, owned dogs kept indoors are confined and those kept outdoors are leashed. Therefore, if the owner of an infected dog does not release it, the risk of secondary cases is negligible. However, a rabid dog may accidentally be released by its owner, therefore unintended release was modeled. If a stray dog becomes rabid, the dog may tend to bite stray dogs, which are more accessible than owned dogs. Rabid owned dogs were modeled to bite owned and stray dogs with probabilities corresponding to the proportions of owned and stray dogs in each cell, whereas, rabid stray dogs were modeled to bite stray dogs and owned dogs with equal probability despite a greater proportion of dogs being owned.

2.2.6. Risk assessment

To assess the current risk of dog rabies spread, vaccination coverage in the contemporary dog population was used. The probability of unintended release of a rabid dog was set as 50%, as there was no prior information on this probability. The models for Hokkaido and Ibaraki Prefectures were each run for 1000 iterations, and outbreak sizes recorded when all cases had either died or been captured. The relationship between outbreak size and the proportion of rabid dogs that were stray was examined using a logistic regression with quasi-binomial errors.

To assess the efficacy of rabies control measures, vaccination coverage was reduced to 0% to reflect discontinuation of the current mandatory vaccination scheme and compared to the status quo. Four outbreak response parameters were explored to assess the efficacy of contingency plans: (1) time until the response, (2) ability to detect rabid dogs and dogs contacted by rabid dogs, (3) speed of capturing stray dogs, and (4) speed of emergency vaccination. In this assessment, only Ibaraki Prefecture was modeled and vaccination coverage was set to 0% because under current coverage, too few cases were generated to assess the effect of outbreak responses.

The initial response to a rabies outbreak is, by law, an immediate epidemiological investigation by the prefectural government to search for dogs contacted by the index case. This involves detection of secondary dog rabies cases, capture of stray dogs, and emergency vaccination of dogs around the area of the detected case(s). The daily number of detected rabid dogs and dogs contacted by rabid dogs was modeled using a binomial distribution, where the total number of rabid and contacted dogs in a cell is denoted as N_{Cont} (Table 2). Investigations were modeled as being implemented within a 5-km radius from the centroid of the cell with the detected case, on the basis of discussions with responsible prefectural government officers. Both the speed of capturing stray dogs and of emergency vaccinations were modeled as the number of dogs captured or vaccinated per day, drawn from Poisson distributions (Table 2). We assumed that vaccinated dogs became immune 14 days post-vaccination.

Table 3 summarizes the parameter values used for assessment of the efficacy of contingency plans, agreed upon as plausible scenarios through discussions with prefectural government officers.

To assess the risk of rabid dog bite injuries, two approaches were taken: (1. stochastic approach) each rabid dog generated in the model was assigned either it bit at least one person or not, and the number of people to bite if the dog was assigned to bite, and (2. ratio approach) according to the bite injury cases – rabid dog ratio (0.83 persons/rabid dog; 3,805 victims versus 4,584 rabid dogs) reported in the past epidemic in Osaka Prefecture [26], the number of bite injury cases was calculated using the dog rabies outbreak size for each simulation. For the stochastic approach, rabid dogs were stochastically assigned to bite with the probability of 25.7% based on the published report (of 1,000 rabid dogs, 743 dogs do not bite people) [12], and the number of bite injuries by a rabid dog was modeled using bootstrapping of 116 historical records from Tokyo. A set of 1000 samples of total numbers of bite injuries was generated for each incursion simulation. As final epidemic size of dog rabies was simulated for 1000 iterations, in total 1 million estimates of numbers of bite injuries were generated, and injuries per outbreak summarized (mean, median, and 2.5th and 97.5th percentiles), for both Prefectures.

2.2.7. Sensitivity analysis

This model depends on two parameters for which no information was available: the unintended release of a rabid dog by their owner and preferential contact by rabid stray dogs. Sensitivity of the model to these parameters was explored, with the probability of unintentional release changed from 10% to 90% and contact with stray dogs increased from 50% to 90% (Table 3).

Table 3. The parameter set of each scenario for rabies control options

Scenario	Change of parameter values
Delay of initial response	Start of initial response at day 90
Increasing capacity of detecting rabid and contacted dogs	Probability of detection: 80%
Increasing capacity of capturing stray dogs	Capturing 20 dogs per day
Increasing capacity of emergency dog vaccination	Vaccinating 200 dogs per day
Sensitivity of unintended release of a rabid dog	Probability of release: 10 and 90%
Sensitivity of selective bites by a rabid stray dog	Selection of stray dogs to bite: 90%

2.3. Results

2.3.1. Parameter estimation

Estimated parameter values for rabid dog movement (α, δ, ε, ζ) from fitting the model to the historical Osaka outbreak data are reported in Table 2. We found no significant difference between numbers of observed and simulated rabies cases ($p = 0.8$).

2.3.2. Risk assessment

The mean outbreak sizes, including the index cases, in Hokkaido and Ibaraki Prefectures under current vaccination coverage were 3.1 (median, 2; range, 1 - 27; 95% CI, 1 - 14) and 3.8 (median, 2; range, 1 - 50; 95% CI, 1 - 20), respectively (Figure 2a and b), with 6.9% and 9.0% of outbreaks ≥10 cases. The mean epidemic durations were 55.3 days (median, 31; range, 1 – 537; 95% CI, 1 - 269) and 64.4 days (median, 32; range, 1 – 634; 95% CI, 1 - 297) in respective prefectures.

In a scenario in which annual mandatory vaccination was discontinued, outbreaks were larger, with a mean of 22.8 (median, 4; range, 1 - 225; 95% CI, 1 - 142) and 17.4 (median, 4; range, 1 - 143; 95% CI, 1 - 98) rabid dogs in Hokkaido and Ibaraki Prefectures (Figure 2c and d, Table 4), with 35.5% and 34.5% of outbreaks ≥10 cases.

Delays of 60 days from initial detection to response increased the final outbreak size, but the probability of outbreaks ≥10 cases remained unchanged (Table 4).

Emergency responses (increasing capacities for detecting rabid and rabies-contacted dogs, capturing stray dogs, and performing emergency vaccinations) did not affect the outbreak sizes, or the proportion of outbreaks with ≥10 cases (Table 4).

In the 116 records of bite injuries caused by individual rabid dogs, the average number of people bitten by a rabid dog was 5.5 (median, 3; range, 1 – 46; 95%CI, 1 - 29). The mean numbers of rabid dog bite injuries per incursion in Hokkaido and Ibaraki Prefectures under current vaccination coverage were estimated to be 4.4 (median, 0; range, 0 – 210; 95% CI, 0 - 35) and 5.4 (median, 0; range, 0 – 277; 95% CI, 0 - 41), respectively by the stochastic approach, and 2.6 (median, 2; range, 1 – 22; 95%CI, 1 - 12) and 3.2 (median, 2; range, 1 – 42; 95%CI, 1 - 17), respectively by the ratio approach.

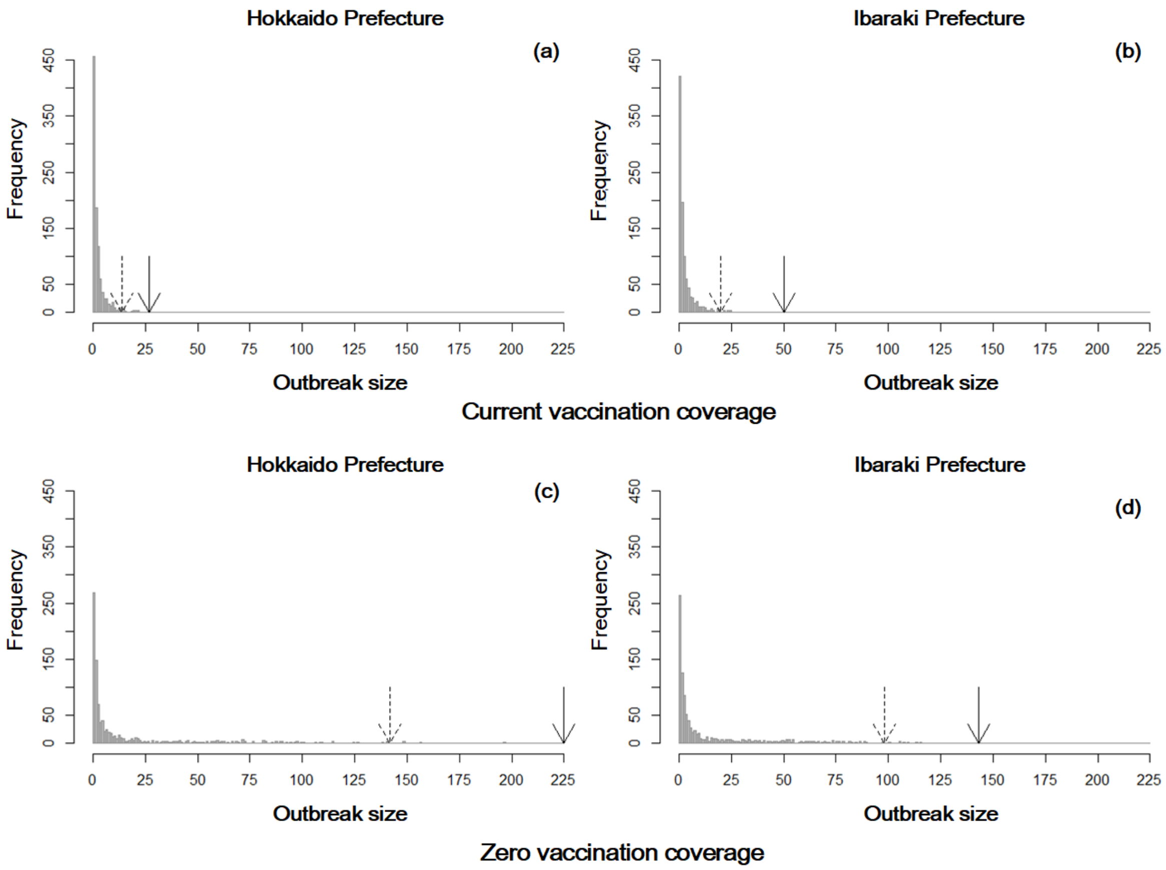

Figure 2. Predicted outbreak sizes in Hokkaido (a) and Ibaraki (b) Prefectures under current vaccination coverage, and without vaccination (c and d). Dashed and solid arrows shows the 97.5 percentile and maximum of final size.

Table 4. Scenario analysis results of final size and duration of the epidemic in Ibaraki Prefecture (vaccination coverage: 0%)

Scenario	Final size			Epidemic period in days (95%CI)
	Mean (95%CI)	Range	Probability of more than or equal to ten cases (95%CI)	
Default setting	17.4 (1 - 98)	1-143	34.5% (31.6– 37.6)	142.7 (1 - 484)
Delayed initial response	17.9 (1 - 103)	1-189	32.6% (29.7– 35.6)	145.8 (1 - 538)
Increasing capacity of detecting rabid and contacted dogs	17.0 (1 - 96)	1-157	34.2% (31.3 – 37.2)	138.1 (1 - 482)
Increasing capacity of capturing stray dogs	18.4 (1 - 105)	1-151	35.2% (32.3 – 38.3)	143.9 (1 - 511)
Increasing capacity of emergency vaccination	18.3 (1 - 97)	1-146	36.4% (33.4 – 39.5)	147.9 (1 - 511)
Releasing a rabid owned dog happens at 10% chance	4.6 (1 - 19)	1-35	10.7% (8.9 – 12.8)	72.1 (1 - 223)
Releasing a rabid owned dog happens at 90% chance	88.2 (1 - 217)	1-263	58.4% (55.3 – 61.5)	265.2 (1 - 700)
Higher chance of a rabid stray dog to bite stray dogs (90%)	18.7 (1 - 104)	1-216	37.8% (34.8 – 40.9)	151.4 (1 - 488)

2.3.3. Sensitivity analysis

Outbreak sizes were highly sensitive to the probability of unintentionally releasing a rabid owned dog under the scenario with 0% vaccination coverage (Table 4). Under current vaccination coverage with a 10% probability of releasing a rabid dog, the mean outbreak size in Ibaraki Prefecture was 2.4 (median, 2; range, 1 – 27; 95% CI, 1-8), and the mean epidemic duration 41.2 days (median, 31; range, 1 – 327; 95% CI, 1 - 154). With a 90% probability of releasing a rabid owned dog, however, the mean outbreak size was 10.4 (median, 2; range, 1 – 110; 95% CI, 1 – 66), and the mean epidemic duration 120.8 days (median, 38; range, 1 – 836; 95% CI, 1 - 550).

Assuming rabid stray dogs were more likely to contact other stray dogs rather than owned dogs had little impact on outbreak sizes (mean 17.4 to 18.7, Table 4). However, a positive relationship was observed between outbreak size and the proportion of stray dogs among rabies cases (slope of logit = 0.03, Standard Error = 0.0004, $p < 0.01$, Figure 3).

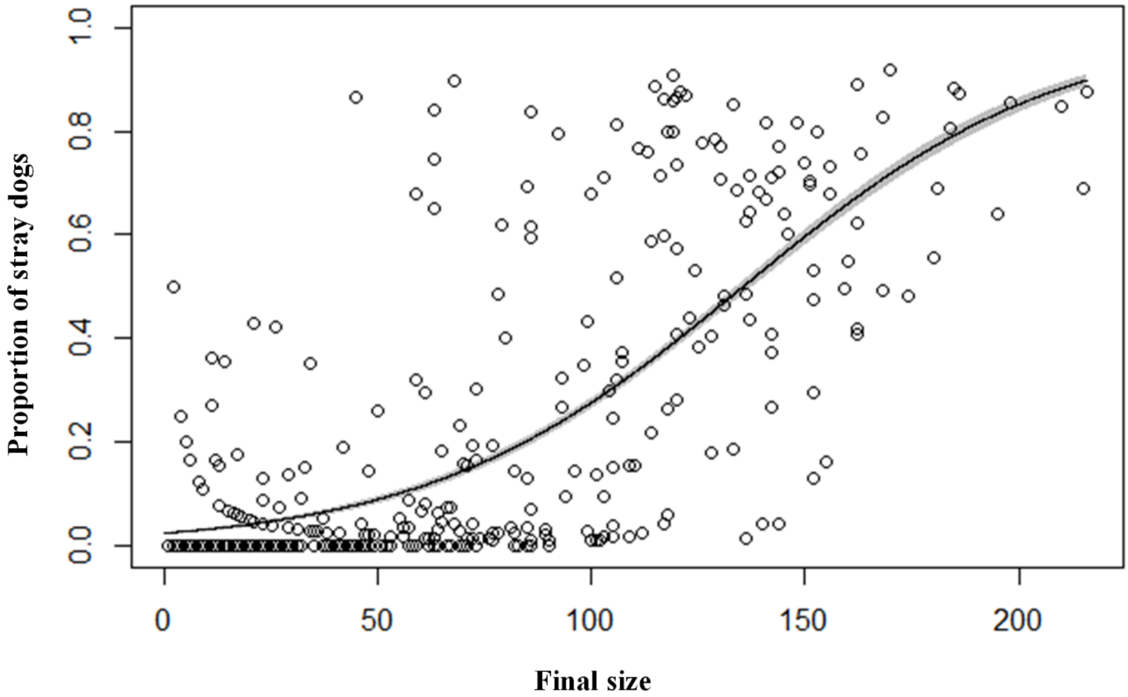

Figure 3. Relationship between the final outbreak size and the proportion of stray dogs among dog rabies cases using the Ibaraki Prefecture model with preferential biting of stray dogs under 0% vaccination coverage. The solid line is the predicted value based on a logistic regression, and grey area shows the 95% confidence interval of the regression parameters

2.4. Discussion

Risk assessment using mathematical modelling is useful for planning disease control options, as models can demonstrate the potential outcomes of an introduction of an infectious disease and the changes on risk achieved by application of counter measures. Our study provides important messages, regarding responses to, and contingency planning for rabies incursions.

The risk of an incursion resulting in an outbreak of 10 or more dog rabies cases was assessed to be between 6.9%-9.0% under current vaccination coverage and dog-keeping practices in Japan. Outbreaks would therefore typically be limited, but due to the extended rabies incubation period (15.5 days) [63], once secondary cases occur, the duration of the epidemic can become long.

The final size of outbreaks was strongly affected by reactions of dog owners if their dogs developed rabies. Even under the current vaccination coverage, a 90% chance of releasing rabid dogs could prolong the epidemic to more than a year. Thus sensitization of dog owners about rabies and recommended actions when rabies is detected is critical. Direct reporting of suspicious signs of rabies to local authorities may be better than bringing symptomatic dogs to veterinary clinics, as such transport incurs additional risks. Veterinary clinicians should, of course, also be reminded to suspect the possibility of rabies.

Results showed that mandatory vaccination for prevention of rabies limits the risk from incursions. However, the cost-effectiveness of mandatory vaccination should be carefully discussed, as it incurs expenses for both dog owners and public services, and the risk of rabies introduction is very low [27]. On the other hand, costs of control can be large without mandatory vaccination. Most rabies-free countries, such as United Kingdom [64,67], France [10], and Australia [2], do not use mandatory dog vaccination.

Assessment of the efficacy of rabies control measures did not show any clear benefit to strengthening contingency plans. By default we modeled a delay of 30 days from detection to initial response. It is assumed that an even earlier initial response, i.e. immediate capture of the primary case would prevent secondary cases. The result showed that once initial response was delayed for a month, further delay would not markedly change the final outbreak size. It should be noted that in settings where rabies outbreaks have been reported in previously rabies-free areas, delays to detection and response have far exceeded 60 days [59], which was the worst-case scenario that we examined. Scenarios with increased capacities for finding contacted dogs, and implementing emergency vaccination employed realistic assumptions. In the case of a dog rabies outbreak, once it has spread to a dog population, it may become challenging to contain in a short period, unless response capacity is dramatically strengthened. The relationship between the outbreak sizes and the proportion of strays among rabid dogs suggested that larger epidemics are likely to be associated with rabies spread among the stray dog population. Control of stray dogs is therefore an important defense against rabies incursion and spread. The effect of stray dog population control was shown during historical outbreaks in Osaka Prefecture [26].

Results suggested that not all rabid dogs bite people, and the estimated number of bite injury cases by rabid dogs would be small under the current situation. Numbers of dog-bite injury were positively correlated with dog rabies cases in historical outbreaks in Osaka [26], and if an incursion were to spread, many rabid dog bites would likely occur. A previous study found that 0%-60% of people develop rabies after being bitten by a rabid dog if untreated, and the probability depends on the site of bite [5]. Awareness of rabies is thought to be low among Japanese citizens; only half of Japanese travelers bitten by stray or domestic dogs in rabies-endemic countries obtained post-exposure prophylaxis [56].

Therefore, given these vulnerabilities, introduction of a rabid dog to Japan, would pose a non-trivial risk of human death. There are four points to be discussed with regard to the validity of mathematical model. First, we used R_0 from the historical epidemic in Osaka Prefecture, where many stray and unleashed dogs were present. It is therefore likely that contact rates may have been higher than they are currently, however, evidence suggests that R_0 does not depend on dog population density [39]. We assumed frequency-dependent transmission and therefore that a rabid dog in present day Japan would infect the same number of dogs as in the past, if the vaccination coverage is the same (0%). Instead of changing R_0 to reflect the difference of dog population density from the past, we did model the probability of unintentionally releasing a rabid dog, because all owned dogs are leashed in present day Japan. However, the model was very sensitive to this parameter and nothing is known about how communities will react in the event of an incursion.

The second point bearing on the validity of the model is the method for determining the geographical locations of cases. The fitted parameter α that relates the distance kernel and dog density had an influence of 50% on determining case locations. We are limited in the estimation, in that we did not have the exact case locations or knowledge of who-bit-whom from the historical data, but results indicate that in the setting of a large-scale epidemic, more cases will be observed in areas with high dog population densities. The adjustment parameter ($\varepsilon = 1.1$) from the distance kernel showed that distances between index and secondary cases were comparable between Osaka and Tanzania [14].

The third point is about the probability of a rabid dog biting at least one person. This information is not available in Japan, and we used data from Tanzania [12]. The number of bite injuries simulated using this data was comparable to the results using the bite-dog rabies ratio in the past Osaka outbreak [26], suggesting reasonable prediction.

Another limitation is that the model does not take into account recreation activities that might facilitate rabies transmission in modern society, such as running facilities for dogs and dog socialization in parks. Results should therefore be interpreted with caution, as transmissions in potential hotspots could result in unexpectedly large epidemics.

Spillover was also not considered in this model. Spillover event occurs when RABV which was normally maintained by original host was transmitted to another species. It is assumed that sustained transmission among second host is unlikely and is considered as dead-end infection [20]. However, such rare event can encompass the new adapted variant to another host, which sustains epidemic within the new host. Thus, rabies control option should be carefully arranged.

In conclusion, following a rabies incursion into Japan, the risk of an outbreak was assessed as moderate, although outbreak sizes are expected to be limited. Reactions of owner to their dog developing rabies were the most influential factor for outbreak control. Rabies education should therefore be targeted to veterinarians, veterinary students, and pet owners, as well as to the general public. Results suggest that outbreak response capacity is currently strong, but that maintenance efforts should not be relaxed. Discussions of mandatory vaccination maintenance should be encouraged, and such discourse must acknowledge and evaluate overall risks considering both introduction and spread of rabies, and cost effectiveness.

2.5. Summary of Chapter 2

Rabies was eliminated from Japan in 1957. In the 60 years since elimination, vaccination coverage has declined and dog ownership habits have changed. The purpose of this study was to assess the current risk of rabies spread in Japan.

A spatially explicit transmission model was developed at the 1-km^2 grid scale for Hokkaido and Ibaraki Prefectures. Parameters associated with dog movement and bite injuries were estimated using historical records from Japan, and were used with previously published epidemiological parameters. The final epidemic size, efficacy of rabies contingency plans, and the influence of dog owner responses to incursions were assessed.

Average outbreak sizes were small and associated with few human rabies exposures with on average 3.1 (95% CI, 1 - 14) and 3.8 (95% CI, 1 - 20) rabid dogs in Hokkaido and Ibaraki Prefectures, respectively, and 4.4 (95% CI, 0 - 35), and 5.4 (95% CI, 0 - 41) dog bite injuries. However, discontinuation of mandatory vaccination increased average outbreaks to 22.8 dogs (95% CI, 1 - 142) and 17.4 dogs (95% CI, 1 - 98) in these prefectures. Sensitivity analyses showed that unintentional release of rabid dogs by their owners (from 0.5 to 0.9 probability) more than doubled outbreak sizes.

The model suggested that at present, incursions of rabies into Japan, are very unlikely to cause large outbreaks. Critically, the reaction of dog owners to their dogs developing rabies considerably impacts the course of outbreaks. Contingency measures should therefore include sensitization of dog owners.

Chapter 3. Socio-economic factors associated with voluntary rabies control measures in Vietnam

3.1. Introduction

Rabies is a fatal zoonosis caused by RABV categorized to the *Lyssavirus* genus of the *Rhabdoviridae* family [61]. Mammals are affected by RABV and almost 100% of infected animals die showing fatal encephalitis [24]. In Asia, transmission of RABV is maintained by dogs, rather than by wild animals as seen in Europe and America [53]. Every year, over 60,000 individuals die due to rabies and over 90% of victims are infected by animal bites, mainly from dogs [13].

Vietnam is one of the countries in which rabies is endemic. Annual human rabies cases recently declined from 410 cases in 1995 to 34 in 2003 after the implementation of rabies control measures [50]. However, human rabies cases unfortunately started to gradually increase from 2004, and 91 rabies cases were confirmed in 2016 despite of the availability of dog rabies vaccination. Rabies thus has not been eliminated from Vietnam and the number of human deaths was higher in the northern part of Vietnam than in the center and the south, accounting for 84% of total cases [50].

Vaccination is one of the most efficient control measures against rabies [21,60]. Other effective rabies control measures include dog population control and confinement of dogs [26]. However, these control options are also not well practiced in the rabies endemic countries. To improve vaccination coverage and dog population and raising management, it is essential to understand socio-economic conditions of livelihood and knowledge, attitudes, and practices associated with rabies control and prevention.

Knowledge, Attitudes, and Practice studies have been used to collect baseline information on what respondents know and what they actually do, and to identify knowledge gaps, cultural beliefs, or behavioral patterns that may represent obstacles to the control of infectious diseases. The Knowledge, Attitudes, and Practice survey model assumes that practices for control and prevention are motivated by knowledge and attitudes in turn, and this has also been applied in rabies studies [8,54]. Although key factors influencing levels of knowledge, attitudes, and practices related to rabies and its prevention and control have been revealed in the previous study [8,54] using uni- and multivariate models, it is still unclear whether these factors influence practices related to rabies control and prevention directly or indirectly. SEM can evaluate the complex relationship between factors at once [48]. This can inform the basis for effective intervention to improve dog rabies control.

The purpose of this study was to understand the direct and indirect relationships among socio-economic factors using the Knowledge, Attitudes, and Practice framework to provide health and veterinary sectors in Vietnam with challenges to be addressed based on the result of the socio-economic questionnaire survey.

3.2. Materials and methods

3.2.1. Study sites and sampling framework

Thai Nguyen Province was selected in discussions with the health authorities in Vietnam, because elevated incidences of rabies cases were perceived during the first three months of 2016 [65]. Thai Nguyen is a province in the northeast region of Vietnam (Figure 4). This mountainous, midland province has a natural land area of 3534.5 km^2 and a population of 1,149,100.

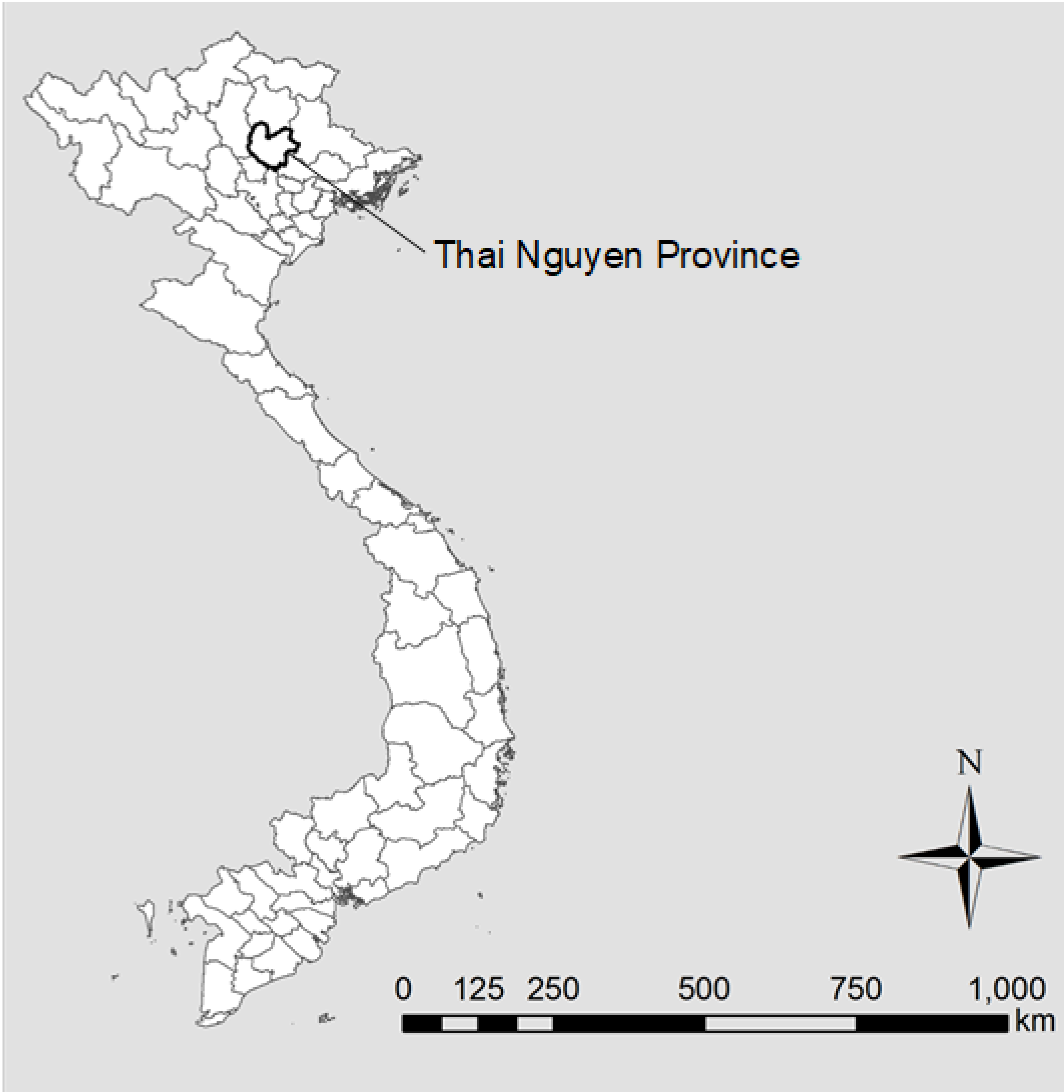

Figure 4. A map of Vietnam

The sampling framework employed multistage cluster sampling to estimate the proportion of households conducting vaccination and dog tethering, with the first sampling unit district, the second unit sampling commune, and the third unit sampling household. Sample size was calculated using C-Survey software. The expected vaccination coverage was assigned a value of 0.754, based on a previous study in Vietnam [28]. The number of clusters to be included in this study was 18. Design effect adjustment was 2, assuming a low intra-class correlation. Based on these parameters, a sample size of 450 was calculated as needed. The calculated sample size was then increased by 10% to account for refusals and invalid interviews, resulting in 495 households from 18 communes. Second, sample size at the household level was proportionally allocated to the districts of Thai Nguyen Province according to district populations. All communes in the districts of Thai Nguyen Province were categorized into mountainous or plain communes, and within each district, one each of mountainous and plain-area communes were randomly selected. In the districts where there were only either mountainous or plain communes, two communes with the same feature were randomly selected. Allocation of sample size to the selected communes was performed in either of two ways: 1) in cases where the two selected communes within a district belonged to mountainous and plain areas, sample size was proportionally allocated according to the total populations of mountainous and plain-area communes within the district; or 2) in cases where the selected communes had the same features, sample size was allocated to these communes according to the populations of the communes. The reason total populations of mountainous and plain-area communes within the district were used was that total population is less sensitive to variations in population at the commune level. Table 5 shows the sampled commune and number of households selected in each commune, and Figure 5 shows the locations of sampled communes in Thai Nguyen Province.

Table 5. Districts and communes, and number of households studied in Thai Nguyen Province

District	Commune	Area	Households
Song Cong	Mo Che	Plain	13
	Cai Dan	Plain	8
Dinh Hoa	Bao Linh	Mountainous	17
	Dong Thinh	Plain	25
Phu Luong	Yen Do	Mountainous	4
	On Luong	Plain	44
Dai Tu	Hoang Nong	Mountainous	15
	Ban Ngoai	Plain	60
Pho Yen	Ba Hang	Plain	34
	Thuan Thanh	Plain	28
Phu Binh	Nga My	Plain	41
	Thanh Ninh	Plain	22
Dong Hy	Nam Hoa	Plain	1
	Khe Mo	Plain	45
Vo Nhai	Dan Tien	Mountainous	20
	Binh Long	Mountainous	8

Table 5. Districts and communes, and number of households studied in Thai Nguyen Province (Continued)

District	Commune	Area	Households
Thai Nguyen	Phu Xa	Plain	38
	Quang Trung	Plain	72

Figure 5. Map showing study sites and names of districts in Thai Nguyen Province. Red bold line shows the sampled commune in Thai Nguyen Province.

3.2.2. Questionnaire survey

In the questionnaire survey, demographic information such as family structure, number of dogs, style of confinement, birth control, and socio-epidemiological information such as knowledge, attitudes, and practices regarding rabies and its prevention and control, status of dog vaccination, willingness-to-pay for vaccination, and willingness-to-change behavior of confinement were surveyed.

To assess the amount of knowledge about dog rabies, participants were asked three questions, about the reservoir, transmission route, and control measures of dog rabies. The score of each question ranged from 0 to 3. One correct reservoir, for example, was scored as 1 point. Thus, the total score ranged from 0 to 9.

To reveal the willingness-to-pay for dog rabies vaccinations, contingent valuation using double-bounded dichotomous choice was performed [1]. Participants were asked to respond to the question of whether they would be willing to pay for vaccinating their dogs against rabies at a specific price. First, the current situation of vaccination was asked. If the respondent indicated that all their dogs were vaccinated at the time of the survey, the question was given as how many dogs they would vaccinate if the price were to increase beyond the current actual one, by providing a hypothetical price prepared in the questionnaire. Otherwise, a cheaper hypothetical price than the actual price was proposed. In the questionnaire survey, the first-bid price was the actual price, 21,000 Vietnamese dong (VD) (United States Dollar (USD) 0.93 as of 2017 November 27, 1 USD = 22,605 VD). The second bid was proposed with four combinations; (10,000; 60,000), (5,000; 50,000), (3,000; 40,000), and (1,000; 30,000). These four combinations were randomly assigned to 495 questionnaires.

Interviews were administered by face-to-face communication in the respondent households. Before starting interviews, the purpose of this study and the protection of data were explained to participants, as well as the fact that personal information would not be collected, and honest responses were encouraged. Questionnaires were translated into Vietnamese with the cooperation of Hanoi School of Public Health, and the survey was conducted in cooperation with the Department of Animal Health, and province and commune veterinary offices in Thai Nguyen Province. Results of the questionnaire survey were re-translated into English and digitized using Excel software®.

Ethical approval was obtained from the Hanoi School of Public Health Institutional Review Board.

3.2.3. Descriptive epidemiology

The frequency of the answers in the questionnaire about personal attributes and KAP for dog rabies control and willingness-to-pay for vaccination were shown by the ecological features of communes (either mountainous or plain areas) using cross-tabulations.

3.2.4. Statistics

Analyses were performed to reveal associations between knowledge and attitude, and between vaccination and confinement of dogs using R version 3.3.3 statistical software [49].

3.2.4.1. Univariate analysis

In univariate analysis, generalized mixed-effects models were applied. Vaccination coverage of dogs in the household was used as a response variable and items in the questionnaire were used as explanatory variables. The ecological feature of either mountainous or plain area was set as a random effect in the model. In addition, generalized mixed-effect models were applied to actual confinement of dogs in the household as response variables in the respective models.

3.2.4.2. Multivariate analysis

In the multivariate analysis, variables with *p*-values less than 0.2 in univariate analyses were used as explanatory variables. As many explanatory variables were included, four generalized linear models (GLMs) were prepared for factors associated with general information, knowledge, attitudes, and practice of rabies control. GLMs were used instead of mixed-effects models to avoid convergence due to the large numbers of explanatory variables. In GLMs, ecological feature was added as one of the explanatory variables to adjust intra-class correlations. Backward stepwise simplification was performed using a likelihood ratio test to examine whether the new simpler model was significantly worse regarding explanation of data. This simplification was conducted for each multivariate model until *p*-values of the remaining factors became less than 0.05.

3.2.4.3. Structural equation modelling

To correctly understand the socio-economic factors associated with voluntary rabies control, SEM was used with the hypothetical structure flow that socio-economic status affects the knowledge of dog owners, which in turn influences attitudes towards rabies, and then the conduct regarding voluntary rabies control in the household. Latent variables were set as socio-economic status, knowledge, and attitude. The observed variables were defined as those factors remaining in each final model in multivariate analyses. Model simplification was performed using the likelihood ratio test [52].

3.2.4.4. Willingness-to-pay for vaccination

Based on the results of the questionnaire survey, mean and probability of willingness-to-pay for vaccination were estimated using the Kaplan-Meier-Turnbull method

[1].

3.3. Results

3.3.1. Descriptive epidemiology

3.3.1.1. Sociological characteristics

Table 6 shows the socio-economic characteristics of the respondents who lived in mountainous and plain areas. Participants in mountainous areas were characterized by minority ethnicity, crop farming, and low level of education. Family size and livelihoods in both areas were not markedly different (p = 0.3 and 0.6, respectively). Number of dogs in the household was between one and three in both areas (2.0 vs 2.4 dogs in mountainous and plain areas, respectively, p = 0.17). Most dogs were kept as a guard dog and were not sterilized or castrated. Participants mostly acquired their dogs by reproduction or purchase.

Table 6. Sociological characteristics including dog ownership by the ecological features of communes in Thai Nguyen Province

Items	Mountainous area	Proportion (%)	Plain area	Proportion (%)	*p*-value
Sex of head					
Female	7	11.1	133	32.5	<0.05
Male	56	88.9	276	67.5	
Ethnicity					
Kinh	16	25.4	320	76.0	<0.05
Other	47	74.6	101	24.0	
Primary activity					
Crop farming	57	89.1	235	57.5	<0.05
Animal keeping	1	1.6	9	2.2	
Trading in ag. products	0	0.0	4	1.0	
Business	2	3.1	28	6.9	
Formal salaried employee	0	0.0	37	9.0	
Not working/unemployed	0	0.0	5	1.2	
Old/retired	3	4.7	76	18.6	
Disabled	0	0.0	1	0.2	
Other	1	1.6	14	3.4	

Table 6. Sociological characteristics including dog ownership by the ecological features of communes in Thai Nguyen Province (Continued)

Items	Mountainous area	Proportion (%)	Plain area	Proportion (%)	*p*-value
Livelihood					
Very good	5	7.8	9	2.1	0.6
Good	14	21.9	128	29.9	
Neutral	40	62.5	279	65.2	
Bad	3	4.7	10	2.3	
Very bad	2	3.1	2	0.5	
Role of dog					
Pet	0	0.0	2	0.5	0.7
Guard	62	93.9	419	94.8	
Others	4	6.1	21	4.8	

3.3.1.2. Knowledge

Knowledge scores on reservoirs of rabies did not differ significantly between mountainous and plain areas (p = 0.09), but those on transmission route and control measures were significantly lower in the mountainous areas than in the plain areas ($p < 0.05$, Table 7).

Table 7. Comparisons of mean knowledge scores on dog rabies (0 to 3) between mountainous and plain areas

Content of question	Mountainous area	Plain area	*p*-value
Reservoir	1.2	1.4	0.09
Transmission route	1.1	1.5	<0.05
Control measure	1.1	1.2	<0.05

3.3.1.3. Practice

3.3.1.3.1. Vaccination of dogs

In Thai Nguyen Province, overall vaccination coverage was 77.4%. Coverage in mountainous areas (63.8%) was significantly lower than that in plain area (79.2%, $p < 0.05$). Table 8 shows comparisons of within-household vaccination coverage between mountainous and plain areas. In the mountainous and plain areas, 17 and 49 households had vaccinated no dogs as of the time of the survey, respectively ($p < 0.05$).

Table 8. Comparison of within-household vaccination coverage by ecological features in Thai Nguyen Province

Vaccination coverage	Mountainous area	Proportion (%)	Plain area	Proportion (%)
0%	17	27.4	49	11.5
≤25%	1	1.6	4	0.9
≤50%	5	8.1	40	9.4
≤75%	2	3.2	18	4.2
≤100%	37	59.7	315	73.9
Overall	62	100	426	100

3.3.1.3.2. Willingness-to-pay for vaccination

The mean estimation of willingness-to-pay was 46,236 VD (Figure 3), more than double the actual cost of 21,000 VD. Mean willingness-to-pay for vaccination was 47,056 VD in plain areas and that of mountainous areas was 39,952 VD. The majority of participants who had vaccinated all their dogs at the time of survey (300/321, 93.5%) answered to maintain vaccination even at a price higher than the current price, while 69.7% (46/66) of the participants who had not vaccinated all their dogs were reluctant to vaccinate them even at a cheaper price.

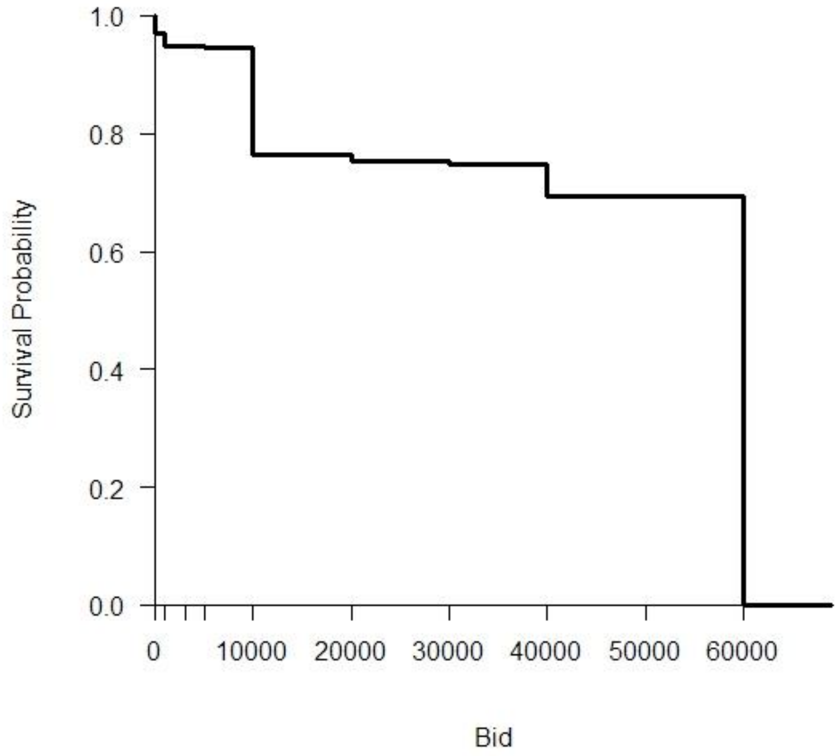

Figure 6. Kaplan-Meier-Turnbull estimate of empirical survival function for dog rabies vaccinations

3.3.1.3.3. Confinement of dogs

Table 9 shows a comparison of the time of confining dogs between mountainous and plain areas. The proportion of households confining dogs all day was significantly lower in mountainous areas (20.3%) than in plain areas (56.5%, $p < 0.05$), while the proportion never confining dogs was significantly higher in mountainous areas (65.6%) than in plain areas (26.5%, $p < 0.01$). Although about half of the participants practiced confinement of dogs in Thai Nguyen Province (256/494, 51.8%), the majority answered that they would confine (479/489, 98.0%) or leash while walking (482/491, 98.2%) if such orders were enforced.

Table 9. Comparison of time of dog confinement between mountainous and plain areas in Thai Nguyen Province

Time of confinement	Mountainous area	Proportion (%)	Plain area	Proportion (%)	*p*-value
All day	13	20.3	243	56.5	<0.05
Morning	2	3.1	3	0.7	
Night	4	6.3	21	4.9	
Noon	0	0	5	1.2	
Not confined	42	65.6	114	26.5	
Others	3	4.7	44	10.2	

3.3.2. Analyses on factors associated with vaccination and dog confinement

In the personal attributes model, factors associated with household vaccination coverage were having a better livelihood (OR = 1.62, $p < 0.05$), female head (OR = 1.71, $p < 0.05$) and minority ethnic status (OR = 0.58, $p < 0.05$) (Table 10).

For the knowledge model, factors associated with household vaccination coverage were having a good knowledge about prevention (OR = 1.80, $p < 0.05$) and knowing the rabies control program in Thai Nguyen Province (OR = 3.78, $p < 0.05$).

In the attitudes model, factors associated with household vaccination coverage were thinking vaccination is to conform to the commune opinion (OR = 1.34, $p < 0.05$) and thinking the vaccination is meaningless (OR = 0.46, $p < 0.05$).

In the practice model, factors associated with household vaccination coverage were not confining dogs all day (OR = 0.46, $p < 0.05$) and higher coverage of castration and sterilization (OR = 3.56, p < 0.05).

Table 10. Results of multivariate analyses for four models of vaccination

Model	Variable	OR	95%CI	*p*-value
Personal attributes model	Having better livelihood	1.62	(1.20-2.17)	<0.05
	Male head	1.00 (reference)		
	Female head	1.71	(1.09-2.69)	<0.05
	Kinh	1.00 (reference)		
	Other ethnic groups	0.58	(0.38-0.87)	<0.05
Knowledge model	Amount of knowledge about prevention	1.80	(1.22-2.67)	<0.05
	Not knowing rabies control program in Thai Nguyen	1.00 (reference)		
	Knowing rabies control program in Thai Nguyen	3.78	(2.55-5.60)	<0.05

Table 10. Results of multivariate analyses for four models of vaccination (Continued)

Model	Variable	OR	95%CI	p-value
Attitudes model	Thinking that vaccination is to conform to commune opinion	1.34	(1.02-1.76)	<0.05
	Thinking that vaccination is meaningless	0.46	(0.35-0.61)	<0.05
Practice model	Confined all day	1.00 (reference)		
	Not confined, referred to confined all day	0.46	(0.32-0.67)	<0.05
	Coverage of birth control	3.56	(1.59-7.95)	<0.05

In the personal attributes model, factors associated with actual confinement were having a better livelihood (OR = 1.58, $p < 0.05$) and minority ethnicity (OR = 0.34, $p < 0.05$) (Table 11).

For the knowledge model, the factor associated with actual confinement was knowing the rabies control program in Thai Nguyen Province (OR = 0.64, $p < 0.05$).

In the attitudes model, factors associated with actual confinement were thinking that vaccination is expensive (OR = 0.77, $p < 0.05$) and thinking that confinement is cruel (OR = 0.61, $p < 0.05$).

In the practice model, the factor associated with actual confinement was higher vaccination coverage (OR = 2.27, $p < 0.05$).

Table 11. Results of multivariate analyses for four models of confinement

Model	Variable	OR	95%CI	*p*-value
Personal attributes model	Having better livelihood	1.58	(1.14-2.21)	<0.05
	Kinh	1.00 (reference)		
	Other ethnic groups	0.34	(0.22-0.53)	<0.05
Knowledge model	Not knowing rabies control program in Thai Nguyen	1.00 (reference)		
	Knowing rabies control program in Thai Nguyen	0.39	(0.24-0.64)	
Attitudes model	Thinking vaccination is expensive.	0.77	(0.62-0.96)	<0.05
	Thinking confinement is cruel.	0.61	(0.47-0.79)	<0.05
Practice model	Vaccination coverage	2.27	(1.34-3.85)	<0.05

3.3.3. Structural equation modelling

Figure 7 and Table 12 show the structure of decision paths associated with voluntary rabies control measures in Thai Nguyen Province. As the latent variables clearly show, social status and level of knowledge (β = 0.75, se = 0.07, $p < 0.05$), knowledge and attitude (β = 1.0, se=0.0, $p < 0.05$), attitude and practices of confinement (β = 0.4, se = 0.05, $p < 0.05$), vaccination (β = 0.52, se = 0.06, $p < 0.05$), and birth control (β = 0.11, se = 0.04, $p < 0.05$) were positively associated with voluntary rabies control measures. Low income (β = 0.30, se = 0.01, $p < 0.05$), other ethnic group status (β = -0.14, se=0.13, $p < 0.05$), and living in a mountainous area (β = -0.24, se = 0.13, $p < 0.05$) were negatively associated with social status. Increased amount of knowledge about preventive measures (β = 0.15, se = 0.08, $p < 0.05$) and knowing the rabies control program in Thai Nguyen (β = 0.51, se = 0.09, $p < 0.05$) indicated good knowledge of rabies.

Positive attitudes regarding rabies control were negatively associated with thinking vaccination is to conform to commune opinion (β = 0.40, se = 0.05, $p < 0.05$) and is meaningless (β = -0.28, se = 0.05, $p < 0.05$).

Goodness-of-fit indices indicated relatively good representation for data (CFI = 0.83, RMSEA = 0.07, SRMR = 0.06).

Table 12. Result of structural equation modelling with acronyms shown in Figure 4.

Variables	Coefficient	SE	*p*-value
Social status			
Livelihood (Liv)	0.30	0.01	<0.05
Ethnic group (Eth)	-0.14	0.13	0.3*
Area of residence (Area)	-0.24	0.13	0.05*
Knowledge			
Amount of knowledge of prevention (Knowprev)	0.15	0.08	0.05*
Knowing rabies control program in Thai Nguyen (Knowcontp)	0.51	0.09	<0.05
Attitudes			
Thinking vaccination is to conform to the commune opinion. (Conform)	0.40	0.05	<0.05
Thinking vaccination is meaningless. (Mnless)	-0.28	0.05	<0.05
Practice of confinement (Confine)	0.40	0.05	<0.05
Coverage of birth control (Cast)	0.11	0.04	<0.05
Vaccination coverage in household (Vac)	0.52	0.06	<0.05

*These factors could not be removed from the model because deviance was significantly different.

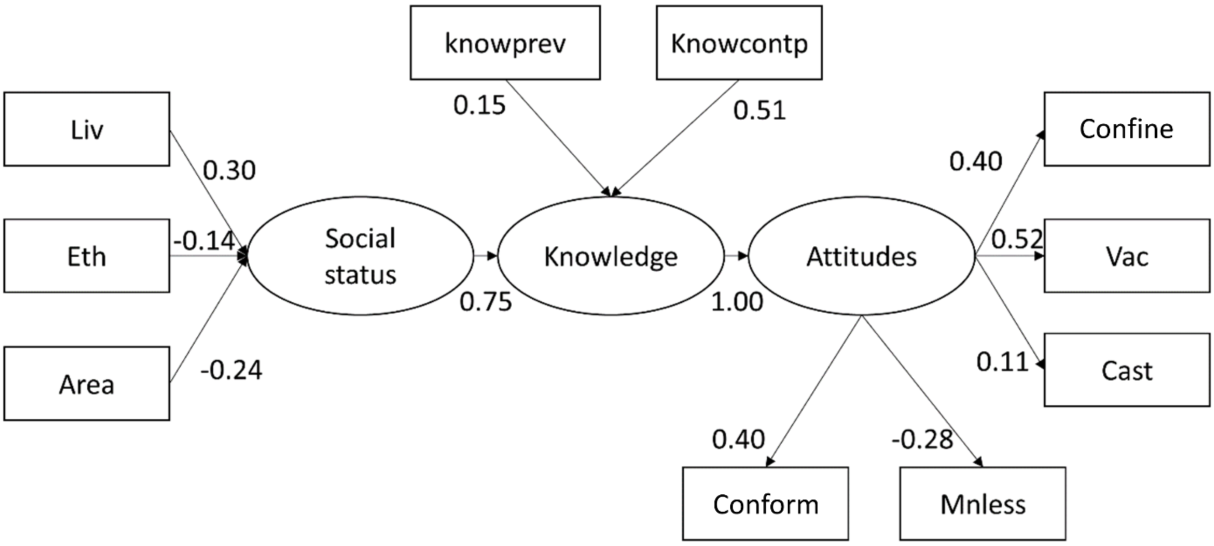

Figure 7. Path diagram of the structural equation model. Circles show latent variables, while boxes show observed variables. Full forms of acronyms are presented in Table 9.

3.4. Discussion

Rabies remains a significant public health problem in Vietnam, and planning feasible control strategies based on a good understanding of the socio-economic factors associated with dog rabies vaccination, husbandry, and dog population control is urgently needed. A structural equation model showed that sending correct messages regarding rabies and its prevention is effective to promote an understanding of rabies control in minority groups.

Vaccination is one of the key control options for rabies. A previous study showed that 60% represents sufficient vaccination coverage [14]. At the time of the survey, vaccination coverage in Thai Nguyen Province was higher than this herd immunity threshold. One study reported similar vaccination coverage of 75.4% in northern Vietnam [28].While vaccination coverage was higher than estimated vaccination coverage of Hokkaido and Ibaraki Prefecture, similar vaccination coverage was achieved. Previous study showed that 70% of owned dogs were vaccinated in Thailand [25] and 64% of owned dogs were vaccinated within a year in Philippines [7] as seen in the surrounding Asian countries. However, vaccination status was confirmed by oral communication and a local veterinary officer surveyed the vaccination coverage, which was lower than the result (personal communication). Vaccination coverage in this study area might thus have been overestimated, although the motivation to perform vaccination was high.

Willingness-to-pay for dog rabies vaccination was high in this study area. The actual vaccination fee per dog per dose was 21,000 VND in Thai Nguyen Province, and the mean willingness-to-pay for dog rabies vaccination was double the actual cost. Even at 60,000 VND, about 70% of participants reported they would perform dog rabies vaccination. However, the fact that about 20% of participants did not comply with performing dog rabies vaccination at half the actual cost cannot be overlooked. This will impose difficulties in achieving high vaccination coverage in this area. To increase vaccination coverage, the

Vietnamese government needs to consider subsidies to reduce the burden on dog owners.

The structural equation model showed relationships among factors associated with knowledge, attitudes, and practice of dog rabies vaccination. Factors influencing social status indicated that the risk of rabies existed in the vulnerable population facing low income and accessibility. Dissemination of information should thus target low-income, mountainous-area, and minority ethnic groups. As the hypothesized model showed, good practice in dog rabies vaccination is motivated by good social status, deep knowledge, and positive attitudes towards dog rabies control. Sending and distributing correct information about rabies and rabies control measures would thus be effective to promote dog rabies vaccination. This questionnaire survey was performed with the head of the household, assuming he or she played a significant role in decision making. However, children are disproportionally affected by rabies [5]. Education in school should thus also be considered.

Tethering dogs is another important control option. Tethering of pets was substantially effective for controlling a dog rabies epidemic in the past in Osaka Prefecture [26]. Although participants in the mountainous areas did not confine their dogs all day, their willingness-to-confine dogs was good. As the results from multivariate analyses showed, those people who were unlikely to be positive and practice rabies control measures did not confine their dogs all day. The government needs to consider the behavior of dog owners when enforcing tethering dogs by law.

However, rabies is endemic in the countries surrounding Vietnam, as well. Vietnam has experienced the penetration of rabies from other countries or vice versa [42]. Even if rabies were controlled in Vietnam, rabies would re-emerge unless strict border control was enforced. Joint collaboration is thus needed for rabies elimination.

In conclusion, findings from this study showed key targets for public education programs. In addition, the high willingness-to-pay for dog rabies vaccination and tethering of dogs would be helpful for decision makers to develop dog rabies control strategies.

3.5. Summary of Chapter 3

Rabies is a fatal zoonosis that kills over 60,000 people annually, mostly in developing countries. In Vietnam, rabies remains problematic despite the availability of dog rabies vaccinations. The purpose of this study was to clarify the socio-economic factors associated with voluntary rabies control measures among the general population using a Knowledge, Attitudes, and Practice framework to provide health and veterinary authorities in Vietnam with baseline information for better planning of policy supports. A questionnaire survey with interviews was conducted in 495 households in Thai Nguyen Province in September 2016. After the survey, uni- and multivarable analyses were performed to detect factors associated with the practices of dog rabies vaccination and tethering dogs. Structural equation modelling (SEM) was performed to understand the structures associated with practice decisions. These results showed that the practice of dog rabies vaccination was promoted by good social status, rich knowledge, and positive attitudes toward dog rabies vaccination. Vaccination coverage in this study area was 77.4%, and mean estimation of willingness-to-pay for a vaccination was 46,236 Vietnamese dong. Although the practice of tethering of dogs was not good, willingness-to-confine dogs if this practice were to be enforced was excellent. We found a key target group for education and recommend development of a dog rabies control strategy to promote dog rabies vaccinations and dog confinement.

Chapter 4. Analysis of factors associated with hesitation to restart farming after depopulation of animals due to 2010 foot-and-mouth disease epidemic in Japan.

4.1. Introduction

Foot-and-mouth disease (FMD) virus causes a highly contagious disease in cloven-hoofed animals, including cattle, swine, wild boar, water buffalo, goats, sheep and some wild animals [4]. FMD virus belongs to the genus *Aphthovirus* in the family *Picornaviridae* and has seven different serotypes, which are O, A, C, South African Territories (SAT) 1, SAT 2, SAT 3 and Asia1.

FMD is controlled mainly by culling animals that are infected or suspected of infection, because of its high contagiousness and great economic impact due to reduced productivity [17]. World Organisation for Animal Health (OIE) member countries can regain FMD-free status three months after slaughtering all animals with or without emergency vaccination, or when all vaccinated animals have not been slaughtered, six months after the last case or the last vaccination (Chapter 8.8, Article 8.8.7 −Recovery of free status) [68].

Culling of livestock during an epidemic causes a psychological impact on farmers, because such events are traumatic and emotionally shattering [11]. After the 2001 UK FMD outbreak, psychological effects were observed in farmers in affected areas: they reported negative feelings including distress, fear of a new disaster and loss of trust in the government and control measures [38,45]. Affected farmers in the Netherlands in 2001 experienced post-traumatic stress; risk factors were identified as higher age and lower education [44].

The first FMD case in Miyazaki Prefecture was confirmed in a beef cattle reproduction farm on 20 April 2010. On 4 May 2010, FMD was confirmed in a large pig farm, and the number of cases rapidly increased. On 19 May 2010, vaccination with culling was announced by the Japanese Government, and vaccination began on 22 May 2010. The last case was detected on 4 July 2010 [62]. Ultimately, 292 premises were identified as infected, and about 290,000 livestock, including vaccinated animals, were slaughtered over a period of three months [62].

In June 2010, the Mental Health and Welfare Center in Miyazaki Prefecture performed a survey of farmers with infected animals to monitor their mental health. The survey used telephone interviews during the outbreak in order to avoid fueling the spread of FMD by farm visits from health workers [29]. One year after the end of the FMD epidemic, Miyazaki Prefecture assessed the health status of affected farmers via direct visits. The rate of restarting farming was reported to be 62% in 2013 [36]. The aim of the present study was to identify the factors associated with resumption of livestock farming after the 2010 FMD outbreak from the view point of farmers' characteristics including their mental health and farm characteristics. The findings of the present study will also benefit any country that wishes to improve preparedness for infectious disease outbreaks in animals.

4.2. Materials and methods

4.2.1. Study areas

This study was conducted in the affected areas during the 2010 FMD epidemic, including Kawaminami, Kijo, Miyazaki, Saito, Shintomi, Takanabe and Tsuno in Miyazaki Prefecture, Japan (Figure. 8).

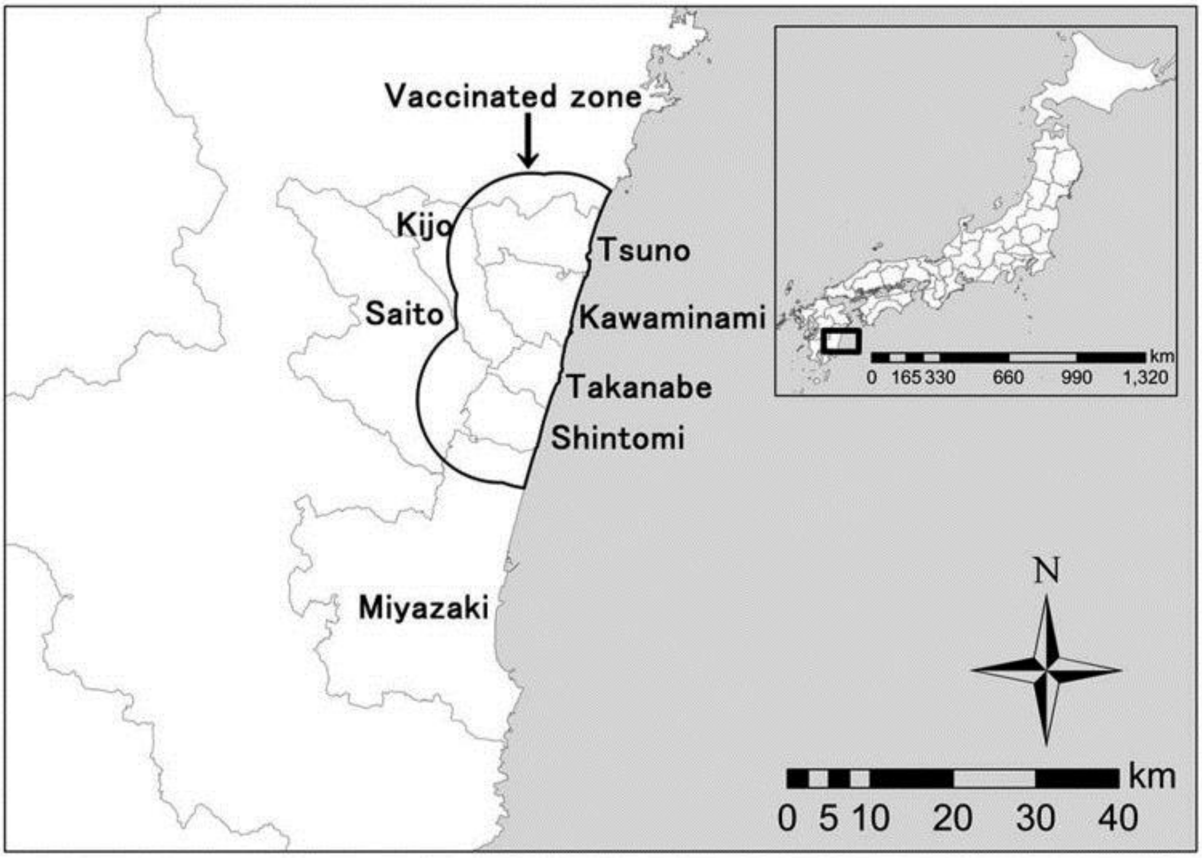

Figure. 8. A map showing administrative units in Miyazaki Prefecture where this study was conducted, and vaccinated zone.

4.2.2. Questionnaire survey

Between August 2011 and January 2012, health workers from city and town council offices visited all farms in the study areas who lost animals either because their premises were infected or their animals had to be vaccinated. In the epidemic, not only cattle and pig but also goat, sheep, boar and water buffalo were slaughtered. In this study, the farms which health workers from city and town council offices visited were cattle, pig and boar farms. During these visits, farmers were interviewed using a structured questionnaire. All of the responses were recorded on paper by interviewers and were digitized into a spreadsheet (Microsoft® Excel).

Health and veterinary professionals jointly designed the questionnaire, in order to understand farmers' mental health status, factors associated with severe mental illness (SMI) and factors associated with hesitation to restart farming. The scope of the questions included personal attribution, types and characteristics of farm operations, whether the farm was an infected farm or a vaccinated farm, occurrence and control of FMD, status of resumption of farming, socio-economic status, and physical and mental health status (Table 13). The questionnaire included questions about the level of satisfaction ("dissatisfied very much"=1 to "satisfied very much"=5) with the information and support provided by the government during the epidemic on how to prevent FMD and financial supports.

Table 13. Contents of the questionnaire

Categories	Contents	Name of model which includes
Personal attribution	Administrative unit	All model
	Name, age and sex of respondents, family structure and farm owner	Personal attributes model
Farm operation	Animal species, farm size, type of operation and number of employees	Farm characteristics model
	Status of restarting farming	Response variable
Occurrence and control of FMD	Status of farm as to infected or vaccinated	FMD model
	Date and place of occurrence, vaccination, culling and burial	FMD model
	Existence of supporter during outbreaks	FMD model
	Participation or attendance in culling	FMD model
	Farmer's satisfaction on the provision of information by the government during the outbreak [1]	FMD model

[1] This score ranges from 1 to 5 (dissatisfied very much =1 to satisfied very much = 5).

Table 13. Contents of the questionnaire (Continued)

Categories	Contents	Name of model which includes
Socio-economic status	Farmer's satisfaction on the financial support for restoration from the government [1]	FMD model
	Farmer's difficulties in economic conditions and human relationships	Personal attributes model
Physical health	Physical health problems	Personal attributes model
	Emerged health problems after FMD outbreaks	Personal attributes model
Mental health	Psychological health problems	Personal attributes model
	Emerged health problems after FMD outbreaks	Personal attributes model
	K6 [2]	Personal attributes model

[1] This score ranges from 1 to 5 (dissatisfied very much =1 to satisfied very much = 5).

[2] K6 is assessment scale of mental health status. The total score can range from 0 to 24, and higher score indicates sever mental stress.

Ethics were examined and approved by the ethical committee of the National Center of Neurology and Psychiatry (number A2014-155).

4.2.3. Measurement of mental stress

The status of mental distress was assessed by the Japanese version of the Kessler (K6), which is an internationally used assessment scale of mental health status. Assessment using K6 is based on the answers to six questions about depressive and anxiety symptoms that a person experienced [22]. Each scored on a five-point scale ("none of the time"=0 to "all the time"=4). The total score can range from 0 to 24, and the cut-off point for SMI is 13. This cut-off point equalizes false positives and false negatives, with a sensitivity of 0.36 and a specificity of 0.96 [23]. The Japanese version has been already standardized [9].

Data cleaning and integration of individual-level responses into farm-level data: Data cleaning was performed, because of inconsistencies in the answers from some farmers. Contradictions were observed between answers associated with physical or mental health and the farmers' own descriptions of their stresses. To keep the dataset consistent, answers that were responded later in the interview were regarded to be correct, and those that were responded early in the interview were carefully amended, because it was generally assumed that respondents became comfortable enough to disclose problems later in the interview. The free comment, which was the final question, was considered to be the most reliable source for data cleaning. Interviews were sometimes conducted with several individuals in a household, because the primary purpose of the interviews was to monitor the mental health status of individuals in affected farming households. In such cases, digitized individual-level data were integrated into representative responses at the farm level. During this process, two sections in particular were carefully dealt with. For the integration of responses about satisfaction with the information and support provided by the government, farm owners' answers were used, because the owner's intention should be the most influential factor in restarting a business. When an owner was not interviewed, an answer with lower satisfaction was selected. The integration of individual K6 scores into a farm-representative score was carried out by using the highest score (poorest mental health status) among the respondents as the farm K6 score; this was done, because poor mental health status of any individual in a household might affect the decision at the farm level to restart farming.

4.2.4. Statistical analysis

Statistical analyses were performed to reveal the associations between the restart of farming and factors associated with disease control during the epidemic, farm characteristics and personal attributes. In the univariate analysis, the Wilcoxon rank sum test was performed to compare counts and score data between farms that did and did not restart operation. The chi-squared test, Fisher's exact test and generalized linear models (GLMs) were used for the categorical data to compare proportions of farms that did and did not restart. Significant farm characteristics factors were further examined for the association with administrative units using GLMs.

In multivariable analysis, a logistic regression model was used; status of restarting or not restarting farming was used as a response variable (restarting: 1 and non-restarting: 0), and variables with *p*-values less than 0.2 in the univariate analyses were used as explanatory variables. Collinearity was checked for all the combinations of these explanatory variables with the cut off correlation coefficient 0.9; no collinearity was found among these variables. As there was a significant difference in the proportion of restarted farming between city-township administrative units (see Results), intra-class correlation should have been dealt with statistics assigning hierarchical structure, such as a mixed effects model. However, as the numbers of both administrative units and explanatory variables were many, and mixed effect models do not converge, GLMs were used with administrative units included as one of explanatory variables adjusting intra-class correlations.

Explanatory variables were classified as factors associated with disease control during the epidemic, farm characteristics and personal attributes, and three multivariable models were developed for these factors: FMD model, farm characteristics model and personal attributes model. Moreover, the farm characteristics and personal attributes models were subdivided into three models using data from all farms, cattle farms and pig farms, because farmers' feelings and stress responses to the epidemic were thought to differ depending on these circumstances. For farm types, beef cattle fattening (feedlot) and integrated (integration of cow-calf and feedlot operations) farms were combined as feedlots for analysis, because published sociological studies reported that farmers in cow-calf operations had higher stress levels than did those in fattening and integrated-management farms [30]. Although the variable of poor physical condition did not have a *p*-value less than 0.2 in the univariate analysis, this item was included in a personal attributes model, because it best represented farm owners' or family members' physical conditions.

Backward stepwise simplification was performed using likelihood ratio test to test whether the new simpler model was significantly worse regarding the description of data. Looking down the list of parameter coefficient and *p*-value, the variable which had highest *p*-value was removed and was tested whether removing variable significantly changes the deviance. This simplification was conducted for each multivariable model until *p*-values of the remaining factors became less than 0.05. Finally, a generalized mixed-effects model with binomial errors was performed to estimate more precise coefficients in final models, selecting the restarting status of a business as a response variable, the significant variables estimated in the each multivariable model as explanatory variables and the administrative units as a random effect.

To better understand the associations remaining in the final multivariable model, associations between owner's age and physical condition and between owner's age and farm size were additionally tested using both the Wilcoxon rank sum test and Spearman's correlation test. All analyses were conducted using the computer software R, version 2.15.2 [44], and package lme4 was used for mixed effect model.

4.3. Results

4.3.1. Summary statistics

Of 1,358 affected farms, 782 (57.6%) participated in this study; of these, 212 were infected, and 566 were vaccinated farms. Four farms did not provide information on the status of infection (Table 14). Most participating farms (698; 152 infected, 542 vaccinated and 4 unknown) were cattle farms; only 80 were identified as pig farms.

Table 14. The number of farms participated according to the types of farms

	Infected farms (%)		Vaccinated farms (%)		Unknown (%)*	
Cattle farms						
Dairy	13	(1.7%)	22	(2.8%)	0	(0.0%)
Beef reproduction	102	(13.0%)	460	(58.8%)	4	(0.5%)
Fattening	18	(2.3%)	16	(2.0%)	0	(0.0%)
Integrated	10	(1.3%)	13	(1.7%)	0	(0.0%)
Unknown**	9	(1.2%)	31	(4.0%)	0	(0.0%)
Total	152	(19.4%)	542	(69.3%)	4	(0.5%)
Pig farms						
Reproduction	15	(1.9%)	6	(0.8%)	0	(0.0%)
Fattening	5	(0.6%)	4	(0.5%)	0	(0.0%)
Integrated	30	(3.8%)	11	(1.4%)	0	(0.0%)
Unknown**	8	(1.0%)	1	(0.1%)	0	(0.0%)
Total	58	(7.4%)	22	(2.8%)	0	(0.0%)
Cattle and pigs	2	(0.3%)	1	(0.1%)	0	(0.0%)
Boar	0	(0.0%)	1	(0.1%)	0	(0.0%)
Grand total	212	(27.1%)	566	(72.4%)	4	(0.5%)

* Status of farms as to infected or vaccinated was not provided.

** Category of farms was not provided.

Of 782 farmers, 55.4% (428/773) restarted or were planning to restart business. Nine farms didn't provide information regarding the status of resumption. The proportions of farmers who restarted or were planning to restart according to animal species raised were 54.8% (379/692) in cattle, 60.3% (47/78) in pigs, 50.0% (1/2) in farms raising both cattle and pigs, and 100% (1/1) in a boar farm. According to K6 score, only one cattle farmer (1/782, 0.1%) had SMI at the time of the survey; the other farmers (781/782) did not.

Table 15 shows the resumption of farming according to administrative units. The proportions of restarted farms in Saito ($p < 0.01$) and Tsuno ($p < 0.01$) were significantly lower than in Kawaminami, which was the center of the epidemic. On the other hand, the proportions of restarted farms in Miyazaki and Shintomi were significantly higher than in Kawaminami ($P<0.01$).

Table 15. Comparison of restarting rate by administrative units

Township	Restarted	Not-restarted	Proportion of restart (%)	Coefficient	*p*-value
Kawaminami	164	104	61.2	Reference	−
Kijo	43	20	68.3	0.31	0.30
Miyazaki	30	6	83.3	1.15	0.01
Saito	4	62	6.1	-3.20	<0.01
Shintomi	117	40	74.5	0.62	<0.01
Takanabe	45	22	67.2	0.26	0.37
Tsuno	25	91	21.6	-1.75	<0.01

4.3.2. Effects of disease control and supports on the restarting rate

Table 16 shows the results of univariable analyses for the effects of disease control and supports on the restarting rate. Factors significantly associated with hesitation to restart farming were vaccinated farm ($p < 0.01$), not having helped slaughtering at other farms during the FMD epidemic ($p < 0.01$), slaughtering and burying animals in a communal burial place ($p < 0.01$), having no one with whom to talk about stress from FMD or no supporter during the epidemic ($p < 0.01$), and not being troubled by business matters and finances after the epidemic ($p < 0.01$). On the question regarding satisfaction with information provided by the government during the outbreak, farmers who resumed farming scored lower than those who did not (1.1 vs. 1.5, $p < 0.01$, not shown in Table 16).

Table 16. Effects of disease control and support on the restarting rate

Contents of question	Restarted	Not-restarted	Proportion of restart (%)	*p*-value
Farm status in the outbreak				
Infected farm	145	63	69.7	<0.01
Vaccinated farm	282	281	50.1	
Help slaughtering at other farms				
Helped	76	22	77.6	<0.01
Not helped	321	308	51.0	
Observation of slaughtering				
Observed	110	76	59.1	0.19
Not observed	287	252	53.2	
Place for slaughter				
In farm	191	102	65.2	<0.01
Outside farm	24	15	61.5	
Communal burial place	190	218	46.6	
Both in farm and communal burial place	5	2	71.4	

Table 16. Effects of disease control and support on the restarting rate (Continued)

Contents of question	Restarted	Not-restarted	Proportion of restart (%)	*p*-value
Someone to talk to about FMD				
Existed	173	71	70.9	<0.01
Not existed	229	242	48.6	
Supporter in the epidemic				
Existed	268	170	61.2	<0.01
Not existed	117	128	47.8	
Trouble with their business and finance				
Troubled	187	106	63.8	<0.01
Not troubled	218	222	49.5	

4.3.3. Effects of the farm characteristic on the restarting rate

Table 17 shows the results of univariable analyses for the effects of the farm on the restarting rate. The factors significantly associated with hesitation to restart farming were beef reproduction farms ($p < 0.01$), multiple sources of income ($p < 0.01$) and family-owned farms ($p = 0.03$). In order to understand why restarting rate was low in Saito City (6.1%) and Tsuno Town (21.6%, see Table 1), additional analyses were conducted for these three factors. In the GLM choosing Saito City as the reference, the proportion of farmers with multiple source of income in Saito City (81.4%) was not significantly different from Miyazaki City (62.9%, $p = 0.051$) and Tsuno Town (78.7%, $p = 0.7$), but was higher than all the other towns and cities (mean 51.8%, $p > 0.05$). There was no significant difference between Saito City and Tsuno Town, and the other towns and cities in the proportions of beef reproduction farms and family-owned farms ($p > 0.05$).

Table 17. Effects of the farm characteristics on the restarting rate

Contents of question	Restarted	Not-restarted	Proportion of restart (%)	*p*-value
Sex of owner				
Male	401	312	56.2	0.16
Female	27	32	45.8	
Species of livestock				
Cattle	379	313	54.8	0.74
Pig	47	31	60.3	
Cattle and pig	1	1	50	
Boar	1	0	100	
Type of operation (cattle farm)				
Beef reproduction	285	276	50.8	<0.01
Fattening and integrated	43	14	75.4	
Type of operation (pig farm)				
Reproduction	12	9	57.1	0.96
Fattening and integrated	30	19	61.2	
Business style of farming				
Source of income from only farming	207	91	69.5	<0.01
Multiple sources of income	200	225	47.1	
Farm management types				
Family-owned farm	383	318	54.6	0.03

Corporate farm	29	10	74.4

Table 18 shows the results of univariable analysis for count data on farm characteristics. Factors significantly associated with hesitation to restart farming were smaller number of cattle ($p < 0.01$), smaller number of pigs ($p < 0.01$) and smaller number of non-family employees ($p < 0.01$).

Table 18. Univariable analysis for count data on farm characteristics.

Contents of question	Restarted (95 percentile)	Not-restarted (95 percentile)	*p*-value
Number of cattle in a farm	50.2 (1 - 410)	49.0 (2 - 291)	<0.01
Number of pigs in a farm	2249.9 (7 - 6406)	777.4 (333 - 4700)	<0.01
Number of non-family employee	0.3 (0 - 4)	0.04 (0 - 0)	<0.01

4.3.4. Effects of the personal attributes on the restarting rate

Table 19 shows the results of univariable analyses of effects of the personal attribute on the restarting rate. Factors significantly associated with hesitation to restart farming were smaller family size ($p < 0.01$), smaller number of generations in a family ($p < 0.01$), increased age of owner ($p < 0.01$).

Table 19. Effects of the personal attribute on the restarting rate

Contents of question	Restarted (95 percentile)	Not-restarted (95 percentile)	*p*-value
Family size	3.8 (1 - 8)	3.2 (1 - 5)	<0.01
Number of generation in a family	2.1 (1 - 3)	1.9 (1 - 3)	<0.01
Age of owner	58.8 (31 - 79)	64.9 (39 -84)	<0.01

Table 20 shows the results of univariable analyses of categorical data for factors associated with personal attributes. Personal attributes significantly associated with hesitation to resume farming were feeling no distress ($p < 0.01$), having no trouble with personal relationships during and after the epidemic ($p = 0.01$), better psychological condition ($p < 0.01$) and having an illness at the time of the interview ($p = 0.01$). The K6 scores of farmers who did not resume farming (mean = 0.73) were not significantly higher than those of farmers who did resume farming (mean = 0.58, $p = 0.9$; not shown in the table).

Table 20. Univariable analysis for categorical data on personal attributes related factors

Contents of question	Restarted	Not-restarted	Proportion of restart (%)	*p*-value
Sex of owner				
Male	401	312	56.2	0.16
Female	27	32	45.8	
Dissatisfaction on current job				
Dissatisfied	10	7	58.8	0.87
Not dissatisfied	355	305	53.8	
Distress				
Distressed	120	69	63.5	<0.01
Not distressed	247	243	50.4	
Trouble with family member				
Troubled	102	88	53.7	0.74
Not troubled	306	246	55.4	
Illness of family member				
Illed	66	52	55.9	0.87
Not illed	332	276	54.6	
Trouble between family members				
Troubled	8	6	57.1	1
Not troubled	384	320	54.5	
Trouble with child rearing				
Troubled	4	7	36.4	0.24
Not troubled	389	320	54.9	

Table 20. Univariable analysis for categorical data on personal attributes related factors (Continued)

Contents of question	Restarted	Not-restarted	Proportion of restart (%)	*p*-value
Trouble in caring old and disabled family member				
Troubled	24	22	52.2	0.85
Not troubled	370	305	54.8	
Trouble with personal relationships				
Troubled	90	48	65.2	0.01
Not troubled	315	286	52.4	
Trouble with neighborhood				
Troubled	52	32	61.9	0.12
Not troubled	326	297	52.3	
Physical condition				
Bad	320	255	55.7	0.77
Better	100	85	54.1	
Psychological condition				
Bad	257	156	62.2	<0.01
Better	158	181	46.6	
Death of family member within a year after outbreak				
Died	11	16	40.7	0.17
Not died	417	329	55.9	

Table 20. Univariable analysis for categorical data on personal attributes related factors (Continued)

Contents of question	Restarted	Not-restarted	Proportion of restart (%)	p-value
Previous illness				
Had	199	166	54.5	0.27
Did not have	209	146	58.9	
Present illness				
Had	216	201	51.8	0.01
Did not have	196	122	61.6	

4.3.5. Multivariable analysis

In the FMD model, the factors associated with hesitation to restart farming were higher level of satisfaction with the information from the government (slope = −0.20, se = 0.09, p = 0.02), not having helped animal slaughter at other farms during the FMD epidemic (difference of logit = −1.00, se = 0.31, $p < 0.01$) and being vaccinated farms (difference of logit = −0.73, se=0.24, $p < 0.01$) (Table 21).

Table 21. Results of multivariable analysis for three models

Model	Variable	Coefficient	SE	*p*-value
FMD model	All farm			
	Level of satisfaction on the information from the government	-0.20	0.09	0.02
	Not helping slaughtering at other farms	-1.00	0.31	<0.01
	Being vaccinated farms as compared to infected farms	-0.73	0.24	<0.01
Farm characteristics model	All farm			
	Number of livestock in a farm	0.0004	0.0002	0.06 [1]
	Multiple source of income	-0.59	0.18	<0.01
	Cattle farm			
	Number of cattle in a farm	0.02	0.004	<0.01
	Pig farm			
	Number of pigs in a farm	0.0006	0.0003	0.02

[1] This factor couldn't be removed from final model, because deviance was significantly different.

Table 21. Results of multivariable analysis for three models (Continued)

Model	Variable	Coefficient	SE	*p*-value
	All farm			
	Family size	0.16	0.06	<0.01
	Age of owner	-0.04	0.008	<0.01
	Having better psychological condition	-0.46	0.2	0.02
	Having bad physical condition	-0.54	0.26	0.04
Personal attributes model	Cattle farm			
	Family size	0.14	0.06	0.01
	Age of owner	-0.04	0.009	<0.01
	Pig farm			
	Family size	0.34	0.14	0.02
	Having better psychological condition	-1.36	0.64	0.03
	Having bad physical condition	-3.60	1.19	<0.01

For all farms in the farm characteristics model, the factors associated with hesitation to restart farming were small scale (slope = 0.0004, se = 0.0002, $p = 0.06$) and having multiple sources of income (difference of logit = −0.59, se = 0.18, $p < 0.01$). For cattle farms, the factor associated with hesitation to restart farming was a smaller number of cattle in the farm (slope = 0.02, se = 0.004, $p < 0.01$). Similarly, for pig farms, a smaller number of pigs were associated with hesitation to restart farming (slope = 0.0006, se = 0.0003, $p = 0.02$) (Table 21).

For all farms in the personal attributes model, the factors associated with hesitation to restart farming were smaller family size (slope = 0.16, se = 0.06, $p < 0.01$), higher age of the owner (slope = −0.04, se = 0.008, $p < 0.01$), better psychological status (difference of logit = −0.46, se = 0.2, $p = 0.02$) and poor physical condition (difference of logit = −0.54, se = 0.26, $p = 0.04$). For cattle farms, the factors associated with hesitation to restart farming were smaller family size (slope = 0.14 se = 0.06, $p = 0.01$) and higher age of the owner (slope = −0.04, se = 0.009, $p < 0.01$). For pig farms, the factors associated with hesitation to restart farming were smaller family size (slope = 0.34, se = 0.14, $p = 0.02$), better psychological status (difference of logit = −1.36, se = 0.64, $p = 0.03$) and poor physical condition (difference of logit = −3.60, se = 1.19, $p < 0.01$) (Table 21).

Additional statistics revealed a significant correlation between small farm size and higher age of the owner for both cattle (rho = −0.34, $p < 0.01$) and pig farms (rho = −0.32, $p < 0.01$). Moreover, the age of owners with poor physical condition (mean = 63.0 years) was significantly higher than that of owners with good physical condition (mean = 57.2 years), suggesting that poor physical condition and higher age are statistically related.

4.4. Discussion

Locally and internationally published reports of the impact of FMD outbreaks are mostly related to economic losses. However, affected farmers also experience mental distress due to loss of their animals [45], and studies of this problem are still scarce. The questionnaire survey revealed three factors associated with hesitation to restart farming: (1) mental distress caused by the disease epidemic, inadequate support, and conflicts with other farmers and associated organizations during FMD control, (2) limited capacity in small farms of elderly owners with physical health problems and (3) farmers' degree of intensity toward livestock farming.

Several causes of distress as well as relief for the farmers were identified by the survey. A locally published paper also described substantial daily stress caused by anxiety and fear of their farms becoming infected with FMD virus, and sadness and fear caused by culling animals on infected farms [29]. However, according to the multivariable model, vaccinated farms hesitated to resume farming rather than infected farms. Vaccinated farmers suffered from sadness, because healthy and non-infected animals had to be culled due to the disease control [29]. Some older farmers misunderstood that animals would not be culled after vaccination [29]. Vaccination was conducted on 1,066 farms in only four days, and informed consent might be insufficient for farmers because of the limited time. Moreover, farmers who had vaccinated their animals felt a sense of unfairness compared to those who had not vaccinated. In principal, both infected and vaccinated farms were fully compensated for the lost animals based on the market value of animals by the government. However, vaccinated farms and infected farmers not participating in the Agricultural Insurance Scheme received 100% of the market value of animals, while infected farms participating in the insurance scheme did 120% [41]. For the infected farms, 80% of the value was compensated from the national government by the Act on Domestic Animal Infectious Diseases Control, and if participated in the insurance scheme, 20% of the value was paid as insurance money. However, as non-insured farms could not receive the insurance money, special allocation tax equivalent to 20% of the value was paid from the prefectural government to both insured and non-insured infected farms; eventually insured infected farms received 120% of the value of lost animals. For vaccinated farms, 100% of the value of lost animals was compensated from the national government by the Act on Special Measures Concerning FMD, which was issued just after the start of vaccination. These vaccinated farms did not receive insurance money.

As for other causes of distress, conflicts with rice- and crop-producing farmers were also concerned. A previous report suggested that rice- and crop-producing farmers complained that livestock farmers were compensated for losses incurred by the restriction of movement, but they were not [31]. Moreover, the magnitude of epidemic seemed to affect the restarting their business. The first case of FMD was detected in Tsuno Town, and Kawaminami Town was the epicenter of the epidemic [40]. The devastating damage in these areas might lead to the low restarting rate.

On the other hand, two factors associated with relief from the distress of the FMD epidemic were found to have encouraged resumption of farming. Farmers who had someone to talk to about their stress during the FMD epidemic resumed farming significantly more often than those who did not. The therapeutic effect of discussing one’s own emotions has been reported among veterinarians who participated in FMD control [15], as well as among the evacuees after the Great East Japan Earthquake [31]. Another relieving factor was participation in animal depopulation on other farms after one’s own animals were culled. During the epidemic, the Miyazaki Prefectural Government employed farmers whose animals had been slaughtered to assist with depopulation activities on other farms [29]. Farmers were likely able to share their experiences and feelings, alleviating their distress.

Multivariable analyses showed that advanced owner age, small farm size and poor physical condition were factors associated with hesitation to restart farming. Additional analyses suggested that older owners with small farms and poor physical condition gave up farming. Farmers do not have a labor force to help run the farm when the owner and family members are physically ill. In Miyazaki Prefecture, 70% of the agricultural work force was over 60 years old [37], and a lack of successors was also associated with elderly farmers not restarting farming. Larger family size was associated with resumption of farming; this can be explained by the similar hypothesis that higher capacity (sufficient labor force and financial resilience) was a prerequisite for resumption of farming.

Psychological illness among farm owners and/or family members was associated with resumption of farming. It is possible that those who resumed farming recalled their experiences from FMD epidemic in the course of everyday farming activities, while those who did not resume farming were not exposed to activities associated with past tragedy. It implies that farmers still remain psychological distress even after one year past the epidemic. Meanwhile, K6 scores higher than the cut-off point, which is the measure of SMI, were not associated with resumption of farming. Because K6 score is a screening tool for SMI and is more suitable for the acute phase of a tragic event [31], in the present survey conducted one year after the epidemic, K6 might fail to pick up less severe but persisting psychological illness which the respondents had. Thus, the Impact of Event Scale-Revised instrument, which is used to detect post-traumatic stress disorder [3], might have been better for this study.

Farmers' dedication to their businesses seemed to positively influence resumption of farming. These results showed that the level of satisfaction with the information provided by the government during the epidemic had a significant negative association with resumption of farming. According to the previous investigation to farmers and the locally published paper [29], two main frustrations among farmers against the government during epidemic were lack of information on exact geographical locations of infected farms and effective disinfectants against FMD virus. Highly motivated farmers who resumed farming might particularly have had such frustration, although there are no supporting scientific data available to test the hypothesis. Farmers who relied only on livestock farming had a higher restarting rate than those with multiple sources of income; this fact also supports the hypothetical association between attitude towards farming and resumption of farming. According to farmers and field veterinarians, many livestock farmers with multiple farming activities, including rice and crop cultivation, shifted to less risky crop production after the epidemic (personal communication). These results also showed that the restarting rate was the lowest in Saito City, where the proportion of farmers with multiple source of income was high.

The present study shows that hesitation to restart farming after animal depopulation due to an FMD epidemic is caused largely by mental distress, but also by a lack of capacity and resources (even with economic support from the government) and by degree of intensity toward livestock farming. Results indicate that three kinds of support may effectively encourage farmers to restart: relief of mental distress at the time of the epidemic, maintenance of economic security, and improved and regular provision of information on disease prevention for greater biosecurity. This paper highlights farmers affected by the FMD epidemic; however, another study reported that local restaurateurs who lost customers wishing to avoid fueling the spread of disease were economically and psychologically most affected during and after the epidemic [66]. Public services should consider coordinating different sectors to improve preparedness for future disasters caused by highly contagious animal diseases.

4.5. Summary of Chapter 4

An outbreak of foot-and-mouth disease (FMD) occurred in Miyazaki Prefecture, Japan, in 2010. This epidemic was controlled with culling and vaccination, and resulted in the death of nearly 290,000 animals. This paper describes the factors associated with hesitation to restart farming after the epidemic. A questionnaire survey was conducted to assess the mental health of farmers one year after the end of the FMD epidemic in affected areas, and univariable and multivariable analyses were performed. Of 773 farms which had answered the question about restart farming, 55.4% (428/773) had resumed or were planning to resume operation. The farms hesitated restarting were characterized by small scale (p = 0.06) and having multiple sources of income (p < 0.01). Personal attributes associated with hesitation to restart were advanced age of the owner (p < 0.01), with someone with bad physical conditions (p = 0.04) and small family size (p < 0.01). Factors related to disease control during the epidemic that were associated with hesitation to restart were vaccination of animals (p < 0.01), not assisting with culling on other farms (p < 0.01), and higher satisfaction with information provided by the government (p = 0.02). We found that farmers hesitated to resume farming because they had a limited labor force, had an alternative business or were mentally distressed during disease control.

Chapter 5. General discussion

5.1. Highlight of this thesis

This thesis demonstrated the usefulness of veterinary epidemiology in decision making on animal and zoonotic infectious diseases control by studies on two important diseases, FMD and rabies.

The results from Chapter 2 showed the risk of spread of rabies once it is introduced into Japan. The model suggested that incursions of rabies into Japan are very unlikely to cause large outbreaks in current condition. The reaction of dog owners to their dogs developing rabies considerably impacts the course of outbreaks. Contingency measures should therefore include sensitization of dog owners. Thus, this chapter emphasizes that it is necessary to take behavior of animal as well as human into account when considering the control options against infectious diseases. In addition to this, the result from Chapter 2 demonstrated that the mathematical model was useful to consider and compare the control options for future outbreak of infectious disease. However, the development of mathematical model requires high level of both biological and mathematical knowledge.

The results from rabies research in Vietnam (Chapter 3) showed the association among socio-economic factors under the framework of KAP. The results suggested that the practice of dog rabies vaccination was promoted by good social status, rich knowledge and positive attitudes toward dog rabies control and prevention in this study area. Vaccination coverage in this study area was high and mean estimation of willingness-to-pay for a vaccination in mountainous and plain areas was twice higher than the actual cost of 21,000 VD. Although the practice of tethering of dogs was not common, especially in mountainous area, their willingness–to-confine their dogs if it is enforced was excellent. Awareness-raising campaigns targeting poor and minority people to send the information on rabies control should be considered by stakeholders to reduce the disease burden. This would be helpful in other areas of Vietnam.

Consideration of infectious zoonotic diseases must be arranged from perspective of animal and human health. Dog is important reservoir maintaining rabies in the world and human and dogs live together. Human-dog relationship and practice of rabies control is determined by socio-cultural factors. Thus, careful understanding of these factors is necessary when planning the disease control strategy. In addition to this, neglected diseases mostly affect vulnerable population such as poor and minority people. Therefore, finding targeted population of intervention is also important. Integration of mathematical model (Chapter 2) and sociological study (Chapter 3) will provide good insight to discuss the disease control plan.

In the Chapter 4, the risk factor analysis on the hesitation to restart farming after 2010 FMD epidemic was shown. The questionnaire survey revealed that mental distress caused by the disease epidemic, limited capacity in small farms and farmers' degree of intensity toward livestock farming was associated with the hesitation of restart farming. These results indicate that support to release their obstacle to the restart farming is needed. This chapter emphasizes that the contingency plan should be arranged taking psychological impact into account because the outbreak of infectious disease with destruction of livestock population imposes the dismal consequence to both human and animal health.

5.2. Integrated significance of the thesis

In considering the control options for such infectious diseases, prediction of the disease course provides basis of concrete discussions. Mathematical modelling technique is one of the best tools to achieve this goal. On the other hand, veterinary and health authorities must consider the economic aspect of the control option and psychological and sociological impacts. Economic analysis offers *a-priori* scenario assessment in terms of both cost and acceptability, as shown in this thesis. Psychological effect of a control option may be qualitatively predicted in the consideration of control planning, and authorities may need historical evidence on it. Reporting quantitative psychological impact in past disease control, as shown in the 2010 FMD outbreak in Miyazaki, is therefore important.

Recently, importance of One Health and ecohealth are globally recognized. One Health advocates the importance of collaboration between veterinary medicine, medicine, and environmental sciences, while ecohealth includes transdisciplinarity, which embraces communications and collaborations between different levels of a society such as policy, research, and community [69]. This thesis exactly realized these two important concepts through collaborations between veterinary medicine, medicine, and socio-economics, as well as engagement with communities in the fields.

5.3. Future research opportunity

This thesis also provided some insights into future research opportunities using veterinary epidemiology. Future research opportunities on rabies in Vietnam include integration of mathematical modelling and KAP analysis to inform *a-priori* assessment of control options, and collaborative and interactive researches with international organizations and the government. Mathematical model reflecting the behavior of dog owners related to their willingness-to-pay for vaccination and willingness-to-change for the practice of confinement may show the realistic probability of success of rabies elimination and provide stakeholders with the scientific evidence on planning rabies control strategies. This result will enhance dog rabies elimination from Vietnam.

The psychological study can also be applied to the people suffering the mental stress due to the disease outbreak with slaughtering such as HPAI. Nowadays, invasion of HPAI has been frequent in Japan. Persisted outbreaks of HPAI in the surrounding countries raise the risk of HPAI outbreak. Thus, the contingency plan for future outbreak must be developed, considering the psychological impacts on farmers and veterinarians. Furthermore, pet loss syndrome is also important issue for veterinarians. Recover from the misery requires the social support from the people who are related with pet owners. Thus, detecting vulnerable people with regard to pet loss can help save such people from pet loss because veterinarians is one of the important key person who is close to pet owner.

The methodologies and ecohealth approach used in this thesis can be applicable to other animal and zoonotic diseases. Epidemiological analysis itself should not be the ultimate goal. Risk managers and general populations also should be well informed about the usefulness of such approaches to realize better future on the disease aspects.

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ABSTRACT IN JAPANESE (和文要旨)

近年、日本はいくつかの重要な家畜感染症の発生を確認している。2001 年には BSE が初めて確認され、2000 年と 2010 年には口蹄疫が発生した。また、高病原性鳥インフルエンザの発生が続いており、これらの家畜感染症は産業動物に甚大な被害をもたらしている。したがって、発生確認後の迅速な対応と拡大防止策が事前に構築されていなければならず、科学的知見に基づいた感染症制御の在り方の議論は、食品安全および食糧安全保障上極めて重要なものである。

疫学は集団を対象として疾病の分布や頻度、そしてそれらを規定する要因を明らかにする研究である。獣医学領域の疫学では、動物のみならず人を含めた集団を対象としているため、獣医疫学の適応範囲は非常に広い。獣医疫学の主な目的としては、疾病の原因を明らかにし疾病の予防や制圧に必要な施策を行うこと、疾病発生の将来予測、疾病の経済評価、動物の生産性の向上および人や動物の福祉の向上などがあげられる。

本研究では、口蹄疫や狂犬病という動物衛生および公衆衛生上極めて重要な二つの感染症を取り上げ、感染症およびそれらに影響を受ける人の社会学的問題の制御方法について定量的検討を実施した。第 2 章では、感染症モデリングを用いて我が国の狂犬病予防対策の有効性について検討を実施した。第 3 章では、ベトナム国タイ・グェン省における狂犬病予防対策に関する知識、態度、行動の構造を明らかにすることを目的とした。第 4 章では、2010 年に宮崎県で発生した口蹄疫被災農家の再開を阻害する因子を探ることで、殺処分を伴う家畜感染症制御時の農家への支援の在り方についての検討を実施した。

感染症モデリングの結果から、現在の日本の状況下では大きなアウトブレイクに繋がる可能性が低いことが示唆された。また、狂犬病発生時の飼主の対応が発生件数に大きく影響することが明らかとなった。したがって、狂犬病発生時の対応には犬の飼主に対する啓蒙活動が含まれるべきであると考えられた。また、感染症モデリングによる将来の発生予想は、感染症制御の在り方の議論に有用であることが示唆された。

ベトナムでの社会学的研究の結果から、経済的に裕福で、狂犬病と予防対策について豊富な知識があり、予防対策に好意的な態度があると飼主によるワクチン接種が促されることが明らかに

なった。研究地域における、ワクチン接種率と犬の狂犬病ワクチンに対する支払い意欲は高かった。犬の繋ぎ飼いは普及していなかったものの、繋ぎ飼いを強制された場合にはほとんどの飼主がこれに応じるという結果が得られた。これらのことから、経済的に困窮している少数民族をターゲットとした狂犬病に関する啓蒙活動を実施が狂犬病撲滅に向けた対策に含まれるべきであると考えられた。また狂犬病において、重要なレゼルボアである犬は人と密接なかかわりを持っている。したがって、人と犬の関係性や狂犬病対策の実施を規定する社会文化的要因を理解したうえで、公衆衛生及び動物衛生に配慮した対策構築を行うべきであると考えられた。

口蹄疫被災農家の精神衛生に関する研究結果から、精神的ストレスや農家の畜産経営に対して熱心であることが口蹄疫被災後の経営再開に関連していることが明らかとなった。このことから経営再開の障害を取り除くことが復興の支援として重要であることが示唆された。また、殺処分を伴う口蹄疫や高病原性鳥インフルエンザといった大規模な家畜感染症制御の在り方を議論する際には、畜産関係者や獣医師の精神衛生に配慮した対策を構築することが重要であると考えられた。

家畜衛生および公衆衛生上極めて重要な家畜感染症の研究を通して、感染症制御の在り方を議論する意思決定者にとって有益な情報を提供したものと考えられた。近年、ワンヘルスおよびエコヘルスの重要性が世界的に認知されてきており、分野横断的に問題解決に取り組むことが家畜感染症制御において重要であるとされている。本研究論文は、動物衛生および公衆衛生上極めて重要な狂犬病と口蹄疫という２つの感染症の研究を通して、家畜感染症制御の構築の在り方と学際的な協調が問題解決において重要であることを示した。