Risk of rabies virus reintroduction on the cost-effectiveness of mass vaccination strategies in Flores Island, Indonesia

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Abstract

Rabies is an important zoonotic viral disease in Flores island, Indonesia. The disease is accounted for approx. 19 human cases each years despite the current mass vaccination campaigns. Moreover, the island is facing the limitation on resources and cultural value which can impact the efficiency of the vaccination and the disease dynamics, especially the risk of virus reintroduction. In this study, deterministic and stochastic simulation models on rabies disease dynamics were developed to examine and estimate the impact of virus reintroduction on the cost-effectiveness of different dog vaccination strategies. The modelling unit within the study represented the dog population in an average village of Flores Island, Indonesia. The cost-effectiveness analysis was performed based on total costs (vaccination costs and post-exposure prophylaxis (PET) costs) per averted rabies case, which were calculated from an animal and a human perspective.

By means of the deterministic approach the effectiveness of alternative preventive mass vaccination strategies were evaluated during a period of 10 years given a single virus introduction. Subsequently, the stochastic modelling was based on the most cost-effective strategies as determined by the outcomes from the deterministic modelling. In total 6 strategies were evaluated; the baseline without vaccination (Scenario 1), annual vaccination with short-acting vaccines (Scenario 2), biannual vaccination with short-acting vaccines (Scenario 3), annual vaccination with long-acting vaccines (Scenario 4), once-every-2-year vaccination with long-acting vaccines (Scenario 5) and combination of annual short-acting vaccines during the normal situation and long-acting vaccines during the outbreak (Scenario 6). Moreover, the variation of vaccination coverage (vc) starting from 50-70% (5% interval) with additional 50-70-50% (Using 50% vc during normal situation and 70% during the outbreak) were simulated in each scenario. Moreover, in the stochastic modelling 2 scenarios with respect to the expected probabilities of reintroduction were evaluated, viz. once-in-a-year (P = 0.019) and once-in-3-years (P = 0.006).

The comparisons between the outcomes from each scenario were made by focusing on the effectiveness for disease control together with the cost-effectiveness ratios measured by the costs per human case averted. The main findings in the deterministic model showed that the most cost-effective scenarios could be ranked as followed; scenario 6, 4, 2 and 3 at 70% vc. In the practical situation, it would be infeasible to perform biannual vaccinations in the rural areas as well as increasing the vc to be higher than 50%. Thus, scenario 4 with 50-70-50% vc, scenario 6 with 50% vc, and 2 with 50-70-50% were considered to be the most cost-effective scenarios regarding the feasibility and the ability to reduce rabies cases, given a single rabies introduction. The stochastic modelling showed that the most cost-effective scenarios that could reduce the rabies cases in dogs and humans when accounting for the risk of reintroduction in the worst case scenario (P=0.019) were scenario 6 at 70% vc and 4 at 70% vc, resulting in an average cost-effectiveness ratio of, respectively, 167 USD per human case averted and 179 USD per human case averted. Ranges in cost-effectiveness varied from 147 to 206 USD USD per human case averted for scenario 6 at 70% and from 156 to 218 USD per human case averted for scenario 4 at 70%.

In conclusion, the findings in both deterministic and stochastic model suggested that if we focus on the effectiveness of control alone, 70% vc was the most effective vc regardless of the scenario used. Given the uncertainty with respect to the likelihood of reintroduction scenario 6 at 70% vc appear to be the most preferable strategy to control the disease. However, according to the field data the current vc that has been achieved on Flores Island, is only 50%. Simulation results on scenario 6 at 50% vc indicated that this strategy also provided better outcomes in reduction of cases and cost-effective ratios than the current vaccination campaign (scenario 2) at the same vc. Based on these results, the preliminary suggestion is to discontinue the current vaccination campaign (annual vaccination with short acting vaccine with 50% vc) and switch from short-acting to long-acting vaccine. However, more efforts and collaboration among stakeholders should be put in place to increase vaccination coverage in dogs to be as high as 70% for effective vaccination and for dealing with the uncertainty of virus reintroduction in the long run.

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1. Introduction

1.1 General background

Rabies is a viral zoonotic disease caused by a virus of the genus Lyssavirus which is a single strand RNA virus. The transmission of rabies is due to direct contact with saliva that contains the virus. Infection through tissue transplant and aerosols has also been reported (CDC, 2012). However, the most common route of infection is through animal bites, especially by domestic dogs which account for almost 99% of the global human deaths from rabies (WHO, 2005). After exposure by being bitten by a rabid dog, the virus will gradually replicate in the muscle around the infection site and rapidly propagates into the central nervous system. This stage can take weeks or months depending on the distance between the infection site and the brain. Once the virus infects the brain, it's 100% fatal. After that the virus will infect other organs throughout the body; especially the salivary glands where the virus will be excreted into saliva to infect other susceptible animals. Rabies is categorized into 2 types. The first type is ‘wildlife rabies’ which is caused mainly by wild carnivores and bats and the second type is ‘urban rabies’ of which dogs are the main source of transmission to human (Garg, 2014).

The distribution of rabies is considered to be worldwide except in Antarctica. The burden of rabies on human health is mainly on developing and poverty-stricken countries. WHO (2005) has indicated that rabies kills at least 55,000 humans each year of which 95% are in Africa and Asia and 40% concern children in the rural area. Using the disability-adjusted life year score, the deaths by rabies in Asia and Africa are accountable for 1.74 million DALY every year (Knobel et al., 2005). However, Garg (2014) suggested that this number might be even underestimated because the majority of affected countries are in developing countries which generally have a low level of surveillance systems and data recording.

Indonesia is one of developing countries where rabies is still endemic. This country is located in the Southeast Asia region which attributes to 45% of the global human rabies cases every year. In Indonesia alone, rabies has accounted for 150-300 human deaths annually (Gongal & Wright, 2011). The first introduction of rabies into Indonesia was reported in 1884 in water buffalo, in 1889 in dog and in 1994 in human (WHO, 1996). Despite the archipelago of 17,508 islands (CIA, 2016), the prevalence of rabies in each of the major islands are closely related (Figure 1) as shown in molecular epidemiological and phylogeographic studies of Susetya et al. (2008) and Dibia et al. (2015). Many prevention and control measures have been implemented in an attempt to eliminate the disease, including mass dog vaccination, restriction of inter-island transportation of animals and dog culling. However, these measures have still not eliminated the disease from areas like Flores, Sumatra, Java, Kalimantan and Bali which are well known areas for their international tourist attraction (Ward, 2011).

1.2 Rabies in Flores Island

Flores Island is located in the east of Indonesia. It is populated by an estimated population of 1.8 million human and 200,000 dogs in an area of 15,624 km2 (Wera et al., 2015). The first introduction of rabies in Flores occurred in 1997 via transportation of dogs from southeast Sulawesi and resulted between 1997-2002 already in 114 registered human deaths (Windiyaningsih et al., 2004). During 1997 – 2001, the emergency control measures consisted mainly of culling dogs in affected regions (approx. 260,000 dogs or 48% of the island's dog population were killed by this measure) followed by mass dog vaccination starting from 2000 onwards (Windiyaningsih et al., 2004, Wera et al., 2013 and Wera et al., 2015).

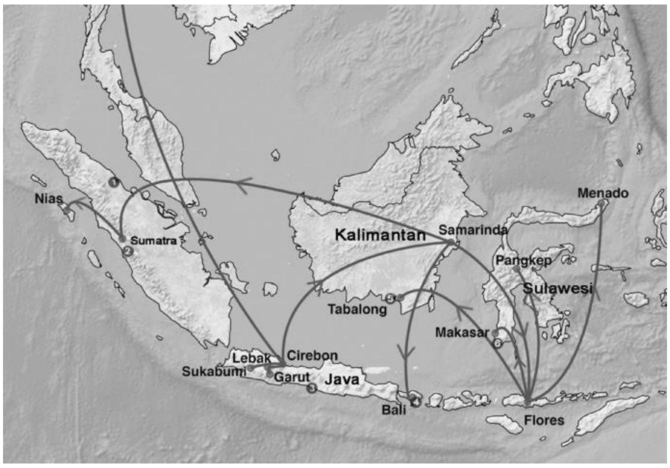

Figure 1 A map of Indonesia and its geographical distribution with proposed dynamics (arrows) of rabies through Indonesia according to the phylogeographic study by Dibia et al. (2015).

Although mass vaccination in dogs has been proven to be successful and effective to control and eliminate dog and human rabies in many areas (Tierkel et al., 1950; Belotto et al., 2005; and Morters et al., 2012), the disease is currently still endemic in the island with approx. 19 human deaths each year (Windiyaningsih et al., 2004). The major constraints for the achievement are related to the low vaccination coverage in combination with the high turn-over rate of the dog population (circa 45%; Wera et al., unpublished data).

Moreover, given specific traditions, people on the island also have a high influence on disease dynamics regarding the probability of transmission. Most of the population on Flores are Catholic, not Muslim like the majority of Indonesia Therefore, dogs are allowed to be part of their life without religious restrictions. They even represent cultural value during traditional ceremonies, when dog meat is consumed (Wera et al., 2013). Beside the cultural value, dogs represent an economic value as they are raised as guard dog against to protect the crops on the agricultural fields from damage by wildlife (Hutabarat et al., 2003).

Apart from vaccination in dogs, post exposure treatment (PET) is essential for rabies prevention in humans after they have been bitten by suspected rabid dogs. PET, in general, consists of wound cleaning, immunoglobulin and series of vaccinations. Wera et al. (2013) have estimated the annual costs for PET in Flores Island to be approx. 0.6 million USD. The burden for the cost of controlling the disease is mainly on the local government which can be separated into veterinary and public health sectors. The question remains in which part of the transmission chain between dogs and humans the local government should allocate their resources to obtain the most cost-effective human rabies control and prevention strategy in Flores island.

Recent model studies on mass vaccination strategies in Flores Island have suggested that elimination of virus by vaccination is possible, especially when starting vaccination at village level (Wera et al., 2016a). However, the risk of reintroduction of the virus was not considered in the evaluation of the cost-effectiveness of the vaccination strategies in the long run. Therefore, given the economic and cultural value of the dogs on the island, a re-introduction of the disease due to human-mediated transportation should be considered as a realistic possibility when evaluating various vaccination strategies.

1.3 Main objective and research questions

The main objective of this study is, therefore, to estimate the impact of virus reintroduction on the cost effectiveness of different mass dog vaccination strategies. In accordance with the main objective the following research questions have been defined;

a. What are feasible canine dog rabies vaccination campaigns in terms of vaccination coverage, vaccination type, vaccination frequency and related costs for vaccination and PET to control rabies in Flores Island?

- what are the costs regarding the vaccination strategies?

- what are the benefits represented by the number of human cases prevented?

b. What is the impact of reintroduction of the virus at village level on the effectiveness of the evaluated mass dog vaccination campaigns?

c. What is the range in the cost-effectiveness of the various specific vaccination campaigns by accounting for the risk of virus reintroduction?

The study was divided into 2 parts. The first part involved epidemiological and economic modelling to estimate the veterinary burden, public health burden and economic impacts of an outbreak of rabies. It was conducted under various scenarios of vaccination strategies within a village in a deterministic manner and as such explicitly excluding the consideration of the risk of virus reintroduction. The results obtained from the first part were used to gain insights in the most feasible and cost-effective strategies for controlling the disease in a village. In the second part, the risk of virus re-introduction was incorporated by the inclusion of a stochastic process. The conclusions from the second part particularly provide insights in the uncertainty around the cost-effectiveness ratios of the evaluated vaccination, resulting from the risk related to virus reintroduction strategies.

2. Rabies reviewed; current situation and lessons learned so far

The objective of this research review is to review literature on previous rabies research that is relevant for this study especially on epidemiological and socioeconomic aspects. The first part of the review considers the current global rabies situation followed by a focus on the situation on Flores island. Moreover, relevant studies on rabies modelling are discussed as well.

2.1 Global rabies situation

Rabies has been threaten human throughout history (Taylor and Nel, 2015). The development of Pasteur's vaccine in 1885 for rabies' prevention, led to a successful control of the disease in many areas, especially America and western Europe. However, the rabies virus has continued to spread into many new areas in the past decades e.g. across the People Republic of China, and Indonesia (Si et al., 2005, Putra et al., 2013 and Windiyaningsih., 2004).

The disease is neglected in most of the developing countries especially in Asia and Africa where most of the victims are poor and undereducated (Lankester et al., 2014). Limited resources and inadequate infrastructure in those countries also preclude an accurate data collection by surveillance and, more importantly, disease control (Fooks et al., 2014). The ineffectiveness of the surveillance systems result in an underreporting of cases and consequently in an underestimation of the actual global rabies burden.

Hampson et al. (2015) attempted to estimate the global rabies burden using a probability decision-tree framework. The study's information was obtained from literature review, questionnaires and international databases. The results showed that the global cumulative economic loss was equal to 8.6 billion USD every year (Hampson et al., 2015) with the highest burden in Asia and Africa. Hampson et al. (2015) also indicated that the greatest loss was mainly due to premature death which was accounted for 55% of total economic burden. However, it is lower than the estimation derived from the Monte Carlo simulation of Anderson and Shwiff (2015) which estimated the global losses to be 124 billion USD per year. Moreover, Hampson et al. (2015) also suggested that despite the importance in controlling the disease in dogs, the investment on dog rabies control is still much lower than the costs that can be prevented in the public health sector resulting from the post exposure treatment after being bitten by a rabid suspected dog. This finding is in line with the studies on economic implications of rabies using field data from areas like Mexico (Lucas et al., 2007), Sri Lanka (Hasler et al., 2014), South Africa (Shwiff et al., 2014), Philippines (Miranda et al., 2015) and Flores in Indonesia (Wera et al., 2013). Apart from economic burden, the health burden was also estimated using the disability-adjusted life year (DALY) score. Knobel et al. (2005) estimated that the deaths from rabies in Asia and Africa accounted for 1.74 million DALYs every year. While, the study of Hampson et al. (2015) estimated the global health burden to be 3.7 DALYs/year.

In conclusion, regarding the global rabies situation, many studies are in line with each other on the estimation of the rabies burden. Suggestions for further development towards efficient control and prevention are also mentioned which are the efforts on dog rabies elimination and improvement of data collection and surveillance system. These improvements could lead to the development of an effective disease monitoring system in affected countries which is a necessity in developing cost-effective control strategies (Banyard et al., 2013).

2.2 Summary on the rabies situation in Indonesia

Since the nineteenth centuries, rabies has been reported as an endemic disease in many regions of Indonesia. The disease is endemic in 24 out of the 33 provinces in Indonesia (Widyastuti et al., 2015). After the first outbreak in Bali in 2008 due to the introduction of unvaccinated dogs from Flores island, international pressure has led to the serious efforts on rabies elimination in Bali because Bali is a popular international tourist destination (Clifton, 2010 and Townsend et al., 2013). Recent studies from Indonesia, therefore, mainly focus on rabies in Bali and the surrounding areas, for example, Lombok and Flores island. The aim of those studies is mainly focussing on determination of the dog ecology, the influence of sociocultural aspects on disease control and the epidemiological studies regarding vaccination and dog management (Susilawathi et al., 2012, Mustiana et al., 2015 and Saputra, 2015). Previously, Bali faced similar problems as Flores and other regions in Indonesia (Davlin and Vonville, 2012) in reaching 70% vaccination coverage due to the high dog density and high turnover rate of dog population (Mustiana et al., 2015). However, the vaccination coverage of

Bali was able to improve to 70% in 2014 due to the collaboration between Balinese government, local non-governmental organization (NGO) and the Bali Animal Welfare Association (BAWA) (Widyastuti et al., 2015). Widyastuti et al. (2015) also emphasized that the achievement on increased vaccination coverage were mainly from the results of sociocultural studied in Bali because the disease involves complicated relationship between humans and dogs. The study in Bali can, therefore, be a promising case study for other endemic areas to focus on improvement of control and prevention strategies through sociocultural studies and dog ecology. Even though, many studies on rabies in many aspects have been conducted in Indonesia especially Bali, the conclusions from those studies on control strategies cannot be directly applied in the same way for Flores island. Differences in dog ecology and human socio-demography characteristics could result in a different control effectiveness in Flores than demonstrated by a strategy in Bali. For example, due to the cultural value of dogs in Flores (dog consumption during traditional ceremonies), the population turn-over rate is higher in Flores than in Bali, reducing the effect of any vaccination strategy. (Hutabarat et al., 2003).

2.3 Rabies control and prevention strategies in Flores island

The current rabies control and prevention measures in Flores island consist of dog mass vaccination, culling of roaming dogs, quarantine of imported dogs, and pre- and post-exposure treatment in humans. In Flores, dog vaccination is provided free of charge by the government annually using 52-week-immunity local vaccines. The campaign is conducted by door-to-door approach which aims to increase participation and vaccination coverage. However, Wera et al. (2013) have shown that the vaccination coverage is 53% which is lower than recommended of 70% by WHO (1987).

Wera et al. (2016b) indicated the 2 key factors for successful dog vaccination campaigns which are vaccination coverage and duration of vaccine-induced immunity. These two factors are related with population turnover rate and vaccination frequency (Wera et al., 2016b). However, due to high turnover rate (>45%) (Siko, 2011) and consumption of dog meat during traditional ceremonies, the number of immune dogs can be dramatically reduced between each vaccination campaign (Wera et al., 2015). Other concerns involve the resource availability and the perception of dog owners toward prevention and control measures, which will be discussed in the next section. Apart from dog vaccination, PET by Zegreb schedule is the important prevention measure for humans on the island, which is also provided by the government free of charge (Wera et al., 2013).

The current annual costs of vaccination and PET were estimated to be, respectively, 268,360 USD and 386,170 USD, (Wera et al., 2013). Wera et al. (2013) also indicated that public costs for rabies control are higher than private costs, and these costs are expected to increase over time. Therefore, the burden of prevention and control in both humans and dogs is clearly on the government of the island.

2.4 Socio-economic aspects of rabies control in Flores island

The study of Hutabarat et al. (2003) provided insights on the role of culture and dog ecology related to the disease control. This study and also the dog ecological study of Siko (2011) are the fundamental studies providing essential information for other studies about rabies in Flores. Recent studies by Wera et al. (2013, 2015, 2016a and 2016c) have focused more on the socio-economic aspect of the disease to improve vaccination strategies on the island. These studies considered 2 main objectives. The first objective aimed to obtain insights on participation of the dog owners to improve vaccination coverage (Wera et al., 2015 and Wera et al., 2016a). The second objective aimed towards an estimation of costs and cost-effectiveness ratios of rabies control measures (Wera et al., 2013, Wera et al., 2016b and Wera et al., 2016c).

In order to gain insights on dog owners' perspectives on rabies control measures, 2 studies were performed by Wera et al. (2015 and 2016a). Wera et al. (2015) studied the risk factors associated with the uptake of rabies control measure by the dog owners on the island. This study was conducted using questionnaires which contained 4 sections of questions regarding; socio-demographic characteristics of dog owners, knowledge of the risk of the disease on humans, uptake of control measures and the reasons for participation in dog vaccination campaign. Another study by Wera et al. (2016a) was conducted based on theory of planned behaviour to determine the intention to participate in different control measures for dog owners. This study is different from the first one due to the main concentration on psychological factors behind the participation of different control measures. The findings from both studies suggested that geographical accessibility and difficulty to handle dogs are the main factors that influence the intention for participation. They also suggested implementation of the vaccination campaign on weekends to prevent the perceived time restriction during the weeks. It could increase the participation and vaccination coverage as also indicated in a study in Africa (Perry et al., 1995). Moreover, the willingness to pay for the control measures and control costs are also considered as a driver for participation in each campaign. In order to reach 70% coverage, the burden of the investment should be on the government, however, collaboration from organizations is considered to be helpful to reduce this burden as suggested by the studies (Wera et al., 2016a and Putra et al., 2013).

By means of simulation studies the cost-effectiveness of various dog vaccination campaign were evaluated, in which costs were distinctively separated into veterinary and public health costs (Wera et al., 2016b and Wera et al., 2016c). In these studies, the disease dynamics in dogs was modelled by means of a deterministic "SEIVR" state-transition model. The studies made use of the information of dog demography from the field and some transmission parameters from expert opinions and literatures. Moreover, Wera et al. (2016c) also calculated the disease impact on humans using the results from the model outputs of Wera et al. (2016b) and statistical data of human rabies in the island. The findings from both modelling studies showed that increasing vaccination coverage to 70% and using long-acting vaccines would be the most effective strategy for Flores, under the assumption of a campaign on village level triggered by the detection of a rabid dog as a result of a single virus introduction. However, to examine the effectiveness of vaccination strategies in the setting of preventive vaccination the modelling requires the consideration of the risk of virus reintroduction, which was not accounted for in the studies of Wera et al. (2016b and 2016c)

2.5 Rabies Modelling in general

Mathematical modelling associated with rabies has been developed for over 30 years in parallel with general analysis for ecology of infectious diseases (Panjeti and Real, 2011). Due to a successful control of rabies in domestic animals in developed countries, the early model studies concentrated primarily on the disease dynamics in wildlife. The very first study on rabies modelling was conducted by Anderson et al. (1981) to study the disease dynamics in the fox population in Europe. The study promoted the explanation of the rabies transmission pattern and the quantitative estimation on the possibilities of controlling when control measures were applied. A simple "SEIR" state-transition model was used, which divided the population into epidemiological classes; susceptible (S), exposed (E), infectious (I) and recovered or removed (R). Subsequent model studies gradually developed by using ordinary differential equations to represent levels of populations, either single or meta-populations. Recently, the more sophisticated mathematical models that have been developed concern both temporal and spatial patterns of the disease (Panjeti and Real, 2011).

In the past, most of the model studies concentrated on the disease dynamics in only a single species. However, to date, many model studies have been developed, according to the One Health approach, to account for the epidemiological and economic aspects of the disease in dogs as well as in humans.

Since then, the concentration of the model studies has been shifted from wildlife in developed countries to dogs and humans in Africa and Asia. The most recent areas of interest are, for example, sub-Saharan Africa (Hampson et al., 2007), China (Wang and Lou, 2008, Hou et al., 2012 and Zhang et al., 2012), Tanzania (Fitzpatrick et al., 2014 and 2012), Flores in Indonesia (Wera et al., 2016) and Philippines (Tohma et al., 2016). Most of these studies used a state-transition model approach with a more complicated division in epidemiological classes by taking into account the interrelationship between species. However, the Baysian framework has also been applied in some studies e.g. the study of metapopulation dynamics of rabies and the efficacy of vaccination in Tanzania (Beyer et al., 2011).

The incorporation of an economic module was also considered in most recent studies, focussing on the cost-effectiveness analyses of rabies control strategies. In these studies, outputs from the epidemiological model are used as inputs for the calculation of the control measures (Zinsstag et al., 2009, Fitzpatrick et al., 2014 and Wera et al., 2016).

In conclusion, model studies on rabies have developed into more sophisticated mathematical approaches using advanced software and technologies. However, Panjeti and Real. (2011) suggested that the most important issue for model studies is not the development of the model itself, of which the structure is very robust now. It is actually the precise data obtained from the field for valid model parameters, which is still limited (Beyer et al., 2011 and Hou et al., 2012).

3. Material and methods

The previous study conducted by Wera et al. (2016b) and Wera et al. (2016c) were focused on the deterministic epidemiological and economic modelling of the disease with existing vaccination strategies by assuming that there is no risk of virus re-introduction. This study extended the study of Wera et al. (2016b) and Wera et al. (2016c) by providing more alternative scenarios regarding the risk of virus re-introduction which may occur due to human-mediated transportation of dogs. Furthermore, this study attempted to capture the reality by considering the effect of virus introduction and reintroduction in a stochastic manner. Therefore, according to the research objectives and questions, the study was separated into 2 parts. The first part referred to the modification of the existing state-transition model of Wera et al. (2016b) to reflect a preventive vaccination schedule (repetitive independent of the moment outbreaks are occurring) instead of a reactive schedule as considered in Wera's study. This part was conducted to gain insights on the cost-effectiveness of alternative vaccination scenarios given a single introduction of the disease. The second part involved stochastic simulation of selected scenarios from the first part regarding the risk of virus re-introduction into the population. The number of animals derived from the state-transition modelling study was used to link the costs from different strategies for the cost-effectiveness analysis. The time period for the simulations was 10 years in a weekly time step. All the steps and calculations were done using Microsoft Excel®, Microsoft® Visual Basic for applications and @Risk software for Monte-Carlo simulation.

3.1 The models considering a single virus introduction

3.1.1 Epidemiological Model

A. Background on the simulation of virus transmission and impact of control measures

The virus transmission among dogs and humans was simulated at village level. Here village is defined as a group of local people, sharing similar culture and tradition, and living closely together as a small community. Most of the villages in Flores Island are separated from each other due to geographical barriers, for example, mountains and/or rivers. The average area for a village in Flores Island is 3.4 X 0.5 km. An average village houses approx. 1,500 humans (308 households) and 400 dogs (233 dogs/km^2) (Siko, 2011). Houses in a village are situated closely and dogs owned by each household can roam freely, therefore, random mixing is assumed in the model simulation which means every animal in the population has an equal chance to interact with each other. In addition, the population dynamic of the model depends on dog birth (b), death (d) and voluntary culling or removal (c) without dog migration as described in more detail in the next section.

B. Dog-to-dog transmission (State transition model; SEIVR model)

The dog-to-dog transmission model in this study was modified from the existing model from the study of Wera et al. (2016b). The model was used to obtain the number of infected and vaccinated dogs for further evaluation on the costs of vaccination per dogs and number of averted rabid dog cases, which were incorporated into the cost-effectiveness analysis. The state-transition model consisted of five different states to describe the different rabies related states of the dogs within the village. Those states were indicated as S, E, I, V and R and correspond to the susceptible, exposed, infectious, vaccinated and immune state, respectively. The transition of one state to another was determined by different transition rates (see Figure 2). Transitions were simulated with a time step of one week during a time horizon of 10 years.

The susceptible state (S) was defined as a naive dog in the population which has no immunity to protect itself against rabies. The number of dogs in this state is mainly controlled by the birth of puppies (b), the loss due to natural death (d) and voluntary culling (c). Moreover, a dog is considered to be susceptible when it has never come into contact with an infectious animal, has never been vaccinated, and/or has been vaccinated with short-acting vaccine for more than 52 weeks or 156 weeks with long-acting vaccine.

The exposed state (E) denoted a dog that has come into close contact with an infectious rabid dog which may potentially lead to infection. The dog as such has not become infectious yet. After approx. 3 weeks of incubation period (Hampson et al., 2009), the exposed animal will finally become infectious. Thus, according to the incubation period, the E state was divided into E1, E2 and E3. In this case, the number of newly exposed dogs (E1) in the first week at time t was determined by the number of susceptible and furious rabid dogs at time t-1. The probability that S and I will come into contact with each other which can lead to transmission was defined by β. According to CSPFH (2009), there are 2 types of clinical rabies forms which are the furious and the paralytic form. The furious form can potentially transmit the virus and it is more common in domestic dogs (Garg, 2014). Therefore, the number of E1 depends also on the probability for infectious dog to become furious (f). The E2 and E3 will be determined by the number of previously exposed dogs in E1 and E2, respectively. Finally, every states were also corrected for weekly natural death (d) and voluntary culling (c).

The infectious state (I) presented a dog which is infected with rabies virus and can potentially transmit the disease to other dogs and humans. This state depends on the number of the previously exposed dogs in E3 and the probability of E3 to become infectious and show clinical signs, otherwise, the E3 dogs will become susceptible again. In state I, a dog will die within 1 week after becoming infectious with 100% probability (μ) CSPFH (2009).

When a vaccination campaign was applied, a certain number of dogs were vaccinated and entered the vaccinated state (V) depending on the vaccination coverage (vc). After vaccination these dogs moved to the immune state (R) within 4 weeks after vaccination (Johnson et al., 2010). While, accounting for the time step of one week, the vaccination state was separated into V1, V2, V3 and V4 in which V2, V3 and V4 were determined by the numbers of dogs in previous vaccinated states due to the development of immunity. The total number of vaccinated dogs (V) used for the cost calculation depended on the number of dog population (I state is not included) in the previous time step (t-1) multiplied by vaccination coverage (vc). As there is no dog registration system on the island, it is assumed that all dogs in the population can be vaccinated regardless of the immune status from the previous vaccination campaign. Therefore, the total number of vaccinated animals was corrected separately by using total number of dog population (N_{t-1}) as can be seen in formula 11 below, to obtain an accurate number of vaccinated animals for the calculation of the vaccination costs.

The immune state (R) reflected a dog with complete protective immunity against rabies virus. The development of this state depended on the number of dogs in V4 and the vaccine efficacy (ve) which is assumed to be 80% (AHHD, 2016). The 20% loss of vaccination efficacy may happen due to immunosuppression, breakage of cold chain (for example, during transportation, storage or handling) and errors during vaccine administration. The R state will be lost depending on the rate of immunity loss (δ) which depends on the duration of immunity protection derived from the applied types of vaccine.

The dynamic of each state representing in the model can be seen according to Figure 2. Furthermore, the state transition model is governed by the following equations;

$$\mathbf{S_t} = (\mathbf{S_{t-1}} + (b * (\mathbf{S_{t-1}} + \mathbf{E1_{t-1}} + \mathbf{E2_{t-1}} + \mathbf{E3_{t-1}} + \mathbf{V1_{t-1}} + \mathbf{V2_{t-1}} + \mathbf{V3_{t-1}} + \mathbf{V4_{t-1}} + \mathbf{R_{t-1}})) - (vc * \mathbf{S_{t-1}}) + (\boldsymbol{\delta} * \mathbf{R_{t-1}}) + (\mathbf{E3_{t-1}} * (1 - \gamma)) - (\beta * f * \mathbf{S_{t-1}} * \mathbf{I_{t-1}}) + (\mathbf{V4} * (1 - ve))) * (1 - c - d) \quad (1)$$

$$\mathbf{E1_t} = (\beta * f * (\mathbf{S_{t-1}} + \mathbf{V1_{t-1}} + \mathbf{V2_{t-1}} + \mathbf{V3_{t-1}}) * \mathbf{I_{t-1}}) * (1 - c - d) \quad (2)$$

$$\mathbf{E2_t} = \mathbf{E1_{t-1}} * (1 - c - d) \quad (3)$$

$$\mathbf{E3_t} = \mathbf{E2_{t-1}} * (1 - c - d) \quad (4)$$

$$\mathbf{I_t} = \mathbf{E3_{t-1}} * \gamma * (1 - c - d) \quad (5)$$

$$\mathbf{V1_t} = (vc * \mathbf{S_{t-1}}) * (1 - c - d) \quad (6)$$

$$\mathbf{V2_t} = \mathbf{V1_{t-1}} * (1 - c - d) \quad (7)$$

$$\mathbf{V3_t} = \mathbf{V2_{t-1}} * (1 - c - d) \quad (8)$$

$$\mathbf{V4_t} = \mathbf{V3_{t-1}} * (1 - c - d) \quad (9)$$

$$\mathbf{R_t} = ((\mathbf{V4_{t-1}} * ve) + \mathbf{R_{t-1}} - (\boldsymbol{\delta} * \mathbf{R_{t-1}})) * (1 - c - d) \quad (10)$$

$$\mathbf{V_t} = (\mathbf{N_{t-1}} * \mathbf{vc}) - \mathbf{I_{t-1}} \quad (11)$$

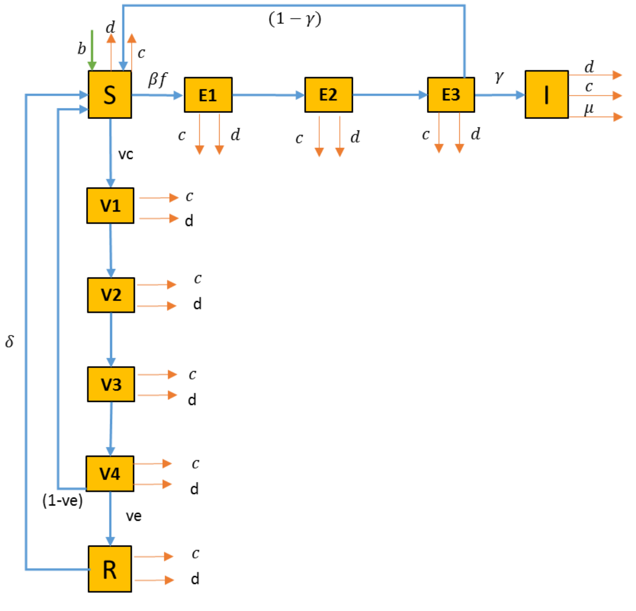

Figure 2 Transition diagram of rabies transmission within a dog population in a village in Flores island. The arrows indicate the transition of dogs between susceptible (S), exposed (E1-3), infectious (I), vaccinated (V1-4) and immune (R) states by parameters as descripted in Table 1. Every state is regulated by death rate (d) and culling rate (c). b is the birth rate which indicates the number of live-born puppies per dog through time. The transition of S to E1 happens when S comes into contact with furious I with probability of being exposed β. Then, E1 will develop to E2 and E3, respectively, within 3 weeks of incubation period. E3 becomes I depending on γ. Finally, I will die after a week based on the disease-related death rate μ. When vaccination is applied, S becomes V1 according to vaccination coverage (vc). V1 gradually develops immunity within 4 weeks until it reaches V4. However, vaccination efficacy (ve) defines whether or not V4 can develop into R. Finally, R becomes S again according to loss-of-immunity rate (δ) which is different between short- and long acting-vaccines.

C. Data and model parameters

The data used in this study (Table 1) are mainly from the performed cost-effectiveness analyses of dog vaccination strategies on this island performed by Wera et al. (2013 and 2016b) Additional information was supplied by the author of those studies and other relevant articles.

a) Birth rate (b) and death rate (d)

The birth rate and death rate were obtained from the study of Siko (2011) on the study of population dynamics on this island. The birth rate of this model is the average number of live-born puppies per dog during time t which is 0.01891 puppy per dog per week. We assumed that there is an equal probability of giving birth in every epidemiological state except in state I, for which it was assumed that puppies, born from a dog in this state, die soon after birth. The modelled death rate reflects the number of dog that naturally die at per time t which is 0.00865 dog per dog per week. These numbers are considered to be stable through the whole simulation period.

b) Voluntary Culling rate (c)

Voluntary culling will happen when the size of the dog population at time t (N_t) is higher than the considered maximum size of the dog population in a village (N_0 = 400; Siko, 2011). In this case, villagers will begin to trade or cull their dogs (mainly for consumption). It also depends on the carrying capacity of the village because those dogs are fed by some leftovers or garbage provided by villagers in the central area of the village. Thus, natural carrying capacity is assumed to have no significant effect in regulation of dog population in the village. However, the number of dogs has to be corrected for the number of infected animal at time t (I_t) because an infectious dog will die because of the disease, as shown in equation (11) (adjusted from Wera et al., 2016b).

$$c_t = ((N_t - I_t) - N_0) / (N_t - I_t)), \text{ When } ((N_t - I_t) - N_0) > 0 \quad (12)$$

c) Probability of a susceptible dog being exposed to an infectious dog (β)

This parameter was derived from the assumption from expert opinion in Flores island in the study by Wera et al. (2016b) which indicated that an infectious animal can bite 4 susceptible animals (N_{dbite}) during 1-week of infectious period (I_p), given a population of 399 dogs (N_s). This assumption gives the estimation for the β to be equal 0.01002506 (Table 1).

d) Vaccination coverage (vc)

The vaccination coverage using in this study was ranged between 0.5 – 0.7. These numbers were derived from current achieving vaccination coverage by the government in the island(53%, Wera et al., 2013) and recommended vaccination coverage from WHO (70%; 1987).

e) Probability of a furious rabid dog among infectious dogs (f)

Basically, there are 2 forms of clinical signs in rabies infection; the furious and paralytic form. The clinical signs for paralytic form are descripted as stupor with progressive paralysis which is less common in dogs. In the furious form, the affected animal shows signs of aggressiveness, excitement, biting and aimless wandering. Domestic dogs were reported to commonly develop the furious form (Garg, 2014, WHO, 2013 and Radostits et al. 2007), therefore, the probability of becoming furious is estimated to be 0.7 according to assumption of Wera et al. (2016b).

f) Clinical outcome of an exposed dog (γ)

The probability of an exposed dog becoming infectious ($\gamma = 0.49$) was obtained from a study in Chad by Zinsstag et al. (2009). This probability indicates that after a dog was exposed to an infectious dog, at the end of the incubation period (3 weeks after exposure), the exposed dog may not become infectious. The main reasons are the intermittent shedding of the virus through saliva of a rabid dog and low level of exposure (Mshelbwala et al., 2013 and Jemberu et al., 2013).

g) Loss-of-immunity rate (δ)

Loss-of-immunity rate is calculated by the indicated duration of protective immunity (v) provided by short- and long-acting vaccine as claimed by the manufacturers. The local or short acting vaccine can provide 3 months of immunity and an additional 52 weeks of protection after booster. Therefore, the loss-of-immunity rate of short acting vaccine is $1/v = 1/52 = 0.019$ per week. In case of commercial or imported vaccine, the duration of immunity after the first dose is 52 weeks with additional 156 weeks after a booster, so loss-of-immunity rate is $1/v = 1/156 = 0.006$ per week. When the duration of immunity is reached without booster, an immune dog will become susceptible again.

Table 1 Input values and model parameter for outbreak simulation

Parameters	Value	Units	Reference	Description
S(0)	400	Dogs	Siko, 2011	Initial susceptible dogs in a village
E(0)	0	Dogs	Assumption	Initial exposed dogs
I(0)	0	Dogs	Assumption	Initial infectious dogs enter a dog population in a village
V(0)	0	Dogs	Assumption	Initial number of vaccinated dogs
R(0)	0	Dogs	Assumption	Initial number of dog with complete immunity
Δt	1	week	-	Transition Time
N(0)	400	dogs	Siko, 2011	Average dog population size within a village
b	0.01891	per dog per week	Siko, 2011	Birth rate per dog per week
d	0.008654	per dog per week	Siko, 2011	Dog Natural death rate
β	0.01002506	per week	Siko, 2011	Probability of a susceptible dog being exposed to an infectious dog

Parameters	Value	Units	Reference	Description
f	0.7	Dimensionless	Assumption	Proportion of a furious rabid dog among infectious dogs
γ	0.49	Dimensionless	Zinsstag et al., 2009	Likelihood of Clinical outcome for an exposed dog
δ (Short-acting)	0.01923077	per week	Calculated	Loss-of-immunity rate of short acting vaccine in dog
δ (Long-acting)	0.00641026	per week	Calculated	Loss-of-immunity rate of long acting vaccine in dog
μ	1	per week	CSPFH, 2009	Dog-disease-related death rate

D. Vaccination Campaigns and outbreak simulations

The vaccination campaign simulated in this study will be focused on proactive vaccinations which are implemented as a mean of prevention measure before the disease occurrence, as currently applied in Flores. The first introduction of the virus into a village is defined by the introduction of 5 newly exposed animals (E1 state) into the population to finally generate 2 infectious dogs in 3 subsequence weeks to start the transmission chain. The reason for introduction of exposed dogs instead of infectious dogs is because we assumed that the introduction of the disease happens due to trading of exposed dogs among villagers. Therefore, dogs should be healthy enough for that purpose.

The time of first introduction of exposed dogs is cooperated into the model at week 26 (t = 26) of the first year because the introduction in this period will lead to the higher cumulative number of infectious dogs than at the beginning or the end of the campaign. This time period will be applied in every scenario.

Moreover, the scenarios differ according to type of vaccine, frequency of vaccination and vaccination coverage. There are 2 types of vaccine currently used on the island which are categorized by duration of protective immunity; short and long acting vaccine. The local short-acting vaccine, Rabivet Supra 92® (Pusvetma, Surabaya), provide 3-month immunity after the first injection and an additional 1-year (52 weeks) immunity after a booster. The imported long-acting vaccine i.e. Rabisin® (Merial, Paris), Rabvac 3® (Fort Dodge Animal Health, USA) and Defenzor3® (Pfizer, Incorperated, USA), provide 1-year immunity after the first injection and an additional 3-year (156 weeks) immunity after a booster. In this study, the first vaccination started at the first week of the simulation (t =1), without the boosters due to dogs registration is not applied on the island.

In the following scenarios, the introduction of the virus is simulated in the middle of the first year (t = 26) with 5 exposed dogs (E1). The simulation will be stopped after there is less than 0.1 infectious dogs (I) for 26 consecutive weeks (approx. 6 months) which defines that the disease is under control or the simulation reaches the period of 10 years. The 26-weeks period is chosen according to the variability of incubation period (OIE, 2016). The vaccination strategies being considered in this study are listed below;

a) ***Scenario 1; The model without vaccination (vc = 0) (based-line scenario)***

The first scenario is consisted of S, E1 to E3 and I state without application of vaccination campaign. The first introduction of the virus is in the middle of the first year (t = 26) with 5 exposed dogs (E1). This scenario will be used to calculate the effectiveness of other scenarios by the number of averted rabid dog cases. Moreover, this scenario will also be used to calculate the number of human cases averted which will be expained further in the next section.

b) Scenario 2; Annual vaccination with short-acting vaccine

The second scenario is the application of annual short-acting vaccine for 10 years which is normal strategy being applied in Flores island (Wera et al., 2015). The vaccination campaign starts at the fisrt week (t=1) of the simulation. The vaccination coverage (vc) is varied from 0.5 to 0.7, with 0.05 interval (same vc throughout 10-year period for each scenario). Moreover, as an additional strategy for this scenario, the vc is varied during time starting with vc = 0.5 before the disease outbreak, then vc = 0.7 during the outbreak until the outbreak is under control (The time delayed for disease detection is not considered in this study). After that, vc will be reduced to 0.5 again and maintained until the simulation ends.

c) Scenario 3; Biannual vaccination with short-acting vaccine

This scenario involves using short-acting vaccine bianually. The vaccination campaign starts at the fisrt week (t=1) and the 27th week of each year. The constant value of vc is used ranging from 0.5 - 0.7, with 0.05 interval for each strategy. The additional strategy is starting of vc = 0.5 for proactive vaccination and increasing of vc to 0.7 after the disease outbreak. Moreover, when the outbreak is under controlled vc = 0.5 will be used again and maintained for the rest of the simulation period.

d) Scenario 4; Annual vaccination with long-acting vaccine

This scenario involves the application of annual long-acting vaccine for 10 years. The vaccination coverage (vc) is varied ranging from 0.5 to 0.7, with 0.05 interval (the same vc is used throughout 10-year period for each scenario). Furthermore, as an additional strategy for this scenario, the vc is varied during time starting with vc = 0.5 before the disease outbreak, then vc = 0.7 will be used during the outbreak until the outbreak is under control. After that, vc will be reduced to 0.5 again and maintained until the end of simulation.

e) Scenario 5; Once-every-2-year vaccination with long-acting vaccine

The application of once-every-2-year vaccination campaign with long-acting vaccine is used in this scenario. The predefined value of vc between 0.5 - 0.7 with 0.05 interval is used. In addition, an additional strategy is simulated starting from vc = 0.5 for proactive vaccination and increase to vc = 0.7 after the disease outbreak. When the outbreak is under controlled, vc = 0.5 will be used again and maintained for the rest of the simulation period.

f) Scenario 6; combination of annual short- and long-acting vaccine

In this scenario, long- and short-acting vaccine are combined in an annual vaccination campaign. The campaign starts with short-acting vaccine for proactive vaccination. Then, after the first infectious dog appears, long-acting vaccines will be administered until the outbreak is under control. After that short-acting vaccines will be used again to maintain the herd immunity for the rest of the simulation period. The value of vc is varied for each campaign, ranging from 0.5 - 0.7 with 0.05 interval. The R state in this scenario was divided into 2 groups; R1 for a dog that recieved short-acting vaccine and R2 for a dog that recieved long-acting vaccine. This division is due to the difference in rate of losing the immunity between short-and long- acting vaccines.

Finally, the effectiveness of each vaccination strategies (dog health aspect) will be calculated as the number of dog case averted using the number of infectious animals in that scenario subtracted by the number of infectious animals from the baseline scenario (without vaccination). The duration of the disease control is also calculated by using the subtraction between the number of weeks that the first infectious dogs appeared in the model and the number of weeks that the disease is under control.

E. Dog-to-human transmission

In order to evaluate the impact of different dog vaccination strategies on reducing human rabies cases, the additional transmission of virus from dogs to humans is considered. Therefore, the number of human rabies at time t+1 (H_{t+1}) is calculated using the equation as proposed by Wera et al. (2016c). H_{t+1} is consisted to the number of infectious dogs at time t (I_t), the proportion of infectious dog becoming furious (f), the proportion of infectious rabid dogs that bite human (f_{BH}), the proportion of bite-victims not receiving PET ($1-P_{pet}$), and the probability of developing rabies in bite-victim (P_{RH}):

$$H_{t+1} = I_t \times f \times f_{BH} \times (1 - P_{pet}) \times P_{RH} \tag{13}$$

The probability of developing rabies (P_{RH}) is obtained from the study of Wera et al. (2016c) which was estimated from the field data provided by Public health department of Sikka regency. It depends mainly on the probability of being bitten in a specific location on the body of a bite victim which can be either in the head or neck (P_1), a lower extremity; arm or hand (P_2), the trunk of the body

(P_3) or a lower extremity; leg or foot (P_4). Moreover, the probability of becoming infected is conditional upon the location of the bite wound, viz. head or neck (P_5), lower extremity (arm or hand) (P_6), trunk of the body (P_7) and lower extremity (leg or foot) (P_8) as considered by Zinsstag et al. (2008). The input values and parameters are shown in Table 2

$$P_{RH} = (P_1 \times P_5) + (P_2 \times P_6) + (P_3 \times P_7) + (P_4 \times P_8) \quad (14)$$

Table 2: Input values and model parameter for dogs-to-human transmission of rabies (Wera et al., 2016c)

Parameters	Value	Description
f_{BH}	0.2	Proportion of furious rabid dogs that bite human
P_{pet}	0.56	Probability of an individual who is bitten by a dog suspected to be rabid and they receive PET successfully
P1	0.07	Probability of a bite to the head or neck
P2	0.21	Probability of a bite to the upper extremity (hand or arm)
P3	0.06	Probability of a bite to the trunk of the body
P4	0.66	Probability of a bite to the lower extremity (leg or foot)
P5	0.55	Probability of developing rabies following a bite to the head by a rabid dogs
P6	0.22	Probability of developing rabies following a bite to the upper extremity by a rabid dog (hand or arm)
P7	0.09	Probability of developing rabies following a bite to the trunk of the body by a rabid dog
P8	0.12	Probability of developing rabies following a bite to the lower extremity by a rabid dog (hand or arm)
P_{RH}	0.1693	developing rabies in bite-victim

3.1.3 Economic Model: Cost effectiveness Analysis

The costs of dog vaccination (CV) and Post Exposure Treatment (C_{pet}) used in this study are based on the actual data collected by Wera et al, (2013 and 2016c). The costs are expressed in USD using 5% discount rate (i) per year (The bank Indonesia, 2016) to express all costs for this study.

A. The costs of dog vaccination (CV)

The costs of dog vaccination (CV) are calculated as vaccination costs per dog. It is the combination of price of the vaccine (P_v), price of consumables (P_{cm}) (i.e. needles, syringe and disinfectant swabs), transportation cost of vaccines from the manufacturer (T_{va}) and operational cost (O_{vc}) (for example, cost of vaccinator, cost of information campaign and capital costs from cooling bags, refrigerators, motorcycles and muzzles):

$$CV = P_v + P_{cm} + T_{va} + O_v \quad (15)$$

The input values used for calculating the costs of dog vaccination mentioned above are shown in the Table 3 which are based solely on door-to-door dog vaccination campaign that is used in Flores island.

Table 3: Input values for the costs of dog vaccination (Wera et al., 2016c)

Parameters	Value	Units (USD)	Description
P_v – short-acting	0.77	per dose	Price of short-acting vaccine
P_v – Long-acting	1.38	per dose	Price of long-acting vaccine
P_{cm}	0.27	per vaccinated dog	Price of consumables, for example, needles, syringes and disinfectant swab
T_{va}	0.03	per vaccinated dog	Transportation cost for vaccine
O_v	2.32	per vaccinated dog	Operational costs

B. The public costs of post-exposure treatment (PET); $\mathrm{PC_{pet}}$

The post exposure treatment for humans, after being bitten by a suspected infectious dog, is comprised of wound cleaning, one dose of human rabies immunoglobulin around the wound (especially for severe wounds) and four doses of vaccine in Zegreb schedule as recommended by The Indonesian Health Ministry (IHM) (Wera et al., 2013). The Zegreb schedule is a series of vaccination on days 0, 7 and 21 with 2 doses on day 0 and one dose on day 7 and 21. Verorab ® is the current vaccine using for human in Flores island (Wera et al., 2013). The public costs of post-exposure treatment ($\mathrm{PC_{pet}}$) depend on the costs of PET ($\mathrm{C_{pet}}$), number of infectious dogs ($\mathrm{I_t}$), probability of infectious dogs to become furious (f), proportion of furious rabid dogs that bite humans ($\mathrm{f_{BH}}$)and probability of an individual who is bitten by a suspected rabid dog to receive PET successfully ($\mathrm{P_{pet}}$):

$$\mathrm{PC_{pet}} = \mathrm{C_{pet}} \times \mathrm{I_t} \times \mathrm{f} \times \mathrm{f_{BH}} \times \mathrm{P_{pet}} \tag{16}$$

$\mathrm{C_{pet}}$ was estimated to be 131 USD per patient (Wera et al, 2016c) according to the information obtained from the field data of Flores island in the study from Wera et al. (2013). The $\mathrm{C_{pet}}$ is comprised of the costs related to immunoglobulin and the costs for vaccine injections. The costs of wound cleaning is considered to be a responsibility for the bite victims, so it will not be used in the calculation of $\mathrm{PC_{pet}}$ in this study as well as the opportunity cost and costs of transportation for bite victims

The costs related to immunoglobulin depends on the number of humans who received PET after exposing to a suspected rabid dog, price of immunoglobulin and the costs of consumables, for example, syringe, needle and disinfectant swab. However, only the patients with severe bitten wound will be given the immunoglobulin, therefore, the proportion of human receiving immunoglobulin should also be considered.

Finally, the costs of vaccination are associated with the number of humans who received PET after exposing to a suspected rabid dog, the costs of vaccines and the physician fee. According to the Zegreb schedule, the costs of vaccines and the physician fee also depend on the number of visits for receiving complete PET and the number of doses of vaccine for PET. The detailed on values used to calculate $\mathrm{C_{pet}}$ can be found in Appendix 1.

C. Cost-effectiveness analysis

There are 2 main components to be considered in this analysis. The first one is the costs for disease prevention and control through dog vaccination and PET in humans, which were derived from different vaccination strategies. The second component is the effectiveness of each strategies in order to reduces the number of rabies cases compare with the baseline scenario or number of rabid cases averted. According to those components, the ratios between the costs and the effectiveness were derived and used to compare the strategies for their feasibility. Moreover, the cost-effectiveness analysis was considered in veterinary and public health perspectives to indicate how the consequences on the effectiveness of different vaccination strategies in dogs can affect the disease prevention in human. The consideration of two relevant aspects intended to provide insights on the trade-off for resource allocation and collaboration between both sectors for the most cost-effective control and prevention strategy according to the 'One Health' concept.

a) Veterinary aspects

The effectiveness of dog vaccination strategies, as mentioned in the previous section, is the number of dog cases averted which is calculated from the number of infectious animals subtracted by the number of infectious animals in the baseline scenario (without vaccination). Therefore, the cost-effectiveness ratios were derived using dog vaccination costs (CV) divided by the number of rabid dog cases averted in 10 years. The cost-effectiveness ratios were used further to compare each vaccination strategies in veterinary perspectives.

b) Public health aspects

The effectiveness of vaccination strategies, in human aspect, is represented by the number of human cases averted which was calculated from the number of human cases subtracted by the number of human cases in the baseline scenario (without vaccination in dogs and PET for humans). The cost-effectiveness ratios were calculated using total costs for disease prevention, which are dog vaccination costs and the public costs for PET (PC_{pet}) in human, divided by the number of human cases averted in 10 years. Finally, the cost-effectiveness ratio will be used further to compare the impact of vaccination strategies for public health aspects.

3.2 Stochastic models accounting for the risk of virus re-introduction

3.2.1 Scenario Selection Criteria

After obtaining the results from the simulations in section 3.1, the most feasible strategies are chosen to perform the stochastic simulation regarding the virus re-introduction into the village. The feasible strategies are defined as 1) being effective to control and lower the amplitude of the outbreak within the 10-year simulation period 2) being the most cost-effective strategies in both dogs and humans and 3) being practically applicable regarding societal and economic situation in the island especially in rural areas.

3.2.2 Monte-Carlo stochastic simulation for risk of virus re-introduction

The Monte-Carlo stochastic simulation considering the risk of re-introduction was introduced into the deterministic state-transition models using the binomial distribution for the probability of re-introduction by human-mediated transportation on a weekly bases which was parameterised by the binomial distribution (1, 0.019). This probability was defined according to the assumption that demand of dog meat is high during the annual traditional ceremonies, therefore, the worst-case scenario is based on a virus reintroduction in every year (Once in 52 weeks = 1/52 = 0.019). Because when there is an outbreak, the movement restriction will be applied (without official checkpoints) and the trading of dogs from the diseased village could be suspended for at least 1 - 2 years (Wera et al., 2016b), therefore, the worst case of virus reintroduction was considered to be once in a year in this study. Additionally, the probability of virus reintroduction in once every three years (1/156 = 0.00641) was also used as an additional simulation with the binomial distribution (1, 0.00641) to represent less risky situation. It was assumed that a random number of exposed dogs (E1) with Poisson distribution ($\lambda = 3$) was introduced into the population when the re-introduction occurred in that time step according to the probabilities. The number of dogs being introduced into the village was obtained from the study of Siko (2011), which estimated the number of dogs being transported on the island to be approx. 3 dogs per weeks. However, the introduction of susceptible dogs (S) with the same distribution was added into the population every week when there was no virus reintroduction in that time step. The models were stochastically simulated for 1,000 iterations. The first outbreak from the simulation was considered to be the first introduction. The subsequent outbreaks were automatically the virus reintroduction regardless of the situation from the first introduction.

The changes in vaccination coverage (between vc = 0.5 and 0.7) and the type of vaccine (from short- and long-acting vaccine) according to the number of I in the population were defined to vary automatically during the Monte-Carlo simulation by coding using Microsoft® Visual Basic for applications. The code are shown in Appendix 2.

4. Results

In line with the setup of the research study, the results of this study are divided into 2 sections. The first section involves the epidemiological and economic model outputs for various preventive vaccination strategies with only one virus introduction into the dog population. Those scenarios vary in level of vaccination coverage, vaccine types and frequency, while ignoring the risk of virus reintroduction. The second section focuses on the results in which the impact of re-introduction has been taken into account.

4.1 Cost-effectiveness of vaccination strategies given a single virus introduction

The results from this section focuses on the outcomes from the epidemiological and economic models without considering the risk of virus reintroduction. The effectiveness is presented in the number of dog cases averted for consideration from veterinary perspective, and in the number of human cases averted, which is the main results for showing the effectiveness in terms of public health aspect. The general findings among the evaluated scenarios are presented first, followed by a detailed description of each evaluated scenario's separately (Table 4).

During the simulation for a 10-year period, the baseline scenario (the situation without any vaccination) showed to generate 1,266 rabid dog cases. The effectiveness of the defined mass vaccination scenarios on the reduction of rabid dog cases compared with the baseline was estimated to range from -416 to 1,255 cases. Scenario 3 (biannual vaccination with short-acting vaccines) at 70% vaccination coverage (vc) was the most effective campaign in veterinary perspective with the highest number of rabid dog cases averted. This scenario accounted for 99.10% reduction in rabid dogs as derived in the baseline scenario. Moreover, it also provided the lowest duration for controlling the outbreak with a duration of 82 weeks. Scenario 2 (Annual vaccination with short-acting vaccines) at 50 - 65% coverage and scenario 5 (once-every-2-year vaccination with long-acting vaccines) independent of coverage level failed to control the disease. Furthermore, scenario 5 at 50, 55 and 60 % vc caused, respectively, 16%, 17% and 7% more rabid dog cases than the baseline scenario (Table 4).

The effectiveness of different dog vaccination strategies in controlling human rabies has been divided according to the situation with and without PET to determine the contribution of dog vaccination strategies on human rabies prevention separately. However, the main focus is on the results in which PET is considered because PET is available in the study area. The number of cases in 10 years from the baseline was 30.01 human cases. According to the number of cases from the different vaccination strategies compared with baseline, the number of human cases averted without the support of PET ranged from -9.86 to 29.74 cases in 10 years. Furthermore, when PET was defined to be available, PET provided 16.80 human cases averted in the baseline scenario and generated 12.47 – 29.89 human cases averted in combination with mass vaccination (Table 4) in 10 years. The highest number of human cases averted (with and without PET) during the simulation period was in scenario 3 at 70% vc, which was in line with the highest number of averted dog cases from the same strategy. This scenario could reduce approx. 99.10% of human rabies by using vaccination alone and 99.60% of human cases with the support of PET.

The costs of vaccination campaign ranged from 3,194 to 16,068 USD throughout the vaccination period of 10 years. The highest vaccination costs were in scenario 3 at 70% vc. Scenario 5 at 50% vc had the lowest costs of vaccination but this strategy failed to control the outbreak within the simulation period. Therefore, scenario 6 (Annual vaccination with combination between short-and long-acting vaccines) at 50% vc was the scenario that provided the lowest cost (6,426 USD), and was able to successfully control the disease within 10 years.

Table 4 The simulated numbers for the cost-effectiveness of vaccination strategies in dogs and humans from the deterministic model, under the assumption of a single virus introduction in 10 years.

Scenario	Cost-Effectiveness for Dog Health aspect						Cost-Effectiveness for Human Health aspect (without PET)			Cost-Effectiveness for Human Health aspect (with PET)				
	vc	**Number of infectious dogs**	**Costs (Vaccination Cost) (USD)**	**Effectiveness (Number of rabid dogs averted)**	**Cost-effectiveness Ratio (USD/rabid dog averted)**	**Duration until the disease is under control (Week)**	**Number of human cases**	**Effectiveness (Number of human cases averted)**	**Cost-effectiveness Ratio (USD/Human case averted)**	**Number of human cases**	**Public Costs of PET (USD)**	**Total Costs (Dog vaccination and PET) (USD)**	**Effectiveness (Number of human case averted)**	**Cost-effectiveness Ratio (USD/Human case averted)**
1 No vaccination	**0%**	**1,266**	**0**	**NA**	**NA**	**NA**	**30.01**	**NA**	**NA**	**13.20**	**10,383**	**10,383**	**16.80**	**618**
2 Annual vaccination with short-acting vaccine	**50%**	1,682	5,711	-416	NA	NA	39.87	-9.86	NA	17.54	13,153	18,863	12.47	>1,513
	55%	1,472	6,341	-206	NA	NA	34.89	-4.88	NA	15.35	11,357	17,698	14.66	>1,207
	60%	801	6,965	465	>14.97	NA	18.98	11.03	>631	8.35	6,188	13,154	21.66	>607
	65%	232	7,543	1,034	>7.29	NA	5.50	24.51	>308	2.42	1,964	9,507	27.59	>345
	70%	101	8,122	1,165	6.97	378	2.39	27.62	294	1.05	924	9,046	28.96	312
	50-70-50%	145	10,587	1,121	9.44	426	3.44	26.57	398	1.51	1,320	11,907	28.49	418
3 Biannual vaccination with short-acting vaccine	**50%**	28	11,477	1,238	9.27	162	0.65	29.35	391	0.29	267	11,744	29.72	395
	55%	20	12,625	1,246	10.13	118	0.48	29.53	427	0.21	196	12,821	29.80	430
	60%	16	13,772	1,250	11.02	106	0.38	29.63	465	0.17	156	13,928	29.84	467
	65%	13	14,920	1,253	11.91	86	0.31	29.70	502	0.14	129	15,049	29.87	504
	70%	11	16,068	1,255	12.81	82	0.27	29.74	540	0.12	112	16,180	29.89	541
	50-70-50%	19	12,276	1,247	9.85	98	0.46	29.55	415	0.20	191	12,467	29.81	418
4 Annual vaccination with long-acting vaccine	**50%**	128	6,798	1,138	5.97	482	3.03	26.97	252	1.33	1,150	7,948	28.67	277
	55%	67	7,478	1,200	6.23	270	1.58	28.43	263	0.69	628	8,105	29.31	276
	60%	44	8,157	1,222	6.68	174	1.05	28.96	282	0.46	427	8,584	29.55	291
	65%	34	8,837	1,232	7.17	158	0.81	29.20	303	0.36	331	9,168	29.65	309
	70%	27	9,517	1,239	7.68	118	0.65	29.36	324	0.28	266	9,783	29.72	329
	50-70-50%	43	7,712	1,224	6.30	134	1.01	29.00	266	0.44	413	8,125	29.57	275
5 Once-every-2-year vaccination with long-acting vaccine	**50%**	1,515	3,194	-249	NA	NA	35.91	-5.91	NA	15.80	11,942	15,137	14.21	1,066
	55%	1,524	3,600	-258	NA	NA	36.12	-6.11	NA	15.89	11,977	15,577	14.12	1,103
	60%	1,358	3,925	-92	NA	NA	32.19	-2.19	NA	14.17	10,872	14,797	15.84	934
	65%	1,266	4,276	>0	NA	NA	30.02	-0.01	NA	13.21	10,134	14,409	16.80	858
	70%	1,212	4,697	>54	87	NA	28.73	1.28	3,674	12.64	9,607	14,305	17.37	824
6 Annual short-, long and short-acting vaccine	**50%**	155	6,426	1,111	5.78	314	3.68	26.33	244	1.62	1,444	7,870	28.39	277
	55%	97	6,859	1,169	5.87	218	2.29	27.72	247	1.01	919	7,778	29.00	268
	60%	71	7,364	1,195	6.16	170	1.69	28.31	260	0.75	686	8,049	29.26	275
	65%	56	7,977	1,210	6.59	158	1.32	28.69	278	0.58	538	8,515	29.43	289
	70%	45	8,433	1,221	6.90	122	1.06	28.95	291	0.47	435	8,868	29.54	300

The public costs of PET in the period of simulation ranged between 112 to 13,153 USD with the lowest number in scenario 3 at 70% vc and the highest number in scenario 2 at 50% vc. However, when calculating the total costs by combining costs of vaccination with the public costs of PET, the highest total costs belonged to scenario 3 (due to the highest number of vaccination costs at 70% vc) with 16,180 USD and the lowest number (7,778 USD) was from scenario 6 at 55% vc.

The costs per rabies case averted among the effective scenarios, which were able to control the disease within the simulation period, varied between 6 to 87 USD per dog cases averted in 10 years. The least cost-effective strategy was from scenario 5 at 70% vc. In humans, the cost-effectiveness ratios, when using vaccination and PET, ranged from 268 to 1,207 USD per human cases averted in 10 years. The most cost-effective scenario, which was successful in controlling the disease in dogs and humans, was scenario 6 with 50% vc. (see table 4).

In summary, the 70%vc was considered to be more robust than the other lower levels of vc to control the disease in each scenarios. However, the 50% vc provided more robustness in generating low vaccination costs and cost-effectiveness ratios, especially in dogs. When comparisons were made by focusing on the effectiveness for disease control together with the cost-effectiveness ratios in humans, the most cost-effective scenarios could be ranked as followed; scenario 4, 6, 2 and 3. In the practical situation, it would be infeasible to perform biannual vaccinations in the rural areas as well as increasing the vc to be higher than 50% through the period of 10 years. Thus, scenario 4 with 50-70-50% vc, scenario 6 with 50% vc, and 2 with 50-70-50% were considered to be the most cost-effective scenarios regarding the feasibility and the ability to reduce rabies cases.

The more detailed results from the epidemiological and economic models for each scenario are shown separately in the following sections.

g) *Scenario 1 (The model without vaccination)*

The first scenrio represents the baseline scenrio when no vaccination was applied in dogs. The dog-to-dog transmission model showed 3 epidemic waves during the period of 10 years (520 weeks). The total number of infectious dogs in 10 years was 1,266 dogs (range: 6 to 361 dogs per year), as shown in figure 3. In humans, the baseline scenario without PET caused 30.01 human cases (range: 0.14 to 8.55 humans per year) in 10 years. Additionally, when PET was applied, the human cases in the baseline scenario was estimated to be 13.20 (range: 0.06 – 3.76 cases per year). The difference between the baseline scenario with and without the application of PET indicated that PET alone contributed to 56% reduction of human rabies cases resulting in 16.8 human cases averted in a 10-years period.

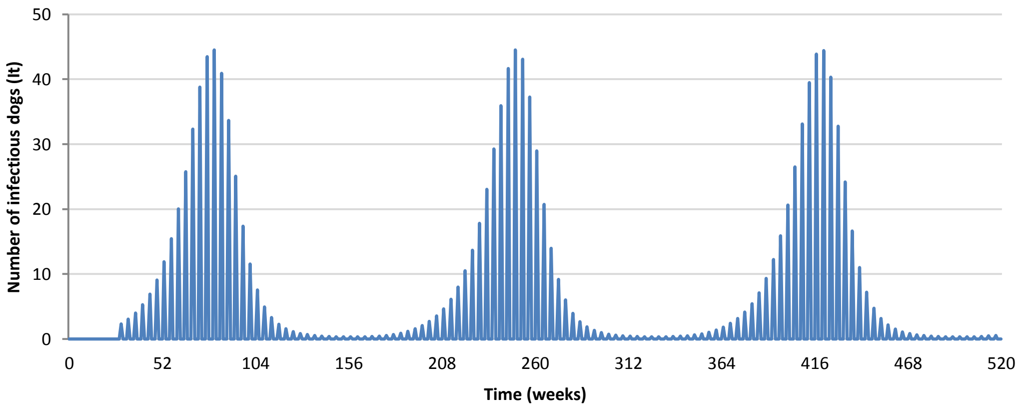

Figure 3 The number of infectious dogs generated from the baseline model (without vaccination) over a 10-years simulation period without consideration of the re-introduction of the virus. The time steps were divided into weekly interval.

In economic aspects, the public costs of PET and the cost-effectiveness in human was the main economic outcomes for this baseline scenario. The public costs of PET, in which, no vaccination was applied, in 10-year period equaled 10,383 USD (range: 40 - 3,442 USD per year). In a single virus introduction, the public costs of PET had incurred mostly in year 2 (3,442 USD), 5 (2,580 USD), 8 (1,277 USD) and 9 (1,600 USD) in which the rabies cases in dogs are the highest (Appendix 2 for the public costs of PET at 0% vc). Finally, the total cost-effectiveness ratio from using PET alone in 10 years was 618 USD per human cases averted.

h) Scenario 2 (Annual vaccination with short-acting vaccines)

The outbreak simulated in this scenario demonstrated that preventive vaccination at 50 - 65% vc could not control the disease with approx. 11 - 211 rabid dog cases per year (figure 4). However, vc at 70% and at 50-70-50% (using 50% vc in the first year in combination with 70% vc during the outbreak and maintaining with 50% vc through the rest of the simulation period) resulted in a smaller amplitude of the outbreak with 0 – 47 rabid dogs per year, controlling the outbreak within 378 - 426 weeks (figure 5E and 5F, respectively). The proactive vaccination with 70% coverage was the most effective strategy. It also provided the shortest duration until the disease was under control and the highest number of cases averted in both dogs (1,165 cases) and humans (28.96 cases). The results in humans had shown that successfulness of dog vaccination campaign played a major role in the reduction of human cases with 96.5% reduction of human rabies compared to the baseline (Without vaccination) with the support of PET.

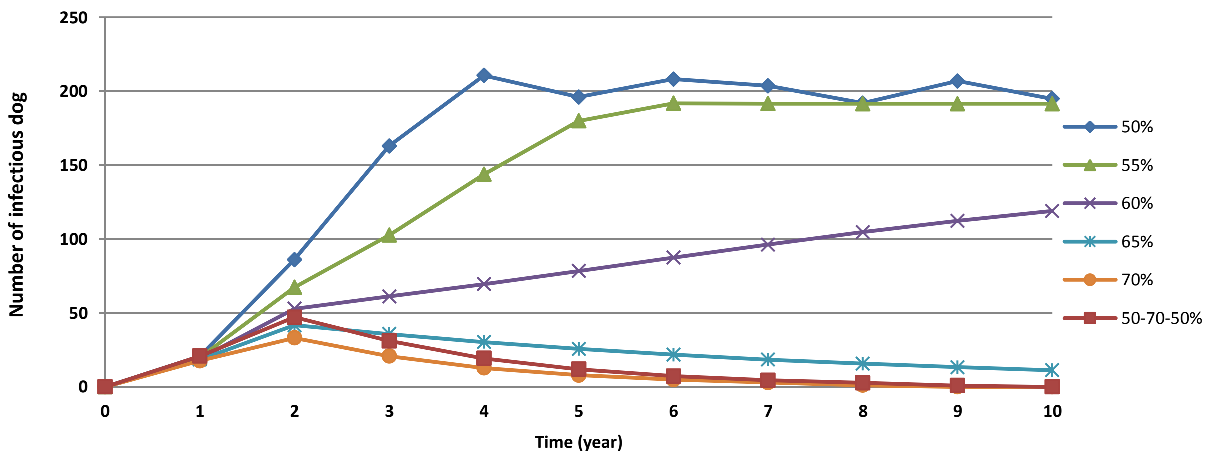

Figure 4 The number of infectious dogs generated in yearly time step from the scenario 2 (Annual vaccination with short-acting vaccines) over the 10-years simulation period without consideration of the virus re-introduction. The comparison was shown between 50% to 70% vaccination coverage (vc) and 50-70-50% (Using 50% vc in the first year in combination with 70% vc during outbreak and maintaining with 50% vc through the rest of the simulation period) as an additonal strategy.

Depending on the applied vc, the costs of vaccination in a 10-years period ranged from 5,711 to 10,587 USD (table 4). The lowest costs of vaccination were at 50% vc but this scenario was not effective against the onging outbreak. Therefore, the lowest vaccination costs were at 70% and 50-70-50% vc with 8,122 and 10,587 USD, respectively.

The public costs of PET in 10 years ranged from 924 to 1,828 USD per year (Appendix 2). The lowest public costs of PET throughout simulation period was at 70% vc (924 USD). It was in line with the number of human cases averted which was the highest at 70% vc as well.

Finally, when considering costs together with effectiveness in cost-effectiveness ratio, the most cost-effective strategy is at 70% vc, which generated the lowest cost-effectiveness ratio equal to 6.97 USD per dog cases averted and 312 USD per human cases averted. The

70% vc with support of PET in this scenario was 50% more cost-effective compared to the baseline with PET as the only measure for controlling the disease in humans.

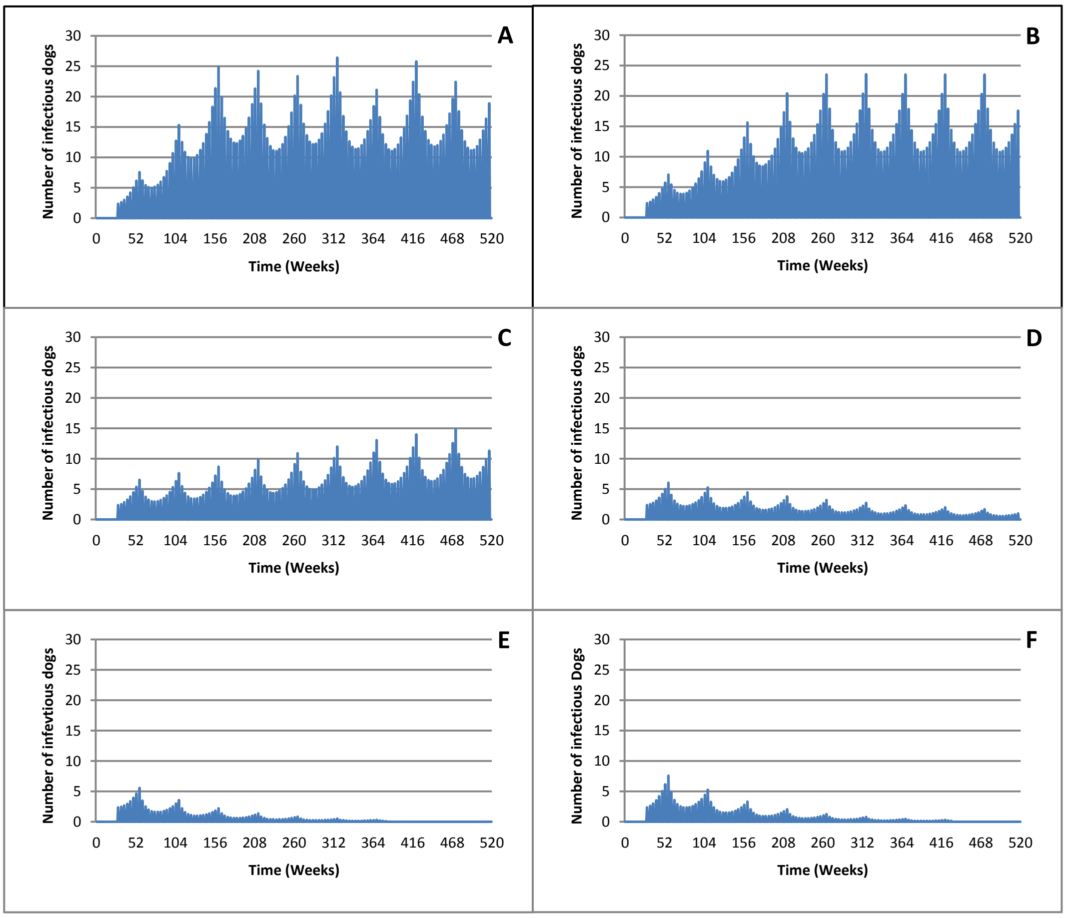

Figure 5 The number of infectious dogs generated from the scenario 2 in weekly interval (Annual vaccination campaign with short-acting vaccines) over the 10-year simulation period without consideration of the virus re-introduction. **A:** 50% vaccination coverage (vc), **B:** 55% vc, C: 60% vc, **D:** 65% vc, **E:** 70% vc and **F:** 50-70-50% (Using 50% vc in the first year in combination with 70% vc during outbreak and maintaining with 50% vc through the rest of the simulation period)

i) Scenario 3 (Biannual vaccination with short-acting vaccines)

This scenario caused one major outbreak that could be contained within 82 to 162 weeks (figure 6 and figure 7A-F). The numbers of cases averted in 10 years ranged between 1,238 to 1,255 averted cases in dogs and 29.72 to 29.89 averted cases in humans (with PET). Thus, the most effective strategies for controlling the disease in both dogs and humans belonged to 70% vc with the highest averted cases in both dogs and humans. These results of averted cases at 70% vc were also accounted for 99.1% reduction in dog cases and 99.6% reduction in human cases compared with the baseline scenario.

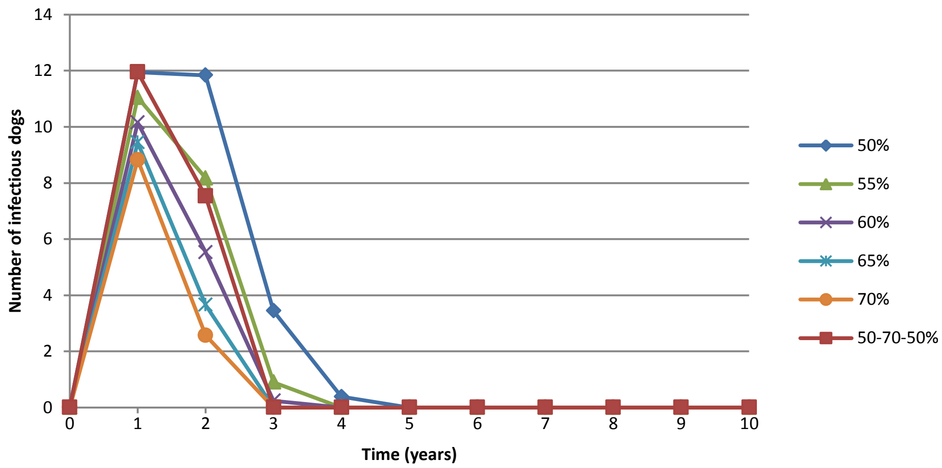

Figure 6 The number of infectious dogs generated in yearly time step from scenario 3 (Biannual vaccination with short-acting vaccine) over the 10-years simulation period without consideration of the virus re-introduction. The comparison is shown between 50% to 70% vaccination coverage (vc) and 50-70-50% vc (Using 50% vc for the first year in combination with 70% vc during outbreak and maintaining with 50% vc through the rest of the simulation period) as an additonal strategy.

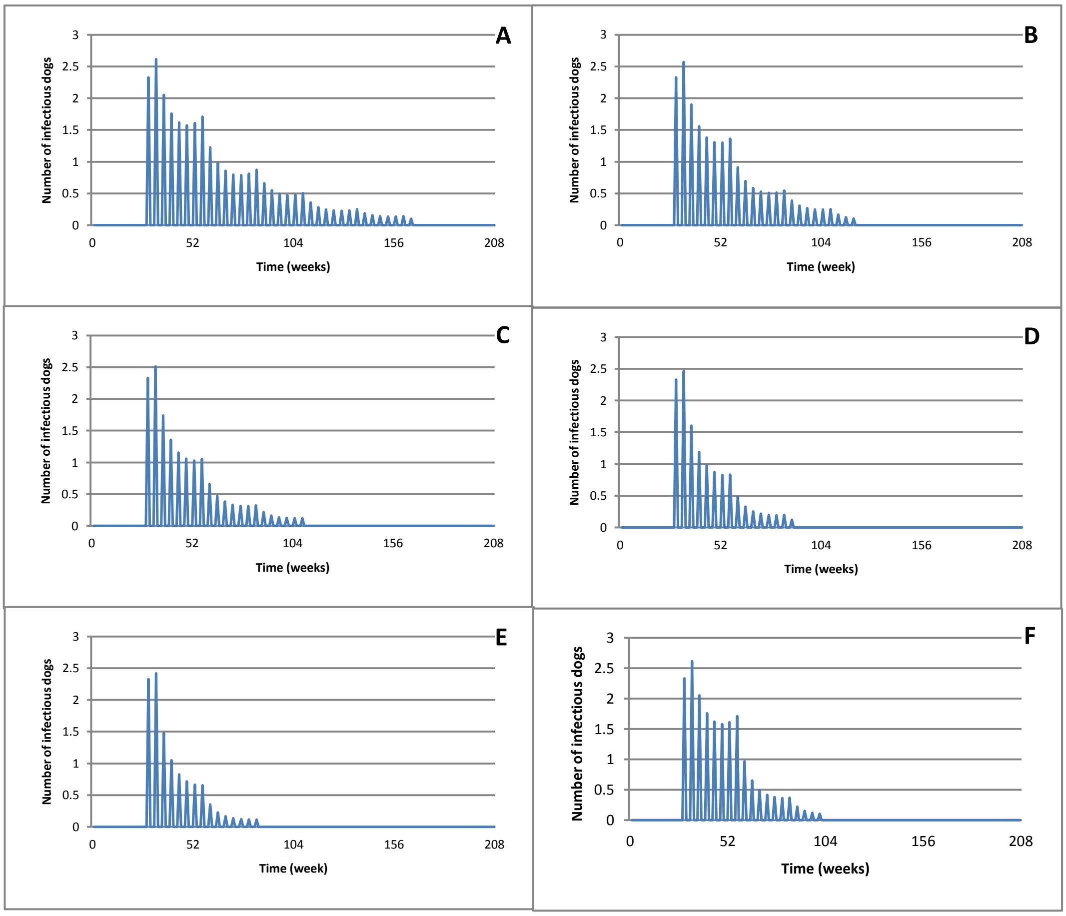

Figure 7 The number of infectious dogs generated from the scenario 3 (Biannual vaccination with short-acting vaccine) in weekly time steps without consideration of the virus re-introduction into the village. **A:** 50% vaccination coverage (vc), **B:** 55% vc, **C:** 60% vc, **D:** 65% vc, **E:** 70% vc and **F:** 50-70-50% vc (Using 50% vc in the first year in combination with 70% vc during outbreak and maintaining with 50% vc through the rest of the simulation period).

Due to two vaccination campaigns per year, this scenario resulted in the highest vaccination costs among the other scenarios with the costs ranging between 11,477 to 16,068 USD (Table 4). The effectiveness in reducing the number of infectious dogs and humans were, as well, the highest compared to the other scenarios. Therefore, the public costs of PET, which ranged from 112 – 267 USD, were the lowest in comparison with the other sceanrios. The public costs of PET incurred mostly in the first 2 years of the simulation because of the subsequent disease outbreak in humans caused by the outbreak in dogs during that time period as shown in appendix 3.

Finally, despite the highest effectiveness to control the outbreak in 70% vc, the lowest cost-effectiveness ratio for this scenario is the strategy at 50% vc which was equal to 395 USD per human case averted (Table 4) with only 0.17 human cases higher than 70% vc. Additionally, 50% vc could reduce the total costs per human cases averted for up to 27% compared to the least cost-effective strategy in this scenario (70% vc) which costed 541 USD per human cases averted.

j) Scenario 4 (Annual vaccination with long-acting vaccines)

All vc simulations on this scenario using annual long-acting vaccines generated the effectiveness on controlling the disease within 118 – 482 weeks (Figure 9A-F). The numbers of rabid dogs ranged from 27 – 128 cases (Figure 8) which resulted in 0.28 – 1.33 human cases in a 10-years period. The results on effectiveness were also positively related with vc. Therefore, the most effective vaccination coverage among these scenarios was 70% with up to 97.85% reduction in the number of infectious dogs (1,239 averted dog cases) and 99.05% reduction in human cases in combination with PET (29.72 averted human cases) compared to the baseline scenario.

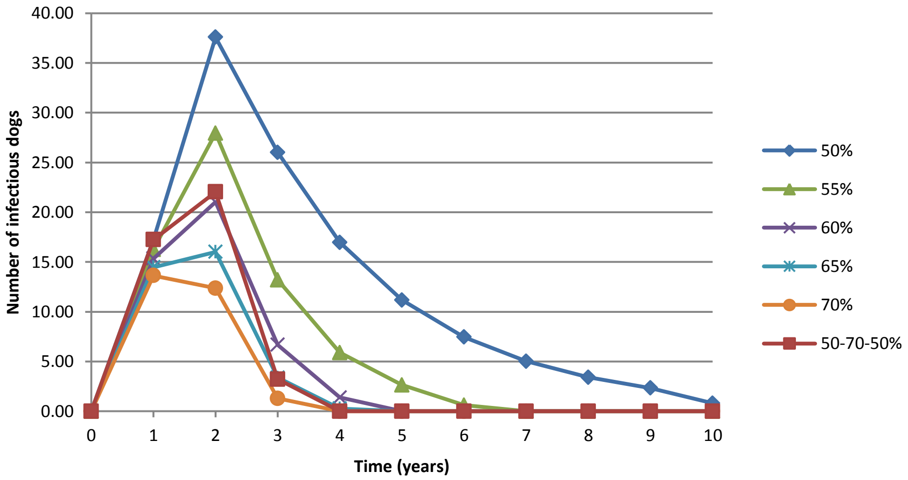

Figure 8 The number of infectious dogs generated in yearly time step from scenario 4 (Annual vaccination with long-acting vaccines) over the 10-years simulation period without consideration of the re-introduction of the virus into the village. The comparison is shown between 50% to 70% vaccination coverage (vc) with 50-70-50% vc (Using 50% vc for the first year in combination with 70% vc during outbreak and maintaining with 50% vc through the rest of the simulation period) as an additonal strategy.

Despite the annual vaccination, this scenario had switched from using short-acting to long-acting vaccines, therefore, the vaccine costs increased with approx. 16% compared to the annual short-acting vaccination at the same vc. The vaccination costs in 10 years ranged from 6,798 – 9,517 USD (Table 4).

The public costs of PET in this scenario during the simulation period ranged from 266 – 1,150 USD (Table 4). The costs incurred mostly during the first 3 – 5 years for 55-70% vc and 50-70-50% vc. The 50% vc caused the highest public costs of PET because of the highest infectious number of dogs and humans with the longest disease disease outbreak (482 Weeks).

Finally, the most cost-effective strategy in humans (with PET) was the strategy at 50-70-50% vc with the cost-effectiveness ratio equaled to 275 USD per human case averted (Table 4). This strategy had a 16% lower cost-effectiveness ratio than the strategy under 70% vc which resulted in the highest cost-effectiveness ratio (329 USD/human case averted). Moreover, 50-70-50% vc, generated only 0.15 (0.5%) lower in human cases averted (with PET) than 70% vc throughout the whole simulation period.

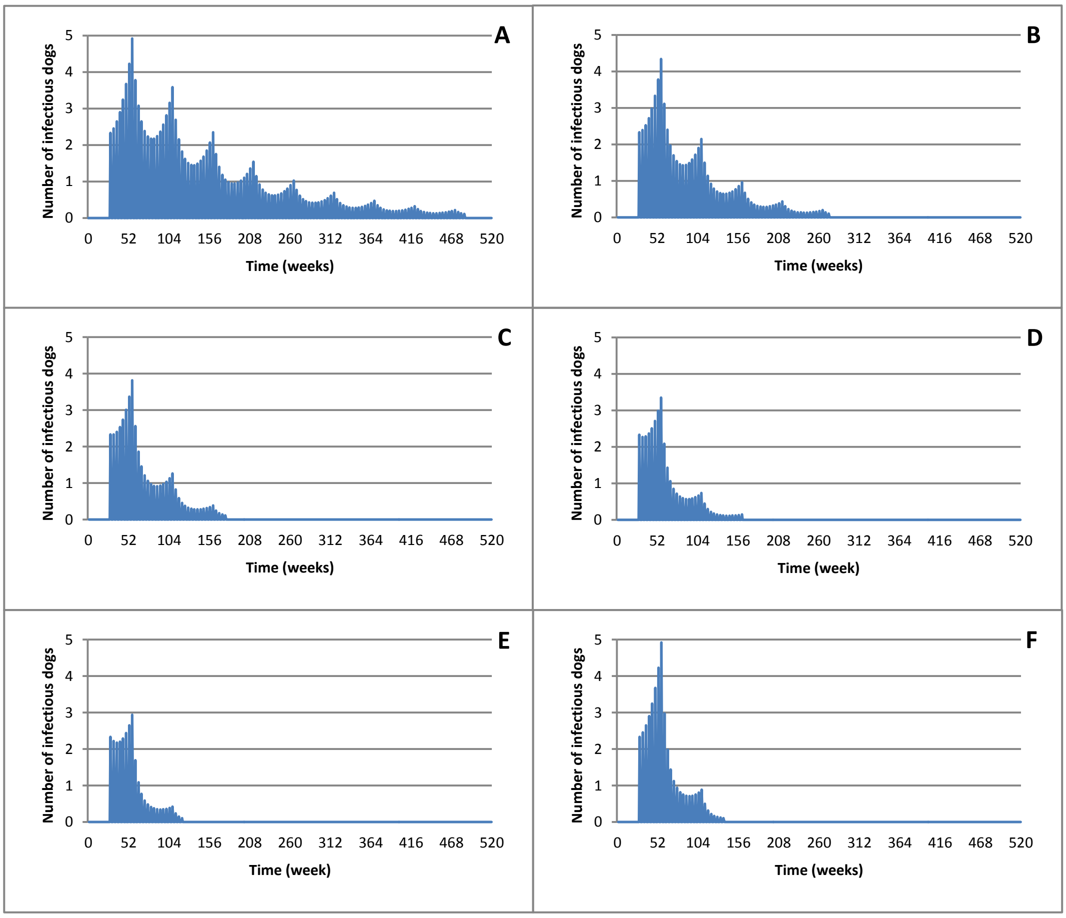

Figure 9 The number of infectious dogs generated from the scenario 4 (Annual long-acting vaccines) in weekly time steps without consideration of the re-introduction of the virus into the village. **A:** 50% vaccination coverage (vc), **B:** 55% vc, **C:** 60% vc, **D:** 65% vc, **E:** 70% vc and **F:** 50-70-50% vc (Using 50% vc in the first year in combination with 70% vc during outbreak and maintaining with 50% vc through the rest of the simulation period).

k) Scenario 5 (Once-every-2-year vaccination with long-acting vaccines)

This scenario was not able to contain the outbreak within the period of 10 years, independent of applied vc (Figure 10 and 11A-E). The numbers of rabid dogs ranged between 1,212 - 1,515 cases in 10 years, which are the highest among the other scenarios (Table 4). Moreover, the number of infectious dogs in 50 - 60% vc were higher than in the baseline scenario. Because vaccination protected some of the population against dying from the disease. Those dogs in scenario 5 could reproduce approx. 20% more puppies than the baseline. Thus, the number of susceptible dogs would be increased in the next time step to promote higher exposure to the virus and resulted in higher number of rabid dogs. In human, this scenario also provided the lowest number of human cases averted, which ranged from 14.12 – 17.37 averted cases.

The costs of vaccination in this scenario were the lowest compared to the other scenarios due to the lowest frequency of the campaign (once in 2 years) as can be seen in appendix 6. The costs for the vaccination campaign in 10 years were estimated between 3,194 - 4,697 USD. The total costs for preventing the disease in humans (14,305 – 15,577 USD) were comparable scenario 3 but it was due to low vaccination costs and high public costs for PET (9,607 – 11,977 USD), while scenario 3 performed the other way around. In conclusion, this scenario was considered to be ineffective to control the disease in dogs and humans regardless of the levels of vc used because of the failure to control the disease and having lowest numbers of dog and human cases averted compared to other scenarios.

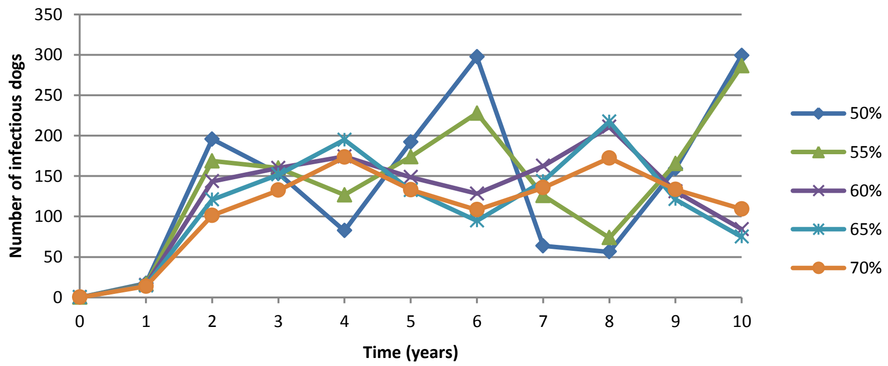

Figure 10 The number of infectious dogs generated in yearly time steps from the scenario 5 (Once-every-2-year vaccination with long-acting vaccines) over the 10-year simulation period without consideration of the re-introduction of the virus into the village. The comparison is shown between 50% to 70% vaccination coverage.

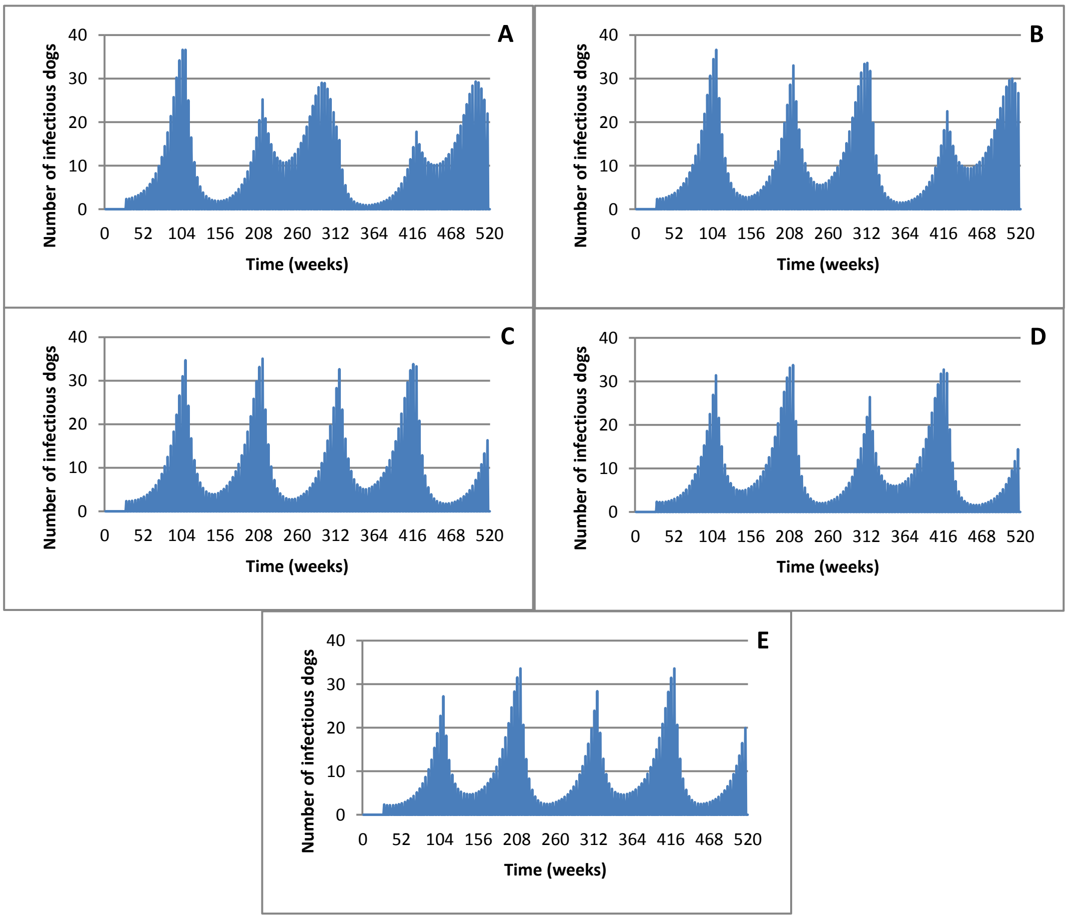

Figure 11 The number of infectious dogs generated from the scenario 5 (Annual vaccination with long-acting vaccines) in weekly time steps for 10-year simulation period without consideration of the re-introduction of the virus into the village A: 50% vaccination coverage, B: 55% vaccination coverage, C: 60% vaccination coverage, D: 65% vaccination coverage and E: 70% vaccination coverage.

l) Scenario 6 (combination of annual short- and long-acting vaccines)

This scenario generated approx. 45 – 155 rabid dogs in 10-year simulation period which could be contained within 122 – 314 weeks (figure 12 and figure 13A-E). The number of human cases averted (with PET) was estimated to be 28.39 – 29.54 human cases averted. The most effective strategy to reduce the number of rabid dogs and human cases was the strategies at 70% vc.

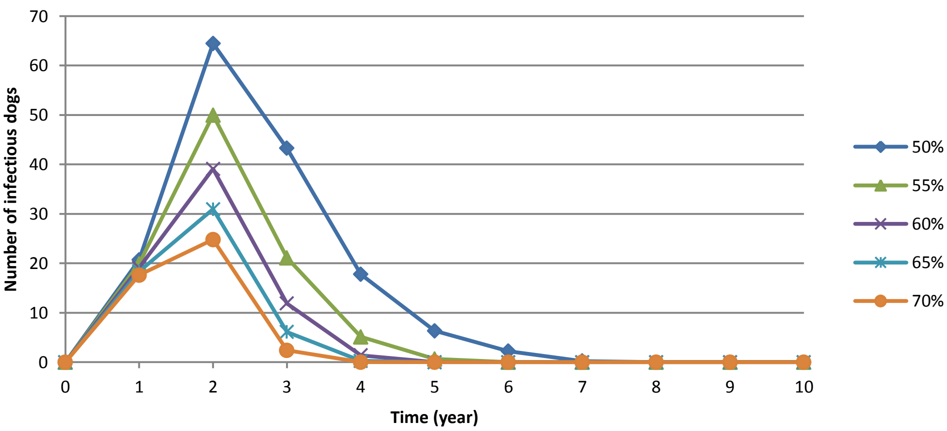

Figure 12 The number of infectious dogs generated in yearly time steps from the scenario scenario 6 (combination of annual short- and long-acting vaccines) over the 10-year simulation period without consideration of the re-introduction of the virus into the village. The comparison is shown between 50% to 70% vaccination coverage.

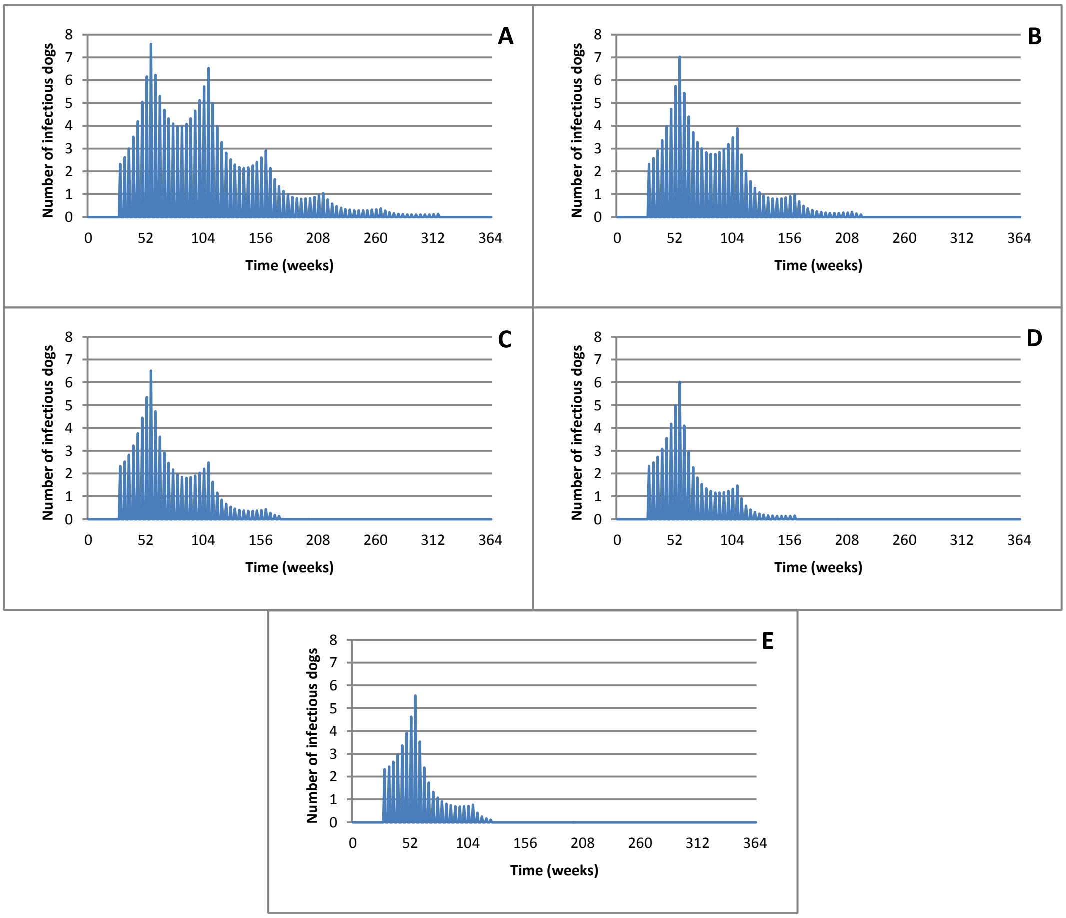

Figure 13 The number of infectious dogs generated from the scenario 6 (combination of annual short- and long-acting vaccines) in weekly time steps without consideration of the re-introduction of the virus into the village. A: 50% vaccination coverage (vc), B: 55% vc, C: 60% vc, D: 65% vc and E: 70% vc.

The total costs for vaccination and PET highly incurred during the first 4 years due to the disease outbreak in dogs and the use of long-acting vaccines during the outreak as seen in Appendix 6. The costs of vaccination ranged between 6,426 - 8,433 USD in the 10-years period. This scenario was considered to lower the cost of vaccination between 5 – 11% compared to scenario 4 (Using only long-acting vaccines) at the same level of vc, while the effectiveness in controlling the disease in humans (with PET) was approx. <0.7% lower than scenario 4.

The 50% vc generated the lowest accumulated number of vaccination costs in 10 years, therefore, it is the most cost-effective strategies for controlling the disease in dogs (cost-effectiveness ratio: 5.78 USD per dog case averted). However, the most cost-effective ratio in humans was at 55% vc (268 USD/human case averted) from the perspective of the absolute monetry value. This strategy could reduce the number of human cases for up to 96.64% compared to the baseline scenario with a 11% lower cost-effectiveness ratio compared to 70% vc. However, the number of human cases (1.62 cases with PET) and duration of the outbreak (218 weeks) in this vc were still 70% and 61% higher the 70% vc, respectively.

4.2 Cost-effectiveness of vaccination strategies accounted for virus re-introduction

Based on the results in the first part, the most cost-effective and pragmatic scenarios were selected to examine the impact of reintroduction on the cost-effectiveness of the preventive vaccination strategies. According to the selection criteria as described in the materials and methods, the selected scenarios included scenario 2, 4 and 6.

The risk of reintroduction was stochastically incorporated into the model. Two series of simulations were run based on 2 assumptions on the average likelihood of virus reintroduction; i.e. once a year and one in 3 years. In the following sections, the overall results are generally described first for both probabilities and will be followed by the detailed description of relevant results from each scenario.

4.2.1 The probability of reintroduction in once every year (P = 0.019)

In the baseline scenario, simulations on the average probability of reintroduction of once in a year resulted in an average of 10 virus reintroductions in 10 years (90% CI: 5 – 15 reintroductions), with 2,681 rabid dog cases (Table 5). The number of human cases in the baseline was 64 cases without PET (Table 7) and 28 cases with PET (Table 6), which indicated that 56% of human cases could be reduced with the support of PET alone. Moreover, this probability of reintroduction impacted the number of cases with approx. 50% of rabies cases higher than the baseline from the deterministic model with only a single virus introduction.

With the application of the selected vaccination scenarios, the mean number of rabid dogs ranged between 137 – 1,128 cases. The number of human cases with PET ranged from 1.43 – 11.76 cases. The mean number of averted cases compared with the baseline ranged between 1,532 – 2,541 cases in dogs and between 51.43 - 61.96 cases in humans (with PET). These outcomes on effectiveness provided a different ranking of effective scenarios compared to the deterministic model when consideration was made from the reduced mean number of rabies cases. The 2 most effective scenarios were switched from the conclusion in the deterministic model so scenario 6 (annual short-acting vaccination during normal situation and long-acting vaccination during the outbreak) at 70% vc was the most effective scenario followed by scenario 4 (annual vaccination with long-acting vaccines) at 70% vc in this case. The ranking for the mean public costs of PET were also in line with the raking in the effectiveness in this case as well. Thus, the 5 most effective scenarios based on the mean of rabies cases and public costs of PET were these following scenarios; 1) 6 at 70% vc, 2) 4 at 70% vc, 3) 4 at 50-70-50% vc, 4) 6 at 50% vc and 5) 4 at 50% vc. Scenario 6 and 4 with 70% vc also generated a narrow range in number of human cases with 90% CI equal to 0.50 -2.79 cases for scenario 6 and 0.79 – 2.93 cases in scenario 4. Therefore, scenario 6 and 4 at 70% vc were the most effective and certain scenarios to be applied.

The ranking of the vaccination costs and total costs were not in line with the ranking of effectiveness. The mean costs of vaccination ranged from 6,598 – 9,566 USD in 10 years. The lowest costs for vaccination were in scenario 6 at 50% vc, which were comparable with scenario 4 at 50% with only 3% difference in term of the vaccination costs. Due to the fact that on average each year an outbreak occurred, scenario 6 resembled scenario 4 by applying long-acting vaccines throughout the simulation period with the only exception for year one. The absolute mean number of human cases in scenario 6 at 50% vc (5.40 cases; 90% CI: 2.06 – 11.19 cases) generated 47% lower in number of cases and also had narrower range of outcomes than scenario 4 (10.18 cases; 90% CI: 4.80 – 16.76 cases).

The mean total costs (combination of the vaccination costs and the public costs of PET) ranged from 10,262 - 16,977 USD (Table 6). The lowest total costs were in scenario 6 at 70% because of the lowest costs of PET (1,128 USD; 90% CI: 373 – 2,309 USD), even though this scenario generated the second highest mean vaccination costs (9,115 USD; 90% CI: 8,767 – 9,374 USD).

Finally, the mean cost-effectiveness ratio in dogs ranged between 3.17 – 6.29 USD/averted dog cases. Scenario 6 at 50% vc had the lowest cost-effectiveness ratio with the narrowest range of outcomes (3.17 USD/averted dog cases; 90% CI; 2.62 – 4.28 USD/averted dog cases). In public health aspect, the cost-effectiveness ratio in humans with the support of PET ranged between 167 – 319

USD/human case averted. The most cost-effective scenario also belonged to scenario 6 at 70% vc (167 USD/averted human case; 90% CI; 147 – 206 USD/averted human case).

In conclusion, the most cost-effective strategy in the situation with on average one reintroduction per year was scenario 6 at 70% vc. As shown in Figure 14, scenario 6 at 70% vc dominated other scenarios especially for the higher value of cost-effectiveness ratio with also lower variation of the outcomes. It was the scenario that reduced the mean number of cases and generated least costs in both veterinary and human health aspects. It was followed, respectively, by 1) scenario 4 at 70% vc, 2) scenario 4 at 50-70-50% vc, 3) scenario 6 at 50% vc and 4) scenario 4 at 50% vc, (Figure 15) as the most cost-effective scenarios in public health aspect. However, the level of vc as high as 70% might be difficult to manage in the real situation. Therefore, in the worst case when only 50% vc could be applied, scenario 6 at 50% vc was considered to be the most cost-effective with the mean cost-effectiveness ratio in human (with PET) equalled to 189 USD/averted human case (90% CI: 144 - 247 USD/averted human case). It also had narrow and comparable range of outcomes in the cost-effectiveness ratios in human (with PET) compared to 70% vc (90% CI: 147 – 206 USD/averted human case).

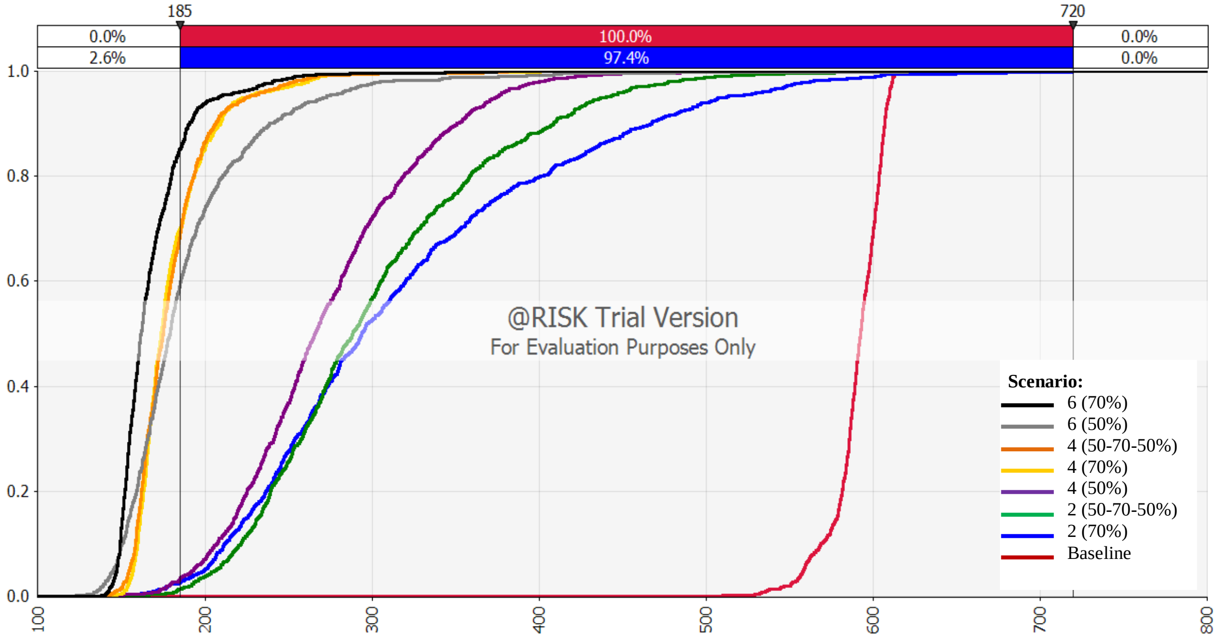

Figure 14: The cumulative probability distribution for the cost-effectiveness ratio in human cases with support of PET, generated from the stochastic model with probability of virus reintroduction in once every year (P = 0.019) over the period of 10 years for different strategies and vaccination coverage (vc). Black line: Scenario 6 (annual vaccination with combination of short- and long-acting vaccines) at 70% vc, Gray Line: Scenario 6 at 50%vc, Orange line: Scenario 4 (Annual vaccination with long-acting vaccines) at 50-70-50% vc (The combination of vaccination coverage), Yellow line: Scenario 4 at 70% vc, Purple line: Scenario 4 at 50% vc, Green line: Scenario 2 (Annual vaccination with short-acting vaccines) at 50-70-50% vc, Blue line: Scenario 2 at 70% vc and Red line: Baseline scenario

Table 5: The simulated numbers for the cost-effectiveness analyses of vaccination strategies in dogs from the stochastic model with average probability of virus reintroduction of once every year

Cost-Effectiveness for Dog Health aspect																
Scenario	Vaccination Coverage (%)	Number of rabid dogs (cases)			Vaccination Costs (USD)			Number of rabid dogs averted (cases)			Cost-effectiveness Ratio (USD/Averted rabid dog)			Number of virus reintroduction in 10 years		
		Mean	Percentile 5	Percentile 95	Mean	Percentile 5	Percentile 95	Mean	Percentile 5	Percentile 95	Mean	Percentile 5	Percentile 95	Mean	Percentile 5	Percentile 95
1 Baseline	0%	2,681	2,058	2,989	0	0	0	0	0	0	0	0	0	10	5	15
2 Annual vaccination with short-acting vaccine	70%	897	319	1,736	8,130	8,026	8,179	1,774	995	2,350	4.94	3.47	8.07			
	50-70-50%	1,128	342	2,353	7,643	6,998	7,891	1,532	478	2,270	6.29	3.39	14.35			
4 Annual vaccination with long-acting vaccine	50%	977	461	1,607	6,799	6,732	6,845	1,702	1,133	2,187	4.18	3.10	5.94			
	70%	172	76	281	9,566	9,540	9,591	2,508	1,779	2,814	3.93	3.40	5.32			
	50-70-50%	226	89	436	8,967	8,306	9,254	2,446	1,777	2,755	3.76	3.25	5.08			
6 Annual short-, long and short-acting vaccine	50%	518	198	1,073	6,598	6,328	6,706	2,152	1,518	2,532	3.17	2.62	4.28			
	70%	137	48	267	9,115	8,767	9,374	2,541	1,813	2,832	3.68	3.21	5.04			

Table 6: The simulated numbers for the cost-effectiveness analyses of vaccination strategies in humans with the support of PET from the stochastic model with probability of virus reintroduction in once every year.

Cost-Effectiveness for Human Health aspect (with PET)																
Scenario	Vaccination Coverage (%)	Number of human cases (cases)			Public Costs of PET (USD)			Total Costs (USD) (Costs of Dog vaccination and PET)			Number of human cases averted (cases)			Cost-effectiveness Ratio (USD/Averted human case)		
		Mean	Percentile 5	Percentile 95	Mean	Percentile 5	Percentile 95	Mean	Percentile 5	Percentile 95	Mean	Percentile 5	Percentile 95	Mean	Percentile 5	Percentile 95
1 Baseline	0%	27.90	19.69	31.20	21,034	14,785	24,032	21,034	14,785	24,032	35.67	28.56	39.75	591	560	609
2 Annual short-acting vaccine	70%	9.35	3.33	18.10	6,711	2,302	13,096	16,977	10,910	26,622	53.97	39.26	62.74	319	199	528
	50-70-50%	11.76	3.56	24.54	8,581	2,505	18,299	15,191	11,320	19,730	51.43	38.19	61.47	301	205	454
4 Annual long-acting vaccine	50%	10.18	4.80	16.76	7,396	3,301	12,402	14,352	10,365	18,962	53.21	38.43	60.96	272	194	387
	70%	1.79	0.79	2.93	1,366	579	2,225	10,937	10,171	11,866	61.62	43.06	68.59	179	156	218
	50-70-50%	2.35	0.92	4.55	1,833	668	3,641	10,851	9,676	12,495	60.97	43.06	67.90	179	155	227
6 Annual short-, long and short-acting vaccine	50%	5.40	2.06	11.19	4,204	1,442	8,912	10,886	8,181	15,423	57.91	42.00	64.89	189	144	274
	70%	1.43	0.50	2.79	1,128	373	2,309	10,262	9,550	11,331	61.96	43.86	69.09	167	147	206

The following sections will describe the results from each scenario separately in details. For more concise results, the outcomes will be shown based on the probability of introduction for once every year because it was the main focus for this study. Moreover, the main findings of once-in-3-years have been described already in the previous section.

a. *Scenario 1 (The model without vaccination)*

The outcomes from this scenario were used to compare the effectiveness of each vaccination strategy. In the period of 10 years, this scenario generated 2,681 (90% CI: 2,058 – 2,994 cases) rabid dogs on average (Figures 15). This number was 53% higher than the number resulting from the outbreak caused by a single introduction in the deterministic model. The mean number of human cases was estimated to be 63 cases (90% CI: 48 – 71 cases) without the application of PET. The support of PET alone showed to lower the mean number of human cases for approx. 52% with the mean cost-effectiveness equal to 591 USD/averted human case (90% CI: 560-609 USD/averted human case).

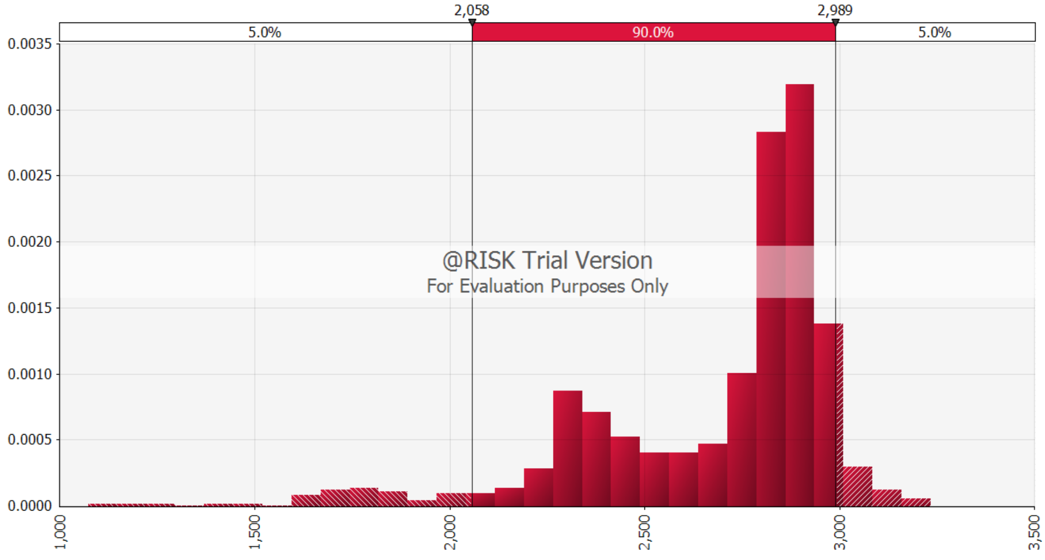

Figure 15 The distribution of infectious dogs generated from the baseline scenario from the stochastic model with probability of virus reintroduction in once every year (P = 0.019) over the period of 10 years

b. Scenario 2 (Annual vaccination with short-acting vaccine)

This scenario was chosen because it is the current campaign being implemented on the island. The 70% and 50-70-50% vc were selected according to the capability to bring the disease under control within the simulation period. The mean accumulated number of infectious dogs were 897 cases (90% CI: 319 – 1,736 cases) at 70% vc and 1,128 cases (90% CI: 342 – 2,353 cases) at 50-70-50% vc, which were approx. 66% and 57% lower than the baseline. When PET was applied, 70% vc could contribute to 85% in reduction of human cases compared to the baseline. It was comparable with 50-70-50% vc which resulted in a 81% lower number in human cases compared to the baseline.

The mean costs of vaccination were 7,643 USD (90% CI: 6,998 – 7,891 USD) for 50-70-50% vc and 8,130 (90% CI: 8,026 – 8,179 USD) (Table 5). When considering the mean annual vaccination costs in 10 years, the vaccination costs in 70% vc incurred mostly during the first few years due to a larger dog population size (Appendix 11). The 50-70-50% vc caused 6% less vaccination costs than 70% vc. However, it generated on average 8,581 USD of PET costs (90% CI: 2,505 – 18,299 USD), which was 22% higher than 70% vc, and it also had higher variation of the outcomes compared to 70% vc as seen in Figure 16. In general, the mean total costs were 15,191 USD for 50-70-50% vc (90% CI: 11,320 – 19,730 USD) and 16,977 USD for 70% vc (90% CI: 10,910 – 26,622 USD) in which 50-70-50% vc iccurred 11% lower in total costs due to lower costs of vaccination.

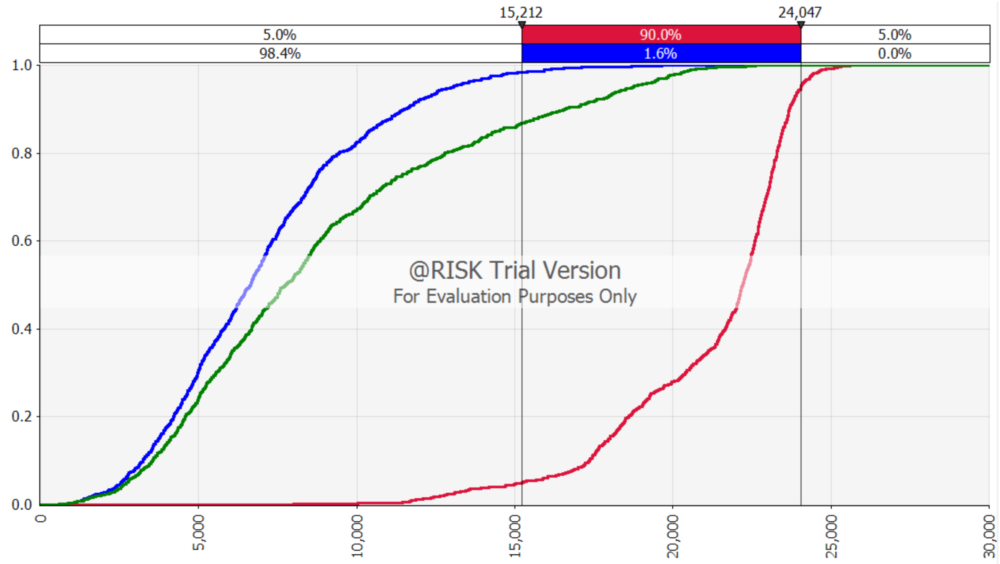

Figure 16 The cumulative probability distribution for the public costs of PET generated from the stochastic model (Scenario 2: Annual vaccination with short-acting vaccine) with probability of virus reintroduction in once every year (P = 0.019) over the period of 10 years. Blue line: 70% vc, Green Line: 50-70-50% vc and Red line: Baseline scenario.

Finally, the mean cost-effectiveness ratio from 50-70-50% vc (301 USD/averted human case) was 6% lower than 70% vc (319 USD/averted human case) with also narrower range of outcomes. However, it generated 4% higher mean number of human cases in 10 years than 70% vc.

c. Scenario 4 (Annual vaccination with long-acting vaccine)

This scenario was considered because it was the most practical way to improve effectiveness of the vaccination campaign due to the fact that the change had to be made for only the type of vaccines. The mean number of rabid dogs ranged between 172 – 977 cases in 10 years (Table 5). The 70% vc had the lowest number of infectious dogs with 2,508 mean rabid dog cases averted (90% CI: 1,779 – 2,814), which was accounted for 94% lower in mean rabid dog cases compared to the baseline. It also resulted in 1.79 human cases, which was estimated to be 61.62 cases averted or 97% lower than the baseline. 70% vc is also the most certain vc to apply using this scenario due to the narrowest range of generated human cases as shown in figure 17. Therefore, the 70% vc was considered to be the most effective vc in both veterinary and public health aspect with lower variation of the outcomes on effectiveness. The finding indicated that it was also more certain vc to reduce the number of rabies cases for this scenario.

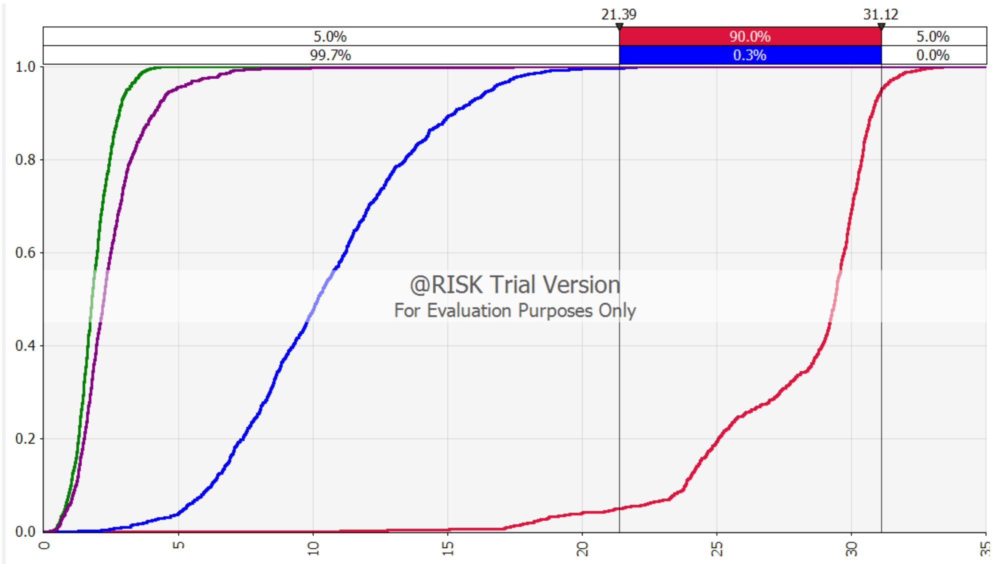

Figure 17 The cumulative probability distribution for the number of human cases with support of PET, generated from the stochastic model (Scenario 4: Annual vaccination with long-acting vaccine) with probability of virus reintroduction in once every year (P = 0.019) over the period of 10 years. Green line: 70% vc, Purple line: 50-70-50% vc, Blue Line: 50% vc and Red line: Baseline scenario.

The mean costs of vaccination were between 6,799 – 9,566 USD in 10 years. The 50% vc promoted the lowest mean vaccination costs (6,799 USD; 90% CI; 6,732 – 6,845 USD), which was 31% lower than the most effective vc (70%). In contrary, it generated the highest number of public costs for PET (1,366 USD; 90% CI: 579 – 2,225 USD) with 87% higher number than 70% vc, and resulted in the lowest public costs of PET in this scenario. When considered the total costs in 10 years, the 50-70-50% vc generated the lowest total costs (10,851 USD; 90% CI: 9,676 – 12,495 USD) in this scenario.

Finally, the most cost-effective vc was considered to be 70% even though 50-70-50% performed better in economic perspective by having comparable mean and variation on the cost-effectivenesss ratio in human (Figure 18). It also generated lower cost-effectiveness ratio in dogs compared to 70% vc. However, 50-70-50% vc still produced approx. 24% higher number of infectious cases in both dogs and humans, which were one of the main considerations for a successful vaccination campaign in this study.

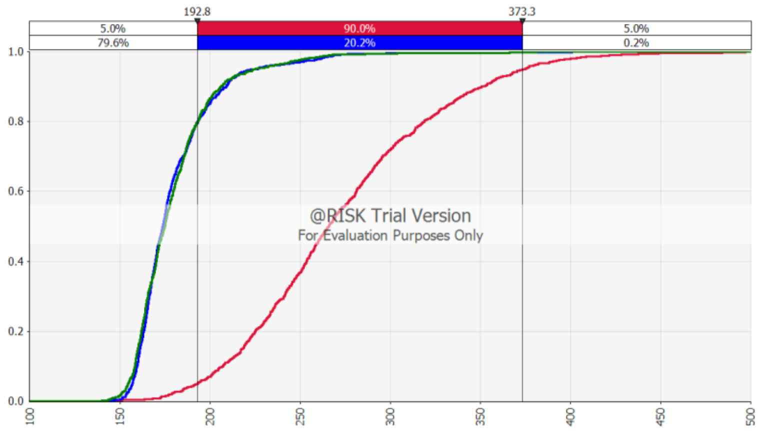

Figure 18 The cumulative probability distribution for the cost-effectiveness ratio in human cases with support of PET, generated from the stochastic model (Scenario 4: Annual vaccination with long-acting vaccine) with probability of virus reintroduction for once every year (P = 0.019) over the period of 10 years. Green line: 70% vc, Blue Line: 50-70-50% vc and Red line: 50% vc.

d. Scenario 6 (combination of annual long- and short-acting vaccine)

This scenario was chosen based on the practical way to lower the costs of vaccination and also the capability to maintain the effectiveness of the vaccination campaign. Over the 10-years simulation period, the numbers of rabid dog cases were on average between 137 and 518 cases. The 70% vc was the most effective vc in veterinary aspect due to the lowest number of rabid dogs (137 cases; 90% CI: 48 – 267 case), and produced lower variation on the outcomes compared to 50% vc (518 cases; 90% CI: 198 – 1,073 cases). Moreover, 70% vc was relatively accounted for 97% reduction on the mean number of human cases (61.62 human cases averted) compared to the baseline, and 74% lower in human cases when compared with 50% vc.

The 50% vc promoted, on average, the lowest number of vaccination costs (6,598 USD; 90% vc: 6,328 – 6,706 USD), which was 28% lower than 70% vc (9,115 USD; 90% CI: 8,767 – 9,374 USD). However, the 70% vc resulted in a 73% lower number in the mean public costs of PET owing to lower number of human cases. It also finally resulted in 6% lower mean total costs than 50% vc. In general, the annual public costs of PET incurred mostly during year 2 – 4 when there were higher numbers of infectious cases (Appendix 12) during that time.

Conclusivly, 70% vc was the most cost-effective vc with 167 USD/human case averted (90% CI: 147 – 206 USD/human case averted). Despite the fact that 50% vc also provided the lowest cost-effectiveness ratio in dogs (3.17 USD/rabid dogs averted; 90% CI: 144 - 274 USD/rabid dogs averted) and lower vaccination costs but it generated a higher number of cases and less certain outcomes compared to 70% vc as shown in figure 19.

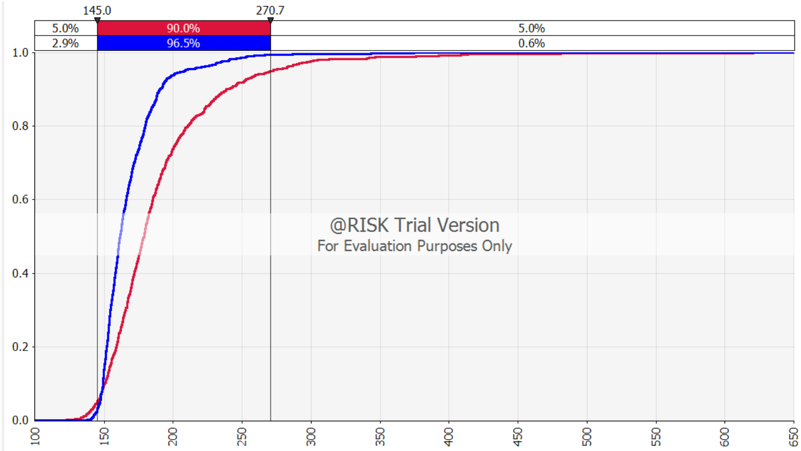

Figure 19 The cumulative probability distribution for the cost-effectiveness ratio in human cases with support of PET, generated from the stochastic model (Scenario 6: combination of annual long- and short-acting vaccine) with probability of virus reintroduction for once every year (P = 0.019) over the period of 10 years. Blue Line: 70% vc and Red line: 50% vc.

4.2.2 The probability of reintroduction in once every 3 years (P = 0.006)

This probability of reintroduction was simulated mainly to examine the changes in the outcomes due to the lower risk of the reintroduction. Given the defined stochastic process, the reintroduction occurred, on average, 3.35 times in 10 years (90% CI: 1 – 7 reintroductions). The baseline scenario generated 2,045 rabid dogs on average (90% CI: 38 – 2,866 cases) as shown in table 7. This number was 24% lower than the number of cases resulting from the situation with an average probability of one reintroduction each year (P = 0.019) and 38% higher than the number resulting from the deterministic model based on a single introduction.

The mean number of dog cases averted ranged between 1,143 – 1,984 averted cases across all simulated scenarios. The mean number of human cases in the baseline was 21.27 cases with PET (Table 8) and 48.35 cases without PET (Appendix 11). Therefore, the mean averted human cases with the application of PET across every scenario was estimated to be 38.95 – 47.71 cases (Table 8). The overall ranking of the effectiveness regarding the mean number of cases and the variation on the outcomes was changed compared to the ranking resulted from the probability of one reintroduction in a year. The most effective scenario was switched to scenario 4 at 70%, followed by scenario 6 at 70% vc and 4 at 50-70-50% vc, respectively.

This probability had also shown that scenario 6 at 50% vc could not reduce the number of infectious dogs because it generated the mean number of rabid dogs (522 cases; 90% CI: 9 – 1,833 cases) that almost equalled to the number of cases from the probability of reintroduction of once in a year (518 cases; 90% CI: 198 – 1,073 cases). It was also the second lowest effective scenario to reduce the mean number of human cases (5.44 cases; 90% CI: 0.09 – 19.11 cases). Even though the number of reintroductions was less than once in a year, the difference in the mean number of infectious dogs and humans compared with the situation with an annual probability of reintroduction was only 0.8% for this scenario with 50% vc. Because of using the long-acting vaccines, at this vc, still took almost 10 years just for a single outbreak to be under control as shown in the deterministic model. Therefore, the once-in-3-years reintroduction basically resulted in almost the same situation as an on-going outbreak throughout the simulated period. However, this was not the case for scenario 6 at 70% vc because of its ability to control the disease in a shorter period of time using long-acting vaccines.

The mean vaccination costs were mostly in line and comparable with the costs from the situation of a yearly reintroduction, ranging from 6,390 – 9,572 USD. The lowest vaccination costs still belonged to scenario 6 at 50% vc (6,390 USD; 90% CI: 5,774 – 6,707 USD) but it was not the scenario with the lowest total costs. The differences in the total costs between each scenario were mainly caused by the public costs of PET, which were accounted for 4 - 50% of the total costs. The contribution of the public costs of PET in the total costs was the lowest in the scenario with the highest effectiveness (scenario 4 at 70% vc) in controlling the disease in humans. The 2 most effective scenarios; scenario 4 (70% vc) and 6 (70% vc), also produced narrower range of outcomes for the public cost of PET and the total costs than the less effective scenarios as seen in table 8. Moreover, due to the differences in the number of reintroductions in 10 years, this case promoted approx. 6 – 32 % lower in the mean total costs than the once-per-year reintroduction when compared across the same scenarios. But the ranges of the outcomes in total costs were larger (Table 8) than P = 0.019.

The mean cost-effectiveness ratio in humans with PET ranged between 1,453 – 2,068 USD/human case averted. It was 80 - 90% higher than the probability of once in a year across the same scenario with also broader range of outcomes. The reason behind the differences will be explained later in the discussion section. The most cost-effective scenario was scenario 4 at 70% vc in this case, which is different from the once-in-a-year probability.

In conclusion, this probability of reintroduction provided different ranking in the cost-effectiveness compared to the once-in-a-year reintroduction. The 4 most cost-effective scenarios, which compared between the mean and variation on the outcomes of the cost-effectiveness ratios in humans (with PET) could be ranked as followed; 1) scenario 6 at 50% vc, 2) scenario 4 at 50% vc, 3) scenario 2 at 50-70-50% vc and 4) scenario 4 at 50-70-50%. However, these scenarios still generated the mean number of infectious dogs and humans that almost equalled to the number produced from P = 0.019, even though the probability of reintroduction was only once in 3 years (P = 0.006). Therefore, the most cost-effective strategies, which were able to reduce the infectious cases considering both probabilities of reintroduction, were scenario 6 at 70% vc and scenario 4 at 70% vc. These scenario should be considered together because of the trade-off between costs and the number of infectious cases. Scenario 6 at 70% had 36% higher human cases (without PET), while the mean cost-effectiveness ratio was 10% lower than scenario 4 at 70% vc. Finally, when actual vc was taken into account (50% vc), scenario 4 was the most cost-effective scenarios. Because it generated more certain outcomes on the cost-effectiveness ratio (90% CI: 161 – 570 USD/human case averted) than scenario 6 (90% CI: 136 – 580 USD/human case averted). Even though, it produced comparable range of human case averted (90% CI: 0.8 – 61 cases) compared with scenario 6 (90% CI: 0.8 – 63 cases)

Finally, when taking 2 probabilities of reintroduction into account scenario 6 at 70% vc were considered to be the most cost-effective scenario due to the ability to control the disease in both situation of reintroductions, and also provided reasonable cost-effectiveness ratios and low variation on the outcomes compared to other scenarios as shown in the ranking summary in table 9.

Table 7: The simulated numbers for the cost-effectiveness of vaccination strategies in dogs from the stochastic model with probability of virus reintroduction in once every 3 years (P = 0.006).

Cost-Effectiveness for Dog Health aspect																	
Scenario	**Vaccination Coverage**	**Number of rabid dogs (cases)**			**Vaccination Costs (USD)**			**Number of rabid dogs averted (cases)**			**Cost-effectiveness Ratio (USD/Averted rabid dog)**				**Number of virus reintroduction in 10 years**		
		Mean	**Percentile**		**Mean**	**Percentile**		**Mean**	**Percentile**		**Mean**	**Median**	**Percentile**		**Mean**	**Percentile**	
			5	**95**		**5**	**95**		**5**	**95**			**5**	**95**		**5**	**95**
1 Baseline	**0%**	2,045	38	2,866	0	0	0	0	0	0	0	0	0	0	3.35	1	7
2 Annual vaccination with short-acting vaccines	**70%**	477	9	1,458	8,150	8,061	8,185	1,568	27	2,530	53.34	4.93	3.24	15.81			
	50-70-50%	902	9	2,522	7,168	5,781	7,891	1,143	1	2,306	45.03	5.88	3.23	30.63			
4 Annual vaccination with long-acting vaccines	**50%**	613	12	1,455	6,814	6,742	6,851	1,432	27	2,304	38.66	4.53	3.02	13.52			
	70%	61	4	136	9,572	9,551	9,595	1,984	32	2,787	41.84	4.53	3.43	17.23			
	50-70-50%	200	5	778	8,276	6,852	9,246	1,845	32	2,714	38.01	4.04	3.15	15.45			
6 annual short-, long and short-acting vaccines	**50%**	522	9	1,833	6,390	5,774	6,707	1,523	30	2,506	30.78	3.78	2.62	14.48			
	70%	96	3	299	8,765	8,177	9,354	1,949	34	2,766	37.91	4.01	3.18	15.99			

Table 8: The simulated numbers for the cost-effectiveness of vaccination strategies in humans with the support of PET from the stochastic model with probability of virus reintroduction in once every 3 years (P = 0.006)

Cost-Effectiveness for Human Health aspect (with PET)																	
Scenario	**Vaccination Coverage**	**Number of human cases (cases)**			**Public Costs of PET (USD)**			**Total Costs (Dog vaccination and PET) (USD)**			**Number of human cases averted (cases)**			**Cost-effectiveness Ratio (USD/Averted human case)**			
		Mean	**Percentile**		**Mean**	**Percentile**		**Mean**	**Percentile**		**Mean**	**Percentile**		**Mean**	**Median**	**Percentile**	
			5	**95**		**5**	**95**		**5**	**95**		**5**	**95**			**5**	**95**
1 Baseline	**0%**	21.27	0.40	29.88	15,626	243	22,897	15,626	243	22,897	26.33	0.28	38.07	564	569	501	604
2 Annual short-acting vaccines	**70%**	4.97	0.09	15.20	3,502	58	10,823	11,601	8,228	18,368	43.38	0.81	63.41	1,894	257	158	659
	50-70-50%	9.40	0.10	26.30	6,800	64	19,398	13,582	7,448	25,604	38.95	0.81	60.76	1,689	335	170	709
4 Annual long-acting Vaccines	**50%**	6.39	0.13	15.18	4,526	79	10,889	11,195	6,909	17,285	41.96	0.81	61.05	1,613	269	161	570
	70%	0.64	0.03	1.42	488	28	1,108	10,054	9,611	10,664	47.71	0.85	66.97	2,068	190	150	732
	50-70-50%	2.08	0.05	8.11	1,561	35	6,010	9,736	8,053	12,693	46.27	0.85	65.90	1,718	197	147	657
6 Annual short-, long and short-acting vaccines	**50%**	5.44	0.09	19.11	4,093	57	14,203	10,192	6,581	19,171	42.91	0.83	63.24	1,453	212	136	580
	70%	1.00	0.03	3.12	764	20	2,355	9,510	8,641	10,947	47.35	0.87	66.67	1,864	183	143	676

Table 9: The summary for the ranking of the vaccination scenario based on the effectiveness in controlling the disease and the cost-effectiveness ratio in human (with the support of PET) from the deterministic and stochastic models.

Ranking	**Deterministic model with a single Reintroduction**			**Stochastic model**											
				Once-in-a-year reintroduction (P = 0.019)					**Once-in-3-year reintroduction (P = 0.006)**						
	Scenario	**Number of human case averted**	**Cost-effectiveness Ratio in human (With PET) (USD/case averted)**	**Scenario**	**Number of human case averted**		**Cost-effectiveness Ratio in human (With PET) (USD/case averted)**		**Scenario**	**Number of human case averted**		**Cost-effectiveness Ratio in human (With PET) (USD/case averted)**			
					Mean	**90% CI**	**Mean**	**90% CI**		**Mean**	**90% CI**	**Mean**	**Median**	**90% CI**	
1	**4 (50-70-50%)**	29.57	275	**6 (70%)**	61.96	43.86-69.09	167	147-206	**6 (70%)**	47.35	0.87-66.67	1,864	183	143-676	
2	**6 (70%)**	29.54	300	**4 (70%)**	61.62	43.06-68.59	179	156-218	**4 (70%)**	47.71	0.85-66.97	2,068	190	150-732	
3	**4 (70%)**	29.72	329	**4 (50-70-50%)**	60.97	43.06-67.90	179	155-227	**4 (50-70-50%)**	46.27	0.85-65.90	1,718	197	147-657	
4	**2 (70%)**	28.96	312	**6 (50%)**	57.91	42.00-64.89	189	144-274	**4 (50%)**	41.96	0.81-61.05	1,613	269	161-570	
5	**4 (50%)**	28.67	277	**4 (50%)**	53.21	38.43-60.96	272	194-387	**2 (70%)**	43.38	0.81-63.41	1,894	257	158-659	
6	**6 (50%)**	28.39	277	**2 (70%)**	53.97	39.26-62.74	319	199-528	**6 (50%)**	42.91	0.83-63.24	1,453	212	136-580	
7	**2 (50-70-50%)**	29.81	418	**2 (50-70-50%)**	51.43	38.19-61.47	301	205-454	**2 (50-70-50%)**	38.95	0.81-60.76	1,698	335	170-709	

5. Discussion

The deterministic model for disease transmission and cost-effectiveness analysis by Wera et al. (2016a) was modified to account for the impact of a virus reintroduction into a village for this study. The cost-effectiveness was calculated to determine the most feasible vaccination strategy regarding vaccination coverage, vaccine types and frequency. The risk of reintroduction was simulated by the assumed average probabilities of P = 0.019 and P=0.006 to evaluate the most feasible vaccination strategy to be applied concerning the uncertainty of the disease status of the island.

The results from the deterministic model in the baseline scenario (without vaccination) regardless of the reintroduction showed that there were 3 epidemic waves during the period of 10 years. This finding is in line with the outcomes from Hampson et al. (2007) and Wera et al. (2016b). They showed that the period of each epidemic cycles is between 3-6 years.

There were 4 vaccination scenarios in this study that were similar to Wera et al. (2016b and 2016c). They were comprised of scenario 2 (annual short-acting vaccination), 3 (biannual short-acting vaccination), 4 (Annual long-acting vaccination) and 5 (once-every-2-years with long-acting vaccination) at 50 and 70% vc. The numbers of cases in dogs and humans were different from the outcomes from Wera et al. (2016b) and Wera et al. (2016c) across the same scenarios in a single introduction. These differences can be mainly explained by the difference in the simulated moment of the introduction. In the study of Wera et al. (2016b), the moment of introduction was at the start of the simulation before the first vaccination campaign. The deterministic model in this study assumed that the disease outbreak occurred at week 26 after the first vaccination campaign. However, the conclusion that scenario 2 at 50% vc and scenario 5 were not the able to control the disease still holds compared with Wera et al. (2016b and 2016c)'s study.

The costs of vaccination with annual long-acting vaccines at 70% vc in 10 years (9,517 USD) in this study were approximately 76% higher than the vaccination costs compared to Wera et al. (2016) (2,264 USD). These differences were also presented in the other similar scenarios as Wera et al. (2016b). The differences resulted from the fact that this study attempted to simulate the costs of a proactive vaccination for disease prevention in the long run, instead of reactive vaccination as used in the study of Wera et al., (2016b and 2016c). Therefore, a continuation of the vaccination campaigns was considered throughout the simulation period. It was applied to account for uncertainty of disease status in the island, even though the disease was under control. Moreover, the numbers of vaccinated animals were calculated based on the total population while Wera et al. (2016b) calculated this number from the group of susceptible animals in the previous time step. These differences also affected the total costs, reflected by the summation between vaccination costs and the public costs of PET, which were structurally higher than in the study of Wera et al. (2016c). Therefore, the outcomes on the vaccination costs and total costs are substantially different from Wera et al. (2016b and 2016c) in which the higher the vc meant the higher vaccination costs in every scenarios regardless of disease situation due to the continuation of the vaccination campaign and the calculation of vaccination costs, as described before.

Apart from the aforementioned scenarios, which were similar to Wera et al. (2016b), 2 additional strategies were simulated in this study. The first one was based on a variation of vc from 50% vc during normal situation to 70% during an outbreak (50-70-50% vc). The additional one was a variation in the vaccine types from short-acting vaccines during the normal situation to long-acting vaccines during the outbreak situation. Therefore, when the differences in costs and additional strategies were taken into account, the conclusion for selecting the most cost-effective scenario was different from the previous study. Because Wera et al. (2016b and 2016c) suggested from the deterministic model without the reintroduction that reactive annual campaign with long-acting vaccines at 70% vc was the most cost-effective campaign. However, the deterministic model in this study suggested that the variation between vaccination coverage with long-acting vaccine (scenario 4 at 50-70-50%) was the most cost-effective strategy. This conclusion was based on both economic and public health point of views. In case the comparison was made using only the cost-effectiveness ratios across the same vaccination scenarios with Wera et al. (2016b and 2016c), the conclusion on the most cost-effective strategy was still the same which was scenario 4 (annual long-acting vaccination) with 70%vc.

Within the stochastic simulation the impact of 2 different average probabilities of reintroduction were evaluated. The first was reflecting an once-in-a-year reintroduction (P = 0.019). This probability generated, on average, 10 reintroductions in a period of 10 years. This scenario should be considered as a worst-case scenario. Wera et al. (2016b) suggested that the disease reintroduction was expected to occur around 1-2 years after the first outbreak due to the movement restriction and public awareness after the first outbreak. Therefore, the probability with once-in-3-years (P = 0.006) reintroduction was also simulated, which produced averagely 3.35 reintroductions in 10 years. However, despite the lower likelihood of introduction scenario 6 at 70% vc remained the most cost-effective campaign regarding costs.

In comparison, the impact of the virus reintroduction on dogs and human cases based on an once-in–a-year situation was estimated to be approx. 50% higher than in the baseline scenario of only one single introduction from the deterministic model. Additionally, the impact from once-in-3-years introduction was approx. 38% higher than the baseline in the deterministic model. The conclusion on the most cost-effective scenario, which considered from the cost-effectiveness ratios together with the reduction of human cases, was scenario 6 at 70% vc in both probabilities of reintroduction. It also provided the narrowest range in outcomes on the cost-effectiveness ratio for both probabilities. However, when considered from the actual vc that can be achieved in the island (50%), the conclusion on the most cost-effective scenario changed to scenario 4 for once-in-3-years reintroduction due to narrower range of outcomes on the cost-effectiveness ratio.

For the once-in-a-year reintroduction scenario, the combination between vaccine types in scenario 6 was initially expected to produce higher or comparable mean number of cases than scenario 4 as shown in the results from the deterministic model. Because the number of reintroductions was once in a year on average, which meant that the long-acting vaccines would be applied in during most of the years in the simulation period. On the other hand, the outcomes showed that the absolute mean and 90% CI for the numbers of cases in scenario 6 were quite lower than scenario 4 with the same vc. The key determination on the lower mean number of cases in scenario 6 were the number of remaining immunized dogs before the first virus introduction. Dogs in scenario 6 were vaccinated with short-acting vaccines before the virus introduction. This type of vaccines subsequently generated a lower number of immunized animals through time due to faster rate of immunity reduction compared to long-acting vaccines. Hence, it caused more population losses from the impact of the first virus introduction than scenario 4 in which dogs were more “well prepared”. Even after the use of long-acting vaccines, the number of dog population in scenario 6 continued to be approx. 6% lower than scenario 4 throughout the simulation period. Because the birth rate was constant and cannot increase the population size in scenario 6 fast enough to be equal to scenario 4. Moreover, higher population in scenario 4 due to high immunized animals at the beginning promoted more number of susceptible puppies to come into contact with infectious dogs. However, when relatively compared the number of infectious dogs with the total population throughout the simulation period, it was shown that both scenarios generated approx. 0.1 infectious dogs per population of 100 dogs. This explanation could also be applied to the difference in the mean number of cases between scenario 4 at 70% vc and scenario 6 at 70% vc as well. Therefore, the conclusion could be deduced by focussing on the costs in this probabilities of reintroduction because of relatively comparable number of cases.

It is essential to take the likelihood of reintroduction into account not only for gaining insights on the outcomes in different disease situation but also on the influence of the preventive vaccination on the cost-effectiveness. Because in some cases, especially in the once-in-3-year reintroduction scenario, when the number of cases averted was really low but it is still necessary to apply preventive vaccination to avoid the excessive public costs of PET. This could cause extremely high number of the costs effectiveness ratios due to the great different between number of case averted and existing costs mainly from preventive vaccination. The incremental cost-effectiveness ratio (ICER) should be taken into account in this cases. It is measured by the differences between total costs of alternative and the baseline (with PET), divided by the effectiveness of the alternative and the baseline (with PET). Therefore, the mean number of ICERs in humans for this probability of introduction were as followed;

scenario 6 equalled -328 at 50% vc (90% CI; 11,663 – (-148)) and -291 at 70% vc (90% CI; 14,445 – (-418)) and scenario 4 equalled -283 at 50% vc (90% CI; 12,737 – (-244)) and -260 at 70% vc (90% CI; 16,702 – (-423)). The mean negative numbers of ICER mean the considered strategy generated more costs per one additional human case averted compared to the baseline. Scenario 6 showed to be more certain on the outcomes than scenario 4 due to narrower range of ICER. Even though, scenario 6 generated more on total costs per case averted than scenario 4. Therefore, the conclusion on the most cost-effective scenario is still the same but provided more reasonable comparison on the actual cost-effectiveness ratio related to the costs in the baseline.

The results from the most cost-effective scenario when accounted for the reintroduction, which was scenario 6 at 70% vc, could be extrapolated to the island level for future resource estimation. The calculation was done based on the total vaccination costs equal to 3.55 USD/dog for short-acting vaccine and 4.16 USD/dog for long-acting vaccine. In the island with approx. 200,000 dogs, the vaccination costs for 70% vc in this campaign were estimated to be approx. 4,216,251 USD in 10 years (421,625 USD per year). It was 32 % higher in the vaccination costs compared to the current campaign in the island (from 285,543 USD/year to 421,625 USD/year). For a decision maker this would be quite a lot of money to invest at the first. However, scenario 6 at 70%vc provided more benefits in long term disease control by a reduction of public costs on PET for approx. 94% (from 386,170 USD/year (Wera et al., 2013) to 21,774 USD/year) from the current campaign. Therefore, using scenario 6 (70%vc) instead of the current campaign, the government in the island could save up approx. 364,396 USD/year for the public costs of PET. This amount of money could be transferred to support the vaccination campaign in dogs to improve the campaign in the long run as well. Thus, in overall budget allocation, the government would not lose money through the vaccination campaign and would still be able to efficiently control the disease in human by using scenario 6 at 70%vc. The benefit of adding the long-acting vaccine in scenario 6 was not only limited at 70%vc but also at 50%vc which is the current vc as well. The scenario 6 at 50%vc costed approx. 11% higher vaccination costs but provided 73% or 196,165 USD/year lower in the public cost of PET.

There were differences on the conclusion of the feasible and cost-effective strategies from the model with a single introduction and the model with reintroductions, which were the differences between scenario 4 and 6. However, the findings in both deterministic and stochastic model suggested that if we focus on the effectiveness alone, 70% vc is the most effective vc regardless of scenario used. It should be aware that the risk of reintroduction is uncertain so scenario 4 at 70% vc is more certain and preferable strategy to control the disease in every kind of situation with or without reintroductions. In case we have limited resources, scenario 6 could be used instead of scenario 4 due to comparable range of the cost-effectiveness ratios.

The study of Wera et al. (2016c) and Shim et al. (2009) used the disability-adjusted life year (DALY) in order to calculate the cost-effectiveness for each vaccination scenario. The DALY was not considered here in this study due to the fact that rabies causes rapid clinical signs with almost 100% fatal, therefore, the effect of clinical rabies for human morbidity was assumed to be minimal as suggested by Fèvre et al. (1999). Moreover, this study only focuses on the impact of vaccination campaign on the human cases not directly on the impact of the campaign on the humans' quality of life.

There is another reason that might affect the number of infectious animals in this model to be different from the field data as suggested by (Wera et al., 2016b). It is the concern on other control measures for controlling the disease during the outbreak. Because people in the community are aware of this disease and will not ignore the existence of suspected rabid dogs in their community during the outbreak. The killing of suspected animals is the common practice as showed in Africa from the study Hampson et al. (2009) and Fitzpatrick et al. (2014). Therefore, the probability of the susceptible dogs to come into contact with rabid dogs can be lower, which could subsequently reduce the number of exposed and infectious dogs in the next time steps. The movement restriction regulated by Manggarai Regency law number 6, 2003 could also lower the number of dogs being introduced into each area during the outbreak. However, there are no official check points so the chance of the dog movement especially the exposed dogs between the village still exists with probably lower number due to awareness of the outbreak. This probability could also affect the number of infectious dogs and the frequency of the reintroduction. Therefore, these measures should be taken into account for further development on the model estimation of dog and human cases.

The variation in the stochastic simulation only took the variation for newly introduced animals and the likelihood of the virus reintroduction into account. However, other parameters should be incorporated to account for the variability in them as well in order to capture the reality, for example, the probability of dogs being bitten by a rabid dog, birth and death rates according to puppy season and the consumption during traditional ceremonies. Some parameters in the epidemiological model can be obtained from fitting the field data on rabid-dog and exposed-human case reports, i.e., transmission coefficient and migratory rate of susceptible dogs as done by Zinntags et al. (2009) in Chad and Zhang et al. (2012) in China.

The time delayed of disease detection was not considered in the model. It is due to the fact that the presence of the virus did not affect the frequency of the preventive vaccination campaign. It could affect the vaccination costs when the variation of vc and the type of vaccines were applied regarding the presence of the virus. It is expected that it would not change the conclusion and the ranking of the most cost-effective vaccination strategies. However, improvements for disease surveillance and data collection in the island are still needed for the alteration of vaccine types, regarding the presence of the virus, to reduce the costs as suggested by the results from this study. The suggestion for this problem during the development of the surveillance and data collection systems is the sharing of information between veterinary and public health sector. For example, every year before the vaccination campaign the veterinary authorities could collect the data of human rabies cases or the number of people who received PET from public health sector to indirectly evaluate the disease status in domestic dogs and change the strategy accordingly. Moreover, better field data on the disease dynamics can accommodate the estimation on the performance of the selected vaccination strategies in the field. It can also be used to examine how well the estimated model parameters fit the data to improve the existing model.

According to the results, it was shown that costs of the vaccine types also influenced the conclusion on the most cost-effective strategies. Apart from the vc, these vaccine costs are considered to be one of the factors that could be controlled. Therefore, further suggestion is the collaboration in the region for development of domestic vaccine production. The goal is to provide higher quality vaccines with longer immunity to use within the region, and to reduce the price of vaccine through reduction in logistic costs. Because the price of vaccine accounts for at least 18% of the total vaccination costs (Wera et al,. 2013). It is also suggested by Ceballos et al. (2014) that it is the priority for the developing countries to reinenforce high quality vaccine production with subsidised prices. This should be done in the regional level as a collaborative commitment to eliminate rabies from the region. However, it probably takes time to develop the collaboration on vaccine production in the regional level. Thus, the preliminary suggestion would be the concentration of the resource allocation to veterinary sectors. Because higher quality of vaccines and vaccination coverage promoted higher effectiveness in controlling the disease in humans. For example, by including the long-acting vaccines in scenario 6 at 50% vc, it was shown that it increased the vaccination costs for 11% (approx.716 USD) from the current campaign (Annual short-acting vaccine at 50%vc) but the public health sector could save up 89% (approx. 11,709 USD) from the public costs of PET in 10 years at a village level. This amount of money that could be saved could also be shared to further improvement of the vaccination campaign for the veterinary sector. Therefore, sharing of the resources for rabies control from public health sector to veterinary sector is possible when we start to improve the performance of vaccination campaign in which the public costs of PET could be saved and shared in the long run.

6. Conclusion

Model simulation is an essential tool for providing insights on the impact of various disease control strategies on both epidemiological and economic perspectives. These benefits can be used as a composition for the decision maker to decide for the most suitable and feasible disease control strategies to be applied in different situations. It is also the way to support the planning of resource allocation between relevant sectors according to the 'one health' concept. This study suggests that the vaccination campaign with 70% vaccination coverage (vc), which varied between short-acting vaccine during normal situation and long-acting vaccine during an outbreak, is the most cost-effective and feasible vaccination strategies by taking the likelihood of the reintroduction into account. However, according to the field data the current vc that has been achieved, is only 50% (Wera et al., 2013 and 2015). Therefore, 50% vc for this campaign was also considered and showed to provide more positive results in reduction of cases and cost-effective ratio than the current vaccination campaign with only short-acting vaccines throughout the simulation period in the long run.

The ranking of the most cost-effective scenarios was quite robust especially the 3 most cost-effective scenarios with low differences and the variation in the outcomes of the cost-effectiveness ratios. However, the risk of reintroduction is still necessary to considered. Because the disease situation in the island is still uncertain. By taking the risk of reintroduction into account, it would be useful to use the outcomes of this study for estimation of the impacts and the resources needed to cope with the reintroduction which could be approx. 58% higher than in the situation of a single virus introduction. Thus, according to the results together with current practical limitations as well as the financial situation on Flores, the preliminary suggestion for the policy maker is switching between the vaccine types based on disease status and the likelihood of reintroduction. As the risk of reintroduction in reality is still questionable for the decision maker, the decision maker should follow the most cost-effective scenarios obtained from the results of $P = 0.019$, which was considered to be worst case scenario. However, it needs to bear in mind that changing the vaccine type is not a sustainable strategies in the long run because, with only 50%vc it took almost 10 years for the long-acting vaccine to break the transmission chain of a single introduction. Therefore, in case of reintroduction, it could be assumed that the disease would not be able to be under control in the long run at all. That is why it is still essential to improve vaccination coverage and domestic vaccine production towards long-acting vaccines for the sustainable rabies control on the island through the collaboration of relevant stakeholders.

Thus, the final conclusion according to the results from this study is to discontinue the current vaccination campaign (annual vaccination with short-acting vaccines with 50% vc) and switch from short-acting to long-acting vaccines, as a preliminary suggestion. More efforts and collaboration should be put in place to increase vaccination coverage in dogs to be as high as 70% in the future. Because the amount of money from the reduction in the public costs of PET due to the improvement of vaccination could also be shared to veterinary sector for further development in vaccination campaign in the long run. Finally, the risk of reintroduction cannot be ignored and is needed for implementing disease control policy as the uncertainty of the disease situation in the island still exists.

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9. Appendix

Appendix 1: The composition for costs of post-exposure treatment (PET) (Wera et al., 2013)

Variable	Value (US$)	Unit (USD)	Description
pr_{ri}	0.01	dimensionless	Proportion of human receiving immunoglobulin
p_{ri}	171.37	per dose	Price of immunoglobulin
c_{ns}	0.22	per patient	Costs of needle, syringe and swab
c_{vac}	27.64	per dose	Costs of vaccine
c_{ns}	0.22	per patient	Costs of needle, syringe and swab
c_{p}	5.53	per patient	Cost for physician
c_{wt}	0.06	per 30 litre per patient	Cost of water
c_{so}	0.22	per patient	Cost of soap
c_{an}	0.33	per patient	Cost of antiseptic
n_{dpet}	4.00	doses per patient	Number of doses of vaccine for post-exposure treatment
n_{vi}	3.00	visits	Number of visits for receiving vaccination post-exposure treatment

Appendix 2: The Visual Basic code for automating the changes in vc and types of vaccines during the vaccination campaign during stochastic simulation.

```
Attribute VB_Name = "Reintroduction"
Option Explicit
Sub Reintro()

    'Defined the variables that were needed to use in this module
    'I = number of infectious dogs
    'VC = Vaccination coverage
    'Counter = Counter for the number of days
    Dim I As Double
    Dim VC As Double
    Dim counter As Integer
    Dim counterI As Integer

'-----------------------------------------------------------------------
'The changes of vaccination coverage for short- and long-acting vaccine
with 50, 70 and 50 vc

    Application.ScreenUpdating = False

    Worksheets("SEIVR_S1-50to70to50").Activate
    Range("F50").Select

    Do Until ActiveCell.Value = ""
        I = ActiveCell.Value
        If I < 0.1 Then
            counter = counter + 1
        Else
            counter = 0

        End If

            If I >= 0.1 And counterI < 25 Then
            VC = 0.7

        ElseIf I < 0.1 And counter > 25 Then
                VC = 0.5

        ElseIf I < 0.1 And counter = 25 Then
                VC = 0.5

        ElseIf I < 0.1 And counter < 25 Then
                VC = 0.7

        Else

        End If

        ActiveCell.Offset(1, 27).Value = VC
        ActiveCell.Offset(1, 0).Select

    Loop

'-----------------------------------------------------------------------
```

```
'The changes between Short-(After the outbreak)- and Long (During the
outbreak)-acting vaccines.

  Worksheets("SEIVR_SLS1-50").Activate
    Range("F50").Select

    Do Until ActiveCell.Value = ""
        I = ActiveCell.Value
        If I < 0.1 Then
            counter = counter + 1
        Else
            counter = 0

        End If

        If I >= 0.1 And counter < 25 Then
        ActiveCell.Offset(1, 5).FormulaR1C1 = "=(R[-1]C-(R22C2*R[-
1]C))*(1-R13C2-R[-1]C[3])"
        ActiveCell.Offset(1, 6).FormulaR1C1 = "=(R[-1]C+(R[-1]C[-
2]*R21C2)-(R18C2*R[-1]C))*(1-R13C2-R[-1]C[2])"
        ActiveCell.Offset(1, 12).FormulaR1C1 = "=(R24C2*RC[-
2])/((1+R26C2)^(RC[-17]))"


        ElseIf I < 0.1 And counter >= 25 Then
        ActiveCell.Offset(1, 5).FormulaR1C1 = "=(R[-1]C+(R[-1]C[-
1]*R21C2)-(R22C2*R[-1]C))*(1-R13C2-R[-1]C[3])"
        ActiveCell.Offset(1, 6).FormulaR1C1 = "=(R[-1]C-(R18C2*R[-
1]C))*(1-R13C2-R[-1]C[2])"
        ActiveCell.Offset(1, 12).FormulaR1C1 = "=(R23C2*RC[-
2])/((1+R26C2)^(RC[-17]))"

        ElseIf I < 0.1 And counter < 25 Then
        ActiveCell.Offset(1, 5).FormulaR1C1 = "=(R[-1]C-(R22C2*R[-
1]C))*(1-R13C2-R[-1]C[3])"
        ActiveCell.Offset(1, 6).FormulaR1C1 = "=(R[-1]C+(R[-1]C[-
2]*R21C2)-(R18C2*R[-1]C))*(1-R13C2-R[-1]C[2])"
        ActiveCell.Offset(1, 12).FormulaR1C1 = "=(R24C2*RC[-
2])/((1+R26C2)^(RC[-17]))"

        Else

        End If

        ActiveCell.Offset(1, 0).Select
    Loop

'-----------------------------------------------------------------------

End Sub
```

Appendix 3: The yearly costs for vaccination campaign, public costs of PET and total cost for preventing the disease in human in scenario 2 (Annual vaccination with short-acting vaccines) from deterministic model categorized by vaccination coverage.

Time (Year)	Total Costs of vaccination (USD)						Total Public Costs of PET (USD)							Total Costs (USD)					
	50%	**55%**	**60%**	**65%**	**70%**	**50-70-50%**	**0%**	**50%**	**55%**	**60%**	**65%**	**70%**	**50-70-50%**	**50%**	**55%**	**60%**	**65%**	**70%**	**50-70-50%**
1	709	780	851	922	993	709	302	204	196	189	181	174	204	914	977	1,040	1,103	1,167	914
2	683	751	819	887	955	1,229	3,442	820	642	505	399	317	451	1,502	1,393	1,324	1,286	1,273	1,680
3	650	715	780	845	910	1,170	226	1,480	932	557	326	189	283	2,130	1,648	1,337	1,171	1,099	1,453
4	610	681	743	805	866	1,170	130	1,828	1,246	603	263	111	167	2,437	1,927	1,346	1,068	977	1,337
5	570	644	708	766	825	1,170	2,580	1,620	1,485	647	212	65	98	2,190	2,130	1,355	978	890	1,268
6	552	609	674	730	786	1,170	730	1,637	1,510	687	171	38	57	2,188	2,119	1,362	901	824	1,227
7	522	580	642	695	748	1,170	56	1,528	1,436	721	138	22	33	2,050	2,016	1,363	833	770	1,203
8	493	553	611	662	**713***	1,170	1,277	1,369	1,367	747	112	**7***	19	1,861	1,919	1,358	773	**720***	1,189
9	476	526	582	630	679	**1,169***	1,600	1,407	1,302	763	90	0	**6***	1,883	1,828	1,345	720	679	**1,175***
10	447	501	555	600	646	462	40	1,261	1,240	770	73	0	0	1,707	1,741	1,325	673	646	462
Total	**5,711**	**6,341**	**6,965**	**7,543**	**8,122**	**10,587**	**10,383**	**13,153**	**11,357**	**6,188**	**1,964**	**924**	**1,320**	**18,863**	**17,698**	**13,154**	**9,507**	**9,046**	**11,907**
min	**447**	**501**	**555**	**600**	**646**	**462**	**40**	**204**	**196**	**189**	**73**	**0**	**0**	**914**	**977**	**1,040**	**673**	**646**	**462**
max	**709**	**780**	**851**	**922**	**993**	**1,229**	**3,442**	**1,828**	**1,510**	**770**	**399**	**317**	**451**	**2,437**	**2,130**	**1,363**	**1,286**	**1,273**	**1,680**

* The point of time where the disease had started to be under control (the number of infectious dogs was lower than 0.1 for 26 consecutive weeks)

Appendix 4: The yearly costs for vaccination campaign, public costs of PET and total costs for preventing the disease in human in scenario 3 (Biannual vaccination with short-acting vaccines) from deterministic model categorized by vaccination coverage.

Time (Year)	Total Costs of vaccination campaign (USD)						Total Public Costs of PET (USD)							Total Costs (USD)					
	50%	**55%**	**60%**	**65%**	**70%**	**50-70-50%**	**0%**	**50%**	**55%**	**60%**	**65%**	**70%**	**50-70-50%**	**50%**	**55%**	**60%**	**65%**	**70%**	**50-70-50%**
1	1,417	1,559	1,700	1,842	1,984	1,417	302	118	109	101	94	88	118	1,535	1,668	1,801	1,936	2,071	1,535
2	1,348	1,483	1,618	**1,752***	**1,887***	**1,887***	3,442	114	79	53	**35***	**25***	**73***	1,462	1,561	1,671	**1,788***	**1,912***	**1,960***
3	1,284	**1,412***	**1,541***	1,669	1,797	1,544	226	31	**8***	**2***	0	0	0	1,315	**1,420***	**1,543***	1,669	1,797	1,544
4	**1,223***	1,345	1,467	1,589	1,712	1,223	130	**3***	0	0	0	0	0	**1,226***	1,345	1,467	1,589	1,712	1,223
5	1,164	1,281	1,397	1,514	1,630	1,164	2,580	0	0	0	0	0	0	1,164	1,281	1,397	1,514	1,630	1,164
6	1,109	1,220	1,331	1,442	1,553	1,109	730	0	0	0	0	0	0	1,109	1,220	1,331	1,442	1,553	1,109
7	1,056	1,162	1,267	1,373	1,479	1,056	56	0	0	0	0	0	0	1,056	1,162	1,267	1,373	1,479	1,056
8	1,006	1,106	1,207	1,308	1,408	1,006	1,277	0	0	0	0	0	0	1,006	1,106	1,207	1,308	1,408	1,006
9	958	1,054	1,150	1,245	1,341	958	1,600	0	0	0	0	0	0	958	1,054	1,150	1,245	1,341	958
10	912	1,004	1,095	1,186	1,277	912	40	0	0	0	0	0	0	912	1,004	1,095	1,186	1,277	912
Total	**11,477**	**12,625**	**13,772**	**14,920**	**16,068**	**12,276**	**10,383**	**267**	**196**	**156**	**129**	**112**	**191**	**11,744**	**12,821**	**13,928**	**15,049**	**16,180**	**12,467**
min	**912**	**1,004**	**1,095**	**1,186**	**1,277**	**912**	**40**	**0**	**0**	**0**	**0**	**0**	**0**	**912**	**1,004**	**1,095**	**1,186**	**1,277**	**912**
max	**1,417**	**1,559**	**1,700**	**1,842**	**1,984**	**1,887**	**3,442**	**118**	**109**	**101**	**94**	**88**	**118**	**1,535**	**1,668**	**1,801**	**1,936**	**2,071**	**1,960**

* The point of time where the disease had started to be under control (the number of infectious dogs was lower than 0.1 for 26 consecutive weeks)

Appendix 5: The yearly costs for vaccination campaign, public costs of PET and total costs for preventing the disease in human in scenario 4 (Annual vaccination with long-acting vaccine) from deterministic model categorized by vaccination coverage.

Time (Year)	Total Costs of vaccination campaign (USD)						Total Public Costs of PET (USD)							Total Costs (USD)					
	50%	**55%**	**60%**	**65%**	**70%**	**50-70-50%**	**0%**	**50%**	**55%**	**60%**	**65%**	**70%**	**50-70-50%**	**50%**	**55%**	**60%**	**65%**	**70%**	**50-70-50%**
1	831	914	997	1,081	1,164	831	302	170	161	152	143	135	170	1,002	1,075	1,149	1,224	1,299	1,002
2	800	880	960	1,040	1,119	1,120	3,442	360	268	202	154	119	212	1,160	1,148	1,162	1,194	1,239	1,332
3	762	838	914	990	**1,066***	**1,066***	226	237	121	61	31	**12***	**30***	999	958	975	1,021	**1,078***	**1,096***
4	725	798	**870***	**943***	1,015	1,015	130	147	51	**12***	**2***	0	0	873	849	**882***	**945***	1,015	1,015
5	691	760	829	898	967	691	2,580	92	22	0	0	0	0	783	782	829	898	967	691
6	658	**723***	789	855	921	658	730	59	**5***	0	0	0	0	716	**728***	789	855	921	658
7	626	689	752	814	877	626	56	38	0	0	0	0	0	664	689	752	814	877	626
8	597	656	716	775	835	597	1,277	24	0	0	0	0	0	621	656	716	775	835	597
9	568	625	682	739	795	568	1,600	16	0	0	0	0	0	584	625	682	739	795	568
10	**541***	595	649	703	757	541	40	**5***	0	0	0	0	0	**546***	595	649	703	757	541
Total	**6,798**	**7,478**	**8,157**	**8,837**	**9,517**	**7,712**	**10,383**	**1,150**	**628**	**427**	**331**	**266**	**413**	**7,948**	**8,105**	**8,584**	**9,168**	**9,783**	**8,125**
min	**541**	**595**	**649**	**703**	**757**	**541**	**40**	**5**	**0**	**0**	**0**	**0**	**0**	**546**	**595**	**649**	**703**	**757**	**541**
max	**831**	**914**	**997**	**1,081**	**1,164**	**1,120**	**3,442**	**360**	**268**	**202**	**154**	**135**	**212**	**1,160**	**1,148**	**1,162**	**1,224**	**1,299**	**1,332**

* The point of time where the disease had started to be under control (the number of infectious dogs was lower than 0.1 for 26 consecutive weeks)

Appendix 6: The yearly costs for vaccination campaign, public costs of PET and total cost for preventing the disease in human in scenario 5 (Once-every-2-year vaccination with long-acting vaccines) from deterministic model categorized by vaccination coverage.

Time (Year)	Total Costs of vaccination campaign (USD)					Total Public Costs of PET (USD)						Total Costs (USD)				
	50%	**55%**	**60%**	**65%**	**70%**	**0%**	**50%**	**55%**	**60%**	**65%**	**70%**	**50%**	**55%**	**60%**	**65%**	**70%**
1	831	914	997	1,081	1,164	302	170	161	152	143	135	1,002	1,075	1,149	1,224	1,299
2	0	0	0	0	0	3,442	1,851	1,596	1,358	1,145	958	1,851	1,596	1,358	1,145	958
3	658	760	862	959	1,049	226	1,276	1,294	1,249	1,149	1,214	1,934	2,054	2,111	2,108	2,263
4	0	0	0	0	0	130	176	306	545	854	1,490	176	306	545	854	1,490
5	691	760	827	882	890	2,580	585	849	1,012	1,027	1,111	1,276	1,609	1,839	1,909	2,002
6	0	0	0	0	0	730	2,135	2,217	2,041	1,125	843	2,135	2,217	2,041	1,125	843
7	465	507	583	767	861	56	677	581	686	970	1,023	1,143	1,088	1,268	1,737	1,883
8	0	0	0	0	0	1,277	78	77	62	341	1,217	78	77	62	341	1,217
9	568	625	682	739	734	1,600	255	207	137	624	916	824	832	819	1,363	1,650
10	0	0	0	0	0	40	1,216	831	442	1,324	700	1,216	831	442	1,324	700
Total	**3,214**	**3,567**	**3,951**	**4,427**	**4,697**	**10,383**	**8,421**	**8,118**	**7,683**	**8,702**	**9,607**	**11,635**	**11,685**	**11,634**	**13,129**	**14,305**
Min	**0**	**0**	**0**	**0**	**0**	**40**	**78**	**77**	**62**	**143**	**135**	**78**	**77**	**62**	**341**	**700**
Max	**831**	**914**	**997**	**1,081**	**1,164**	**3,442**	**2,135**	**2,217**	**2,041**	**1,324**	**1,490**	**2,135**	**2,217**	**2,111**	**2,108**	**2,263**

Appendix 7: The yearly costs for vaccination campaign, public costs of PET and total cost for preventing the disease in human in scenario 6 (combination of annual short- and long-acting vaccines) from deterministic model categorized by vaccination coverage.

Time (Year)	Total Costs of vaccination campaign (USD)					Total Public Costs of PET (USD)						Total Costs (USD)				
	50%	55%	60%	65%	70%	0%	50%	55%	60%	65%	70%	50%	55%	60%	65%	70%
1	709	780	851	922	993	302	204	196	189	181	174	914	977	1,040	1,103	1,167
2	800	880	960	1,040	1,120	3,442	617	479	376	298	239	1,417	1,359	1,335	1,338	1,359
3	762	835	914	990	**1,062***	226	395	193	109	56	**22***	1,157	1,029	1,023	1,046	**1,085***
4	725	798	**870***	**943***	862	130	155	45	**12***	**2***	0	880	842	**882***	**945***	862
5	691	**760***	707	766	824	2,580	53	**6***	0	0	0	743	**765***	707	766	824
6	658	617	673	730	785	730	18	0	0	0	0	676	617	673	730	785
7	**626***	588	641	695	748	56	**2***	0	0	0	0	**628***	588	641	695	748
8	509	560	611	662	713	1,277	0	0	0	0	0	509	560	611	662	713
9	485	533	582	630	679	1,600	0	0	0	0	0	485	533	582	630	679
10	462	508	554	600	646	40	0	0	0	0	0	462	508	554	600	646
Total	**6,426**	**6,859**	**7,364**	**7,977**	**8,433**	**10,383**	**1,444**	**919**	**686**	**538**	**435**	**7,870**	**7,778**	**8,049**	**8,515**	**8,868**
Min	**462**	**508**	**554**	**600**	**646**	**40**	**0**	**0**	**0**	**0**	**0**	**462**	**508**	**554**	**600**	**646**
Max	**800**	**880**	**960**	**1,040**	**1,120**	**3,442**	**617**	**479**	**376**	**298**	**239**	**1,417**	**1,359**	**1,335**	**1,338**	**1,359**

* The point of time where the disease had started to be under control (the number of infectious dogs was lower than 0.1 for 26 consecutive weeks)

Appendix 8: The simulated numbers for the cost-effectiveness of vaccination strategies in humans with the support of PET from the stochastic model with probability of virus introduction in once every year (P = 0.019)

Cost-Effectiveness for Human Health aspect (without PET)										
Scenario	**Vaccination Coverage**	**Number of human cases**			**Number of human cases averted**			**Cost-effectiveness Ratio (USD/Averted human case)**		
		Mean	**Percentile**		**Mean**	**Percentile**		**Mean**	**Percentile**	
			5	**95**		**5**	**95**		**5**	**95**
1 Baseline	**0%**	**63.46**	**47.56**	**70.83**	**0**	**0**	**0**	**0**	**0**	**0**
2	**70%**	21.25	6.97	42.76	42.14	22.12	56.51	**208.72**	142.06	353.38
Annual short-acting vaccines	**50-70-50%**	**26.36**	7.34	55.18	**37.07**	10.99	54.70	273.33	139.94	612.20
4	**50%**	22.93	10.32	37.34	40.49	26.26	52.12	175.86	128.37	257.20
Annual long-acting Vaccines	**70%**	**4.01**	1.76	6.75	**59.66**	44.56	66.52	165.15	143.77	211.49
	50-70-50%	5.40	1.82	10.89	58.34	42.80	65.27	**158.03**	136.95	203.76
6	**50%**	12.13	4.31	24.41	51.52	37.05	59.90	**132.35**	110.14	175.00
Annual short-, long and short-acting vaccines	**70%**	**3.25**	1.08	6.52	**60.44**	45.51	67.25	155.05	135.59	200.48

Appendix 9: The mean yearly costs for vaccination campaign from the stochastic model with probability of virus reintroduction in once every year (P = 0.019)

Time (Year)	Total costs of vaccination campaign (USD)																				
	Scenario 2 (Annual vaccination with short-acting vaccines)						Scenario 4 (Annual vaccination with long-acting Vaccines)									Scenario 6 (Annual short-, long and short-acting vaccines)					
	70%			50-70-50%			50%			70%			50-70-50%			50%			70%		
	Mean	Percentile		Mean	Percentile		Mean	Percentile		Mean	Percentile		Mean	Percentile		Mean	Percentile		Mean	Percentile	
		5	95		5	95		5	95		5	95		5	95		5	95		5	95
1	993	993	993	709	709	709	831	831	831	1,164	1,164	1,164	831	831	831	709	709	709	993	993	993
2	960	948	969	850	678	967	803	789	811	1,126	1,116	1,135	997	797	1,133	755	678	809	1,059	954	1,132
3	913	902	922	873	647	921	763	749	771	1,072	1,063	1,081	1,027	763	1,079	743	647	769	1,046	911	1,077
4	869	858	878	850	623	877	726	714	734	1,021	1,012	1,030	1,002	732	1,029	715	624	732	1,002	870	1,025
5	827	816	835	818	790	835	690	678	699	973	964	981	960	958	981	687	674	697	944	825	976
6	787	774	795	782	756	795	657	645	665	926	919	934	913	909	934	657	648	664	896	784	930
7	748	729	757	745	717	757	625	614	634	882	875	890	870	861	890	626	619	632	854	748	886
8	711	687	721	708	681	721	595	582	603	840	833	847	832	829	847	597	591	602	814	713	843
9	676	651	687	673	647	687	567	554	574	800	794	807	789	785	807	569	562	574	774	678	803
10	641	616	654	640	614	654	539	526	547	762	756	768	748	546	767	541	535	546	735	646	764
Total	**8,126**	**7,973**	**8,212**	**7,650**	**6,863**	**7,924**	**6,796**	**6,682**	**6,869**	**9,565**	**9,495**	**9,637**	**8,969**	**8,014**	**9,299**	**6,600**	**6,288**	**6,734**	**9,117**	**8,122**	**9,430**

Appendix 10: The mean yearly costs for total public costs of PET from the stochastic model with probability of virus reintroduction in once every year (P = 0.019)

Time (Year)	Total Public Costs of PET (USD)																							
	Scenario 1 Baseline			Scenario 2 (Annual vaccination with short-acting vaccines)						Scenario 4 (Annual vaccination with long-acting Vaccines)									Scenario 6 (Annual short-, long and short-acting vaccines)					
				70%			50-70-50%			50%			70%			50-70-50%			50%			70%		
	Mean	Percentile		Mean	Percentile		Mean	Percentile		Mean	Percentile		Mean	Percentile		Mean	Percentile		Mean	Percentile		Mean	Percentile	
		5	95		5	95		5	95		5	95		5	95		5	95		5	95		5	95
1	269	0	1,223	91	0	322	119	0	424	99	0	346	72	0	255	99	0	346	117	0	415	87	0	305
2	2,340	0	4,515	290	0	784	460	0	1,360	353	0	927	162	0	414	272	0	752	489	0	1,351	215	0	576
3	2,197	0	4,246	452	0	1,020	752	0	2,242	569	0	1,184	172	0	397	289	0	796	732	0	1,982	189	0	540
4	2,865	811	4,127	587	69	1,220	891	78	2,502	734	105	1,357	165	8	367	245	21	662	688	81	1,955	132	2	415
5	2,243	845	3,836	707	149	1,411	959	160	2,337	855	240	1,483	157	10	370	207	24	500	550	118	1,407	103	0	291
6	2,669	1,044	3,741	809	216	1,616	1,010	227	2,296	931	370	1,563	147	12	335	179	18	426	433	133	908	91	0	253
7	2,138	862	3,497	901	289	1,879	1,062	308	2,248	979	448	1,590	138	6	326	161	7	384	359	116	665	86	0	253
8	2,343	926	3,381	982	333	1,976	1,111	361	2,172	1,006	511	1,554	134	8	306	151	11	340	317	125	557	86	0	251
9	2,020	791	3,187	1,046	399	2,030	1,147	405	2,108	1,012	548	1,565	127	11	291	140	14	325	288	114	496	81	0	238
10	2,040	816	3,057	1,096	423	1,987	1,174	439	2,015	1,009	566	1,504	122	8	279	137	13	310	270	109	461	80	0	230
Total	**21,123**	**6,095**	**34,810**	**6,961**	**1,879**	**14,244**	**8,685**	**1,978**	**19,704**	**7,547**	**2,788**	**13,073**	**1,397**	**63**	**3,340**	**1,879**	**109**	**4,842**	**4,244**	**796**	**10,197**	**1,150**	**2**	**3,352**

Appendix 11: The simulated numbers for the cost-effectiveness of vaccination strategies in humans without the support of PET from the stochastic model with probability of virus reintroduction in once every 3 years (P = 0.006)

Cost-Effectiveness for Human Health aspect (without PET)												
Scenario	**Vaccination Coverage**	**Number of human cases**			**Number of human cases averted**			**Cost-effectiveness Ratio (USD/Averted human cases)**				
		Mean	**Percentile 5**	**Percentile 95**	**Mean**	**Percentile 5**	**Percentile 95**	**Mean**	**Median**	**Percentile 5**	**Percentile 95**
1 Baseline	**0%**	**48.35**	**0.90**	**67.91**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
2 Annual short-acting vaccines	**70%**	11.30	0.20	34.55	35.83	0.24	59.08	**2,773**	214	138	668
	50-70-50%	**21.37**	0.22	59.78	**26.79**	0.08	54.00	2,378	264	137	1,337
4 Annual long-acting Vaccines	**50%**	14.52	0.29	34.49	32.91	0.24	52.70	2,062	196	128	572
	70%	**1.45**	0.08	3.22	**45.57**	0.29	66.07	2,342	185	145	728
	50-70-50%	4.74	0.12	18.43	42.62	0.29	64.50	2,107	173	133	659
6 annual short-, long and short-acting vaccines	**50%**	12.36	0.21	43.44	35.48	0.27	59.39	**1,694**	165	111	611
	70%	2.27	0.06	7.09	44.81	0.26	65.73	2,158	172	134	677