Cost-effectiveness of mass vaccination programs against dog rabies on Flores Island (Indonesia)

MSc thesis by	**Shanna Rijsemus**
Registration number	**900310-723-130**
Supervisor	**Dr. Ir. M.C.M. (Monique) Mourits**
Course	**BEC 80424**
Number of credits	**24 ECTS**
Period	**January 2013 – Augustus 2013**
Place	**Business Economics Group, Wageningen University**

Abstract

Background: In 1997, rabies was introduced on Flores Island, Indonesia and has been spreading since. Various control programs have been implemented based on a combination of control measures, including mass vaccination of dog rabies . Up until now, these mass vaccination programs have, however, not been successful in eliminating rabies from Flores Island. Approximately 3,500 suspected rabid dog bites and 19 human deaths due to canine rabies occur on Flores Island annually, while the costs of rabies control efforts on Flores Island have been estimated to be more than US$ 1.0 million per year.

There are different reasons for the ineffectiveness of the applied vaccination campaigns, such as a high turnover rate in the dog population, the specific dog demography and the effectiveness of the adapted vaccine itself. Further insights in these aspects are of great influence when determining the future policy to eventually control and eliminate rabies on Flores Island.

Research objective: The objective of this study is to evaluate the cost-effectiveness of different vaccination scenario's for Flores Island Indonesia to support the future decision making process regarding the control of rabies on Flores Island.

Methodology: A financial accounting approach was used to calculate the costs of mass vaccination programs. A transmission dynamics formulation was used to calculate the effectiveness of a program, reflected by the estimated immunity coverage rate through time. The critical immunity coverage necessary for the control of rabies is considered to be equal to 20%. The impact of death rate, population growth rate and the number of vaccinated dogs was taken into account in these effectiveness calculations. The relevance of the vaccination programs was evaluated by their the cost-effectiveness ratio. Three different vaccination programs were evaluated by considering different planning horizons (short = 1 year; long = 10 years). Within these three scenarios, a distinction was made for 3 types of vaccine; the local vaccine without booster with a duration of immunity of 0.775 years, the local vaccine with booster with a duration of immunity of 1.5 years and the import vaccine with a duration of immunity of 3 years.

Results: Given the current policy on Flores, where yearly vaccination is conducted, the results show that this strategy is not effective**.** Even 100% coverage rate of all dogs will not be sufficient to reach an immunity coverage of 20% or more after one year. When the local vaccine with the booster would be applied, a vaccination coverage of 75% would be required to stay above the 20% of immunity. A coverage rate of 75% appears not feasible on Flores, due to previous mentioned factors on the Island. However, a switch to the import vaccine would mean that an immunity coverage of almost 22% will be reached after a year of vaccination, when applying the vaccine at a vaccination coverage of 55%. The costs for this strategy will be $403,210 on a yearly base..

To maintain a minimal immunity coverage rate of 20% throughout the planning horizon of a year, given a vaccination coverage of 55%, the local vaccine without booster needs to be applied 2 times, the local vaccine with booster 1.3 times and the import vaccine only once. Annual campaign costs coincide with ,respectively, $397,296, $510,904 and $403,210 , resulting in cost-effectiveness ratios of, resp., $18,532, $23,911 and $18,531.

When considering a planning horizon of 10 years with at least 20% immunity, the most effective scheme based on the application of local vaccine without booster requires 65% vaccination coverage at a frequency of 20.9. Total costs are 3.7 million dollars, resulting in a cost-effectiveness ratio $185,582. For local vaccine with booster, a vaccination coverage of 55% is sufficient at an application frequency in 10 years' time of 12.63. Total costs are 4.8 million dollars, resulting in a cost-effectiveness ratio of $238,680. The import vaccine requires a vaccination coverage of 55% and a frequency of 9.23 within 10 years. Total costs are 3.7 million dollars at a cost effectiveness ratio of $184,801.

Discussion/conclusion: If Flores Island would stick to the short term planning of their vaccination campaigns and thus vaccinate only once at an annual base, the only cost-effective vaccination strategy is obtained by the use of the import vaccine at a minimum vaccination coverage of 55%. This strategy requires a large investment, since this switch in strategy (from local vaccine to import vaccine) will cost the government $204,500 extra. However, the gain will be an effective vaccination campaign reflected by an immunity coverage of at least 20%.

Looking over a long term planning horizon (10 years' time), the lowest costs are obtained in the strategies of vaccination with local vaccine without booster and import vaccine. The corresponding cost-effectiveness ratio is lower for the import vaccine than for the local vaccine without booster and therefore vaccination with import vaccine is over the long term the most cost –effective strategy.

Concluding, Flores Island should consider the replacement of its local vaccine for the import vaccine in an attempt to control rabies in dogs.

Table of contents

1. Introduction

1.1 Rabies worldwide

Rabies is a viral zoonotic disease, mostly found in canine species (19), which continues to spread worldwide. Rabies can be transmitted to humans via the saliva of infected animals, for example after a dog bite (20). The virus causes an acute, progressive encephalomyelitis in the central nervous system, which is almost always fatal. Incubation time in humans is generally a few weeks to months (21). Treatment is available in the form of vaccination of humans at risk and post-exposure treatment (PET), such as wound cleaning, immunoglobulin injection and series of vaccine injections after being bitten by a potentially infected dog. However, these measures are costly, especially the post-exposure treatment (33).

Every year, around 60,000 people worldwide die because of rabies, despite the fact that it is a vaccine-preventable disease. The most cases occur in Africa and Asia, where a poor economy prevails. Most affected cases are children under the age of 15, especially in rural areas, where rapid access of a post exposure treatment is often not possible (22).

PET is also a less cost-effective control measure of rabies in humans compared to other prevention methods like dog vaccination, as treatment of the disease in humans does not stop the spread of the virus to other humans by dogs (28). If the large amount of expenditures on PET can be (partly) prevented by vaccinating dogs against rabies, this would mean a financial gain for society, because on the long term the effects of dog vaccination will control and eventually eradicate rabies in dogs (36).

Fortunately, there are countries which are currently free of dog rabies. This accounts for the largest part of Europe, Australia and New Zealand. The success of these countries is that they have participated in rabies elimination programmes, which mainly consisted of mass canine vaccination. The only remaining threat in these dog rabies-free areas is the occurrence of rabies in bats (24). New Zealand is completely free of all types of rabies.

1.2 Rabies on Flores island

Flores is a small Island in Indonesia, south East Asia. The size of the island is 143 square kilometres (figure 1) and exists of 8 regencies. The human population size is around 1.8 million. The main sources of income are agriculture, fishing and seaweed production.

In 1997, the rabies virus was introduced on the island by a dog coming from Buton Island, Sulawesi. Hereafter the disease spread and reached most of Flores Island (5). The first cases of canine rabies on Flores Island were officially confirmed in 1998. The initial response against the disease was a total dog culling program in the affected villages in the East Flores district (1998-1999), but despite the program, rabies continued to spread to other regencies of the island. Therefore, in 2000, the Flores Island government implemented a control program based on a combination of control measures, including mass vaccination of dogs, culling of roaming dogs, placing imported dogs in quarantine, and giving pre- and post-exposure treatment to humans. In addition, complementary control measures were applied, such as dog bite investigation, diagnostic testing of suspected rabid dogs, and trace-back of human contacts with rabid dogs (35). However, until now, the program has not been successful in eliminating rabies from Flores Island. Approximately 3,500 suspected rabid dog bites and 19 human deaths due to canine rabies occur on Flores Island annually, while the costs of rabies control efforts on Flores Island have been estimated to be more than US$ 1.0 million per year.

Figure 1. Map of Flores Island (http://www.lavalontouristinfo.com/lavalon/flores.htm)

Theoretically, control and even eradication of rabies on Flores Island should be possible in the future. Mainly because Flores Island is relatively a small island and therefore it is not likely that numerous replacement dogs from potentially infected areas outside Flores will come to Flores. Thereby, the island has a considerably small dog population and therefore has a limited capability to maintain a rabies cycle(16). Flores is, however, an island with limited available financial sources. Currently the animal health authority carries out a yearly dog mass vaccination campaign with the so called 'local vaccine', which until recently has not appeared to be effective. There are different reasons for this ineffectiveness, such as a high turnover rate in the dog population, the specific dog demography and the effectiveness of the adapted vaccine itself.

Further insights in these aspects are of great influence when determining the future policy to eventually control and eliminate rabies on Flores Island.

1.3 Research objective

To gather more insight in the rabies problem to contribute to the future decision making process regarding the control of rabies on Flores, the objective of this study is to evaluate the cost effectiveness of different vaccination scenario's for Flores Island (Indonesia).

Given the previously defined objective, the following research question have been studied:

- What are the costs related to the different types of vaccination scenario's?
- Which factors have a relevant impact on the effectiveness of the applied vaccination program?
- What is the most cost effective vaccination program to control canine rabies on Flores Island, Indonesia?

2. Literature review

2.1 Flores Island and its control of rabies in humans

Between 1997 and 2012 the impact of rabies on public health on Flores Island coincided with 96 registered fatal human cases. In 2011, 3,563 inhabitants were registered to have been bitten by a suspected rabid dog. The majority (81%) of these people were treated with PET. The costs of a PET treatment was on average US$ 178 per patient (33), resulting in the total costs of PET treatment in 2011 of US$ 514,242 (see Table 1). Prevention of expenditures on PET by dog vaccination, would mean a financial gain for the Indonesian government, who pays for the PET treatments.

The remaining 19% of the people bitten by a suspected rabid animal did not undergo the PET treatment. On Flores Island there are only five regency hospitals that provide PET treatment and these hospitals might be unreachable for some individuals. These people may not have transportation, or there is no road between the village and the hospital and therefore the trip to the hospital takes too long for the PET treatment to still be effective. Because these patients are only suspected to be bitten by a rabid dog (there was no examination for the disease), not all of them have developed rabies. However, it is likely that some of these untreated people have died from rabies. Therefore, the registered number of 19 deaths due to rabies might be an underestimation of the actual number of rabies caused deaths on Flores Island.

Table 1. Number of humans bitten by rabies suspected dogs, number of PET treatments and total PET costs per year on Flores Island (33)

Year	Number of bite cases	Number of PET treatments	Total PET costs
2000	2,560	1,821	$324,138
2001	1,143	419	$74,582
2002	718	710	$126,380
2003	967	840	$149,520
2004	1,222	1,061	$188,858
2005	3,073	2,668	$474,904
2006	2,231	2,164	$385,192
2007	3,261	3,020	$537,560
2008	3,448	3,011	$535,958
2009	3,764	3,248	$578,144
2010	4,888	3,743	$666,254
2011	3,563	2,889	$514,242

2.2 Flores Island and its control of rabies in dogs

Besides PET as a control measure for rabies in humans, the government of Flores has complementary costs on control measures for rabies in dogs.

There are basically two different measures to control rabies in dogs. The first measure is by culling dogs in a rabies infected area, by eliminating the number of infected animals as well as restricting the spread by reducing the number of susceptible dogs present. The second measure is by means of mass vaccination, by reducing the susceptibility of unaffected dogs and therefore restricting any spread form affected dogs. Culling is the most costly measurement, because the value of the dog is lost and much labour is required and therefore the labour costs will be a big part of the total costs. These labour costs are also involved in mass vaccination, but the total costs are lower and the social acceptance is higher for this measurement (33).

In 2011 the registered dog population on Flores was 236,447. Since census registration is poor on Flores Island the current dog population has been estimated to be 30 percent higher (307,381 dogs)(33).

In 2011 the costs for mass vaccination were $186,930 and for culling $3,360 (33). At the time of the rabies outbreak in 1997culling was the main measure against the disease and therefore the costs were high. Since dogs are of great value for families on Flores, the culling in 1998 had a large impact on the people, resulting in public unrest. Currently mainly due to ethical issues concerning culling it is not the most preferred measure against rabies anymore.

As stated before after the introduction and spread of rabies on Flores Island in 1997, the first response of the Indonesian authorities was culling of dogs in the affected districts. Approximately 70 percent of all dogs in the affected districts were culled, nevertheless canine rabies continued to spread among Flores Island(35). Subsequently, since 2000, a yearly rabies dog vaccination program, compulsory for dog owners, has been carried out in the Ende and Manggarai regencies of Flores Island. Later, the program has also been applied to the regencies East Flores, Sikka, Nagakeo, East and West Manggarai. The number of dogs vaccinated during the vaccination program of 2012 equalled on average 53 percent (range 23-82 percent) of the total registered dog population(33).

Despite the ongoing annual dog mass vaccination program rabies is still not under control. The success of a mass vaccination program depends on three main features , 1) the coverage rate (proportion of dogs vaccinated) , 2) the dog population turn over and 3) the period of immunity induced by the vaccine.

1) Proportion of dogs vaccinated

Despite the fact that the costs of vaccination is fully paid by the government, participation rate of dog owners in the vaccination campaigns is relatively low, as is reflected by the average vaccination coverage rate. One of the underlying reasons for this is the lack of proper registration systems by the government (8); vaccination teams simply do not know where to find the dogs, moreover they cannot keep track of which dog is vaccinated and which is not (which is relevant when using a booster vaccine).

The large amount of dogs under the age of three months old (30,9% of population) is also an important reason why vaccination coverage was (27) and still is low, because it is recommended by vaccine manufacturers to not vaccinate animals younger than three months old. Furthermore, many dog owners are not able to catch their free roaming dogs, because of the timorous nature of the dogs This was also the case during dog rabies vaccination campaigns on Bali (21).

2) Dog population turnover

The way of keeping dogs on Flores Island is different from the way dogs are kept in for example Europe. In Europe dogs are mainly kept as pets and are trained to obey. They are often living in houses and are fed by their owners. On Flores, most owned dogs (96.17 %) are allowed to roam freely (27)). This means that the dogs do not sleep in the house and they have to provide their own food. The result of this free roaming and subsequently high contact rate between dogs, which facilitates the spread of a disease like rabies, is the freedom of dogs to mate, the presence of many underfed dogs and a low resilience against diseases. Furthermore, dog meat is considered a delicacy for Flores inhabitants and is eaten during particular ceremonies (33).

The above mentioned factors contribute to a high birth and death rate on Flores Island, and therefore a high population turnover. Most dogs (54.9%) die before they reach the age of one year (27).As a result, the population structure is dominated by 0-3 month of age dogs.

A high turnover means that vaccination induced immunity of the total population decreases rapidly. Due to the high population turnover of the dog population on Flores Island, the amount of vaccinated, and hence immune, dogs decreases dramatically within one year (16).

3) Vaccine induced immunity

There are different types of dog vaccines against rabies available. A distinction can be made between parenteral and oral vaccines. Parenteral vaccines are conventional vaccines provided through injection in a vein. Oral vaccines can be given by a bait, which the dog will eat and thereby the animal will be vaccinated.

Vaccination needs to be done after dogs are older than three months of age in order to be effective. Under the age of three months, the vaccination wanes very fast and an additional vaccination is needed later in life, which consequently results in higher costs. Therefore, a dog should be vaccinated after it reaches the age of 3 months (30).

Two different types of parental vaccines are available on Flores. First, the local vaccine, Rabivet Supra 92, which has the lowest cost per vaccine, but only gives immunity for 18 months. Thereby the vaccinated dog should get a boost after 6 months for the vaccine to work properly for the next 12 months (17). This results in extra costs for labour and materials. However, in practice dogs are only vaccinated once a year on Flores Island. This means that the dogs are only protected for 6 months and hereafter go 6 months without protection. The dogs who already received a vaccine in the previous year are fully protected for one year, but due to the high turnover in dog population these dogs only represent a low proportion in the population.
Second, there is also an import vaccine available, called Rabisin. Costs for this vaccine are $1.50 per dose, which is more than five times as high as the local vaccine (which costs $0.29 per dose) (33), but the import vaccine will give immunity for 3 years and does not need a boost (31).

Oral vaccination has not yet been used in mass dog vaccination campaigns, but has proven to be effective in vaccinating wildlife animals, such as skunk (28), and has a high potential for success in dogs (10). Especially on Flores, where most dogs are free roaming and dog owners have problems capturing the dogs on the moment the vaccination team arrives, the use of oral vaccination could be a consideration.

2.3 Critical Vaccination coverage

It is recommended by the World Health Organization (WHO) that – given an annual vaccination campaign with a local vaccine - 70 percent of the dog population needs to be vaccinated, in order to reduce and eventually eliminate the disease (14,23).

The effectiveness of a vaccination campaign depends on the induced immunity level within the dog population over time. This so-called immunity coverage rate depends – as indicated previously - on the proportion of dogs initially vaccinated , the vaccine specifications and the dog demographic characteristics as expressed by the population turnover rate (16). Due to the high population turnover of the dog population on Flores Island, the amount of vaccinated, and thus immune, dogs decreases dramatically within one year.

The proportion of dogs within a population that needs to be vaccinated to effectively control rabies, depends on the basic reproductive number (R_0). This is the average number of secondary infections produced by an infected individual in a susceptible host. For some infectious diseases, such as measles, R_0 is high compared to the low R_0 for rabies; viz. R_0 for measles is 7.7 (19) and R_0 for dog rabies is 1.789 in Indonesia (6). Therefore, vaccination coverage within a measles vaccination campaign needs to be higher than for rabies.

Due to the low R_0 for dog rabies, it can be stated that the critical immunity coverage (P_{crit}), necessary for the control of rabies should be roughly between 20 and 40 percent (19). In the case of rabies, 20 to 40 percent of the dog population should be immune at any time to prevent outbreaks, but short chains of transmission can still happen in the population (16). Eventually R_0 will drop under the value of 1, under which an infected animal infects less than one susceptible animal and ultimately the disease will die out.

Thus, a yearly vaccination coverage rate of 70 percent will be sufficient if the proportion of immunized dogs after 1 year will stay above the critical 20 percent. This proportion of vaccinated dogs fluctuates over time from the initial coverage rate, because in a year time vaccinated dogs will die and new susceptible dogs will be born (see Figure 2).

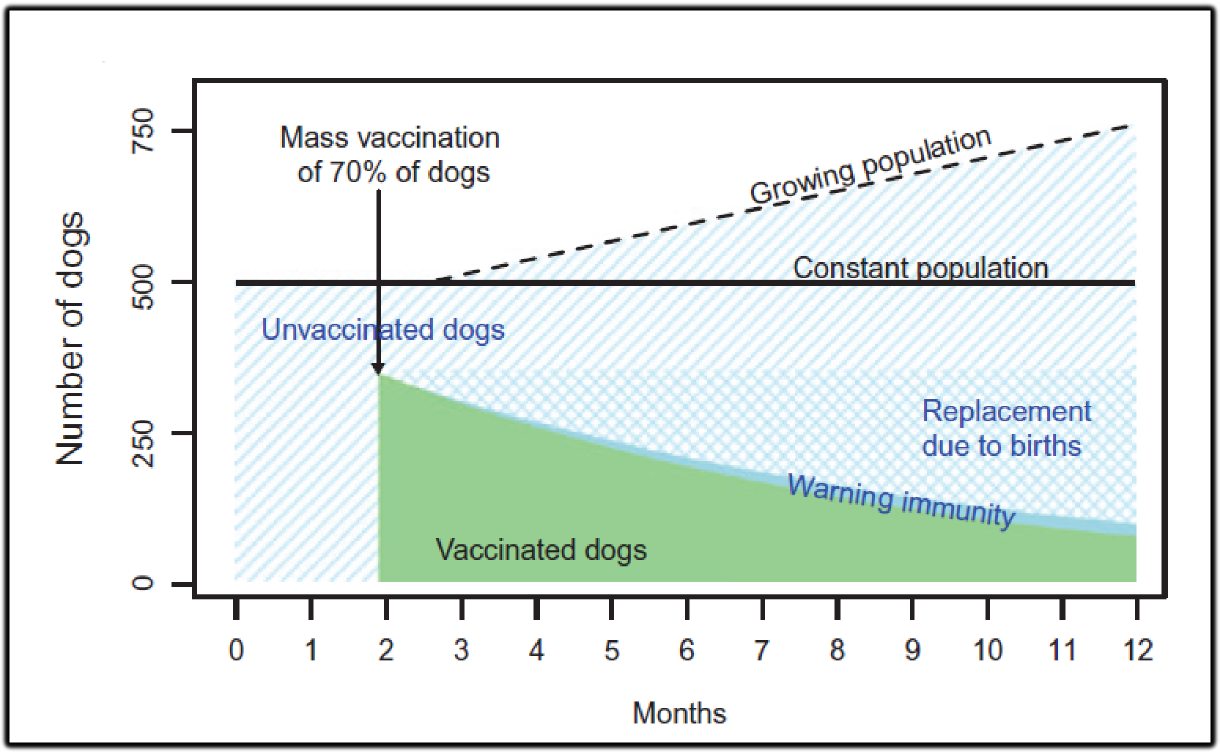

Figure 2. Change in vaccinated individuals in a stable population (solid line) and the corresponding change in a growing population (dashed line), at vaccination coverage of 70% (16)

2.4 Evaluation of mass vaccination campaigns

It is unavoidable that the implementation of vaccination campaigns is limited by budgetary constraints. Choices need to be made in order to achieve the best results, given the available amount of money. Evaluation of campaigns by cost-effectiveness analysis is important to support the task of the decision maker and rank different alternatives.

Cost-effectiveness analysis (CEA) compares the relative costs and outcomes (effects) of two or more courses of action (interventions). Cost-effectiveness analysis is distinct from cost-benefit analysis, which assigns a monetary value to the measure of effect. Cost-effectiveness analysis is often used in the field of health services, where it may be inappropriate to monetize health effects. Typically the CEA is expressed in terms of a ratio where the denominator is a gain in health from an intervention (for example years of life saved, premature births averted, sight-years gained) and the numerator is the cost associated with the health gain.

A campaign is said to be cost-effective when it produces relatively large health gains for relatively low costs, compared to other ways of achieving the same goal. By evaluating both costs and health effects of various programme options, their relative cost-effectiveness can be established. The World Health Organisation states that the most cost effective vaccination method is when ‘the largest health gain for each dollar spent on health’ has been reached (4).

The measurement of financial costs related to the implementation of campaigns is relatively straightforward. The effects of an intervention, however, are more difficult to measure. Health effects can be assessed either in terms of monetary outputs (e.g. the number of
PET treatments), and non-monetary costs (e.g. lives saved, life years gained).
Health economists use measures of health, which summarise changes in both the duration and quality of life in a single figure. Such summary measures are: Quality-Adjusted Life Years (QALYs) or Disability-Adjusted Life Years (DALY), whereby a life year is adjusted to account for changes in the quality of life as well as life expectancy. A DALY is the sum of the life years lost due to premature mortality and disability. A QALY adapts this to account for the quality of the remaining life years (e.g. mobility, pain, self-care), measured in different ways for example by letting patients score their illness. As such, cost-effectiveness studies will estimate the cost of an intervention per DALY averted.

The advantages of cost-effectiveness analysis is that it is a simple and effective method to compare different scenarios with the same objective. It can summarise the outcomes with a single quantifiable indicator and it makes the effectiveness of intervention visible. However, cost-effectiveness also has its limitations. The results of measuring effectiveness will be simplified and it analyses the effectiveness, but not the relevance of it (7).

In the case of a CEA evaluation of mass vaccination campaigns for rabies, the costs are derived from the expenditures for conducting the campaign (including the costs for vaccine and labour), while the benefits represent the monetary and non-monetary costs that are avoided when investing in the mass vaccination (see Figure 3), like the reduction in PET treatment costs and the number of human deaths due to rabid bites.

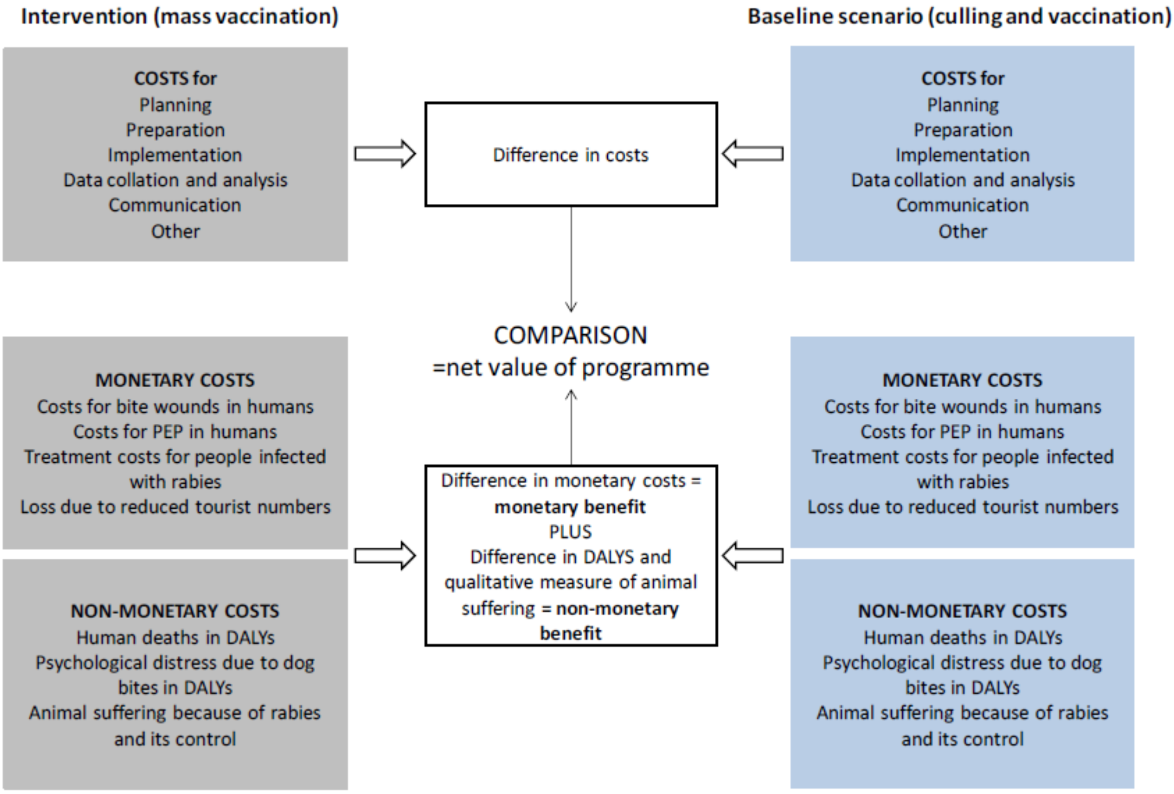

Figure 3. Overview of costs and benefits resulting from alternative rabies control scenarios (based on 14).

In the absence of data on health effects, intermediate outcome measures may provide a good indication of what a programme achieves. For example in the ex-ante evaluation of various rabies vaccination campaigns, information (even predictive) on the reduction in PET treatments over time will be lacking. Indications on the expected vaccination coverage level resulting from the campaign could serve as a good alternative outcome measure.

Once both the costs and the effectiveness of different alternative options have been measured, the cost-effectiveness ratio can be calculated. Because for each option the costs and the effects are measured in the same way and with the same units (e.g. € and DALYs), cost-effectiveness ratios can be compared.

All cost-effectiveness ratios have to be interpreted with care. For example, one option might be most cost-effective, i.e. lowest costs per health effect, but another option might be more effective despite the higher costs. Though the second cost-effectiveness ratio will be higher, it could still be a good choice if there is enough funding available, if it is more efficient and cost-effective than other alternatives or if there are other criteria for funding (e.g. equity, pro-poor, feasibility). Moreover, cost effectiveness depends on what is affordable given the available budget. For example, one could decide that interventions with a cost-effectiveness ratio smaller than income per person of a country are cost-effective in that country, while interventions with a cost-effectiveness ratio of more than 3 times the income per person of the country should not be considered cost-effective in that setting.

Various studies on the cost-effectiveness of the control of rabies have been performed for various developing countries (11,14). In an economic analysis of rabies control on Bali (14) it was assumed that mass vaccination in dogs would lead to eradication of the virus and therefore would generate a benefit in terms of monetary and non-monetary public health costs avoided. To test this hypothesis the vaccination programme was compared to a predicted baseline scenario (see Figure 3). The

baseline scenario was the scenario in which mass vaccination was carried out in the first vaccination campaign and in the intervention a target coverage of 70 percent was used.
A cost benefit analysis was conducted and an epidemiological model was available from which they could determine the costs for PET and the value in DALYs. PET was used as monetary costs and DALY as a measure of non-monetary costs. The baseline scenario was compared to the intervention for different sub-scenarios. Even though ratio's were not used in this research, avoided DALYs and the benefits saved due to PET were used as a measure for the cost effectiveness (7). This gave a proper overview of the benefit of the possible intervention.

In a research of Fitzpatrick *et al*. on cost-effectiveness of canine vaccination in rural Tanzania (11) vaccination coverage was taken in steps of 5 percent and the costs were compared with the effectiveness in terms of Years of Life Saved (YLS). The costs per year of life saved are the so called 'Incremental Costs Effectiveness Ratio' (ICER). The conclusion of the research was that annual vaccination campaigns with vaccination coverage of 70% were cost saving.

However, generalization of these described cost-effectiveness results of the situation on Flores is difficult. Many factors affect the estimates of costs and health effects and, thereby, the cost-effectiveness. Costs vary considerably due to different institutions, health care systems or prices, for example. Health effects may depend on the burden of disease, attitudes of patients or doctors' competence.

3. Material and methods

The objective of this study is to evaluate the cost effectiveness of different vaccination scenario's for Flores Island (Indonesia). First a literature review was performed to obtain insight in the different types of vaccines and the relevant variables influencing the effectiveness of a vaccine campaign. Subsequently the cost-effectiveness has been evaluated by linking the costs of the vaccine campaigns and the expected coverage rate through time.

3.1 Literature review

A literature study was performed, by searching on Google Scholar and PubMed with the specific key words: dog AND rabies, rabies AND Flores, rabies AND control, rabies AND vaccination, rabies AND effectiveness, rabies AND costs and rabies AND cost effectiveness. Information on different elements of the rabies problem, like control in humans, control in dogs, proportion of dogs vaccination, dog population turnover, available vaccines and vaccination costs, was collected to gain knowledge and information of the situation on Flores Island and other countries where dog rabies is or was a human health threat. Main findings have been presented in Chapter 2.

3.2 Cost effectiveness analysis

3.2.1 General

For cost effectiveness analysis, based on human health benefits, a "One Health" approach is necessary (20) making use of an integrated dog-human epidemiological model to estimate the impact of dog vaccination on human health. At this moment, such an integrated model is not available to reflect on the situation on Flores Island and therefor cost-effectiveness will in this study be indirectly determined by the expected immunity coverage.

The cost-effectiveness of the evaluated vaccination campaigns is evaluated by the campaign costs in relation to the resulting, expected coverage rates. A scenario is effective regarding the control of rabies when the immunity coverage over time does not drop under 20 percent, as was explained in the literature part. Given an immunity coverage of more than 20% during a time period of 10 years it is assumed that the disease is controlled and eventually eliminated.

The cost effectiveness of a scenario will be determined by the cost effectiveness ratio, which can be calculated by dividing the total costs by the percentage of coverage rate. The best case scenario will be the scenario with the lowest cost-effectiveness ratio. Since there are limitations on the amount of dogs which can be vaccinated, this so-called ratio should be interpreted according to this limitation in vaccination coverage.

3.2.2 Data

The information and data used for the analysis in this study are mainly based on a study evaluating the cost of current control of rabies on Flores Island (33). Supplementary information was provided by the author of that paper and by related scientific papers.

3.2.3 Immunity coverage resulting from a mass vaccination campaign

The coverage rate was calculated by a formula which had previously been used in a research about dog rabies transmission dynamics in Tanzania (13):

$$P_t = V_t/N_t \qquad (1)$$

P_t is the proportion of vaccination immunity coverage in a given time span t. N_t the population size at time t. V_t is the number of immune dogs following a vaccination campaign declines over time as individuals die and as vaccine induced immunity wanes. V_t can be calculated by:

$$V_t = V_0 \times e^{-(d+v)t} \tag{2}$$

Where V_0 is the amount of vaccinated dogs at time zero (depending on the coverage rate), d is death rate, $1/v$ is the duration of vaccination induced immunity and t is time in years.

$$N_t = N_0 \times e^{rt} \tag{3}$$

Population size at time t (N_t) is based on the number of dogs at time zero (N_0), rate of dog population growth (r) and time in years (t).

Dog population growth (r) and death rate (d)

The rate of dog population growth (r) on Central Java (Indonesia) was determined to be 0.144. Because this is the best and closest estimation available in scientific literature, the *r* in this research was therefore set to 0.144 in the analysis of dog rabies on Flores Island (6). Death rate (d) was estimated to be 0.45 (12).

Duration of immunity (1/v)

On Flores Island, 2 different types of vaccines against dog rabies are available, as was stated before. A local vaccine, Rabivet Supra and an imported vaccine, Rabisin. The local vaccine provides 1.5 year of immunity (after administration of a second boost injection) and the imported vaccine provides three years of immunity (no boost needed). For both types of vaccinations, the first injection should be given after the dog is older than three months of age. Because the local vaccine consists of two vaccination rounds resulting in different immunity durations, two different values for *v* correspond to the application of the local vaccine. The first vaccination of the local vaccine works for six months. After the booster, the vaccination induced immunity exists for another 12 months. So for the first six months of the local vaccine, the value of *1/v* is 0.5. And for the last 12 months of the local vaccine, the value of *1/v* is 1.

However, the current policy on Flores Island is a yearly vaccination with the local vaccine. Which means that v should be adapted. There is a death rate (d) of 0.45, which means that 45% of the dog population will be replaced every year. This means that these animals will come for their first vaccination and will only be protected for 6 months, because they do not receive a booster. The remaining 55% of the dogs will get older than 1 year. Under the optimistic assumption that these dogs have been vaccinated in the previous year and will come back for vaccination, a new (average) duration of immunity (1/v) can be determined:

45% coverage rate based on immunity for 6 months and 55% coverage rate based on immunity for 1 year; 0.45*0,5 year + 0.55*1 year = 0.775 year. Which means that the duration of immunity (1/v) for the vaccination strategy, used in practice on Flores Island is 0.775.

The duration of immunity (1/v) for the import vaccine is 3 years. Only one vaccination is required and no booster is needed. Table 2 provides an overview of the input settings used in the performed analyses.

Table 2. Input values to estimate immunity coverage

Description	Value
Death rate (d)	0.45
Rate of dog population growth (r)	0.144
Duration of immunity (1/v) (local)	
- First 6 months	0.5
- Last 12 months	1
- Average per year	0.775
Duration of immunity (1/v) (import)	3

In the analysis, distinction was between the current situation of local vaccine without booster (1/v=0.775), where there is uncertainty about dogs receiving the booster and local with booster (1/v=1.5), where it is assumed that all dogs come back for their booster.

Immunity coverage through time was calculated in Excel, for different proportions of the dog population vaccinated (vaccination coverage) in steps of 5 percent, varying from 0 until 100 percent.

3.2.4 Costs related to a mass vaccination campaign

The method used for the cost analysis was financial accounting. Costs of rabies vaccination do not solelyconsist of costs for the vaccine itself. There are more factors involved, such as labour and training for the vaccinators as well as transportation costs. Furthermore there are costs for materials, information campaigns, capital costs (which are depreciation costs for materials) and opportunity costs (which is the income the dog owner misses for not working and going to vaccination) as can be seen in table 3.

The costs for the different vaccination scenarios are calculated, according to the input values in Table 3 and following formula's:

$$CMV = C_{va} + C_{ma} + C_{vt} + C_{mt} + C_{ic} + C_{cc} \qquad (4)$$

CMV are the cost for mass vaccination. C_{va} are costs of vaccine, C_{ma} are costs for consumables, C_{vt} are costs of vaccinators, C_{mt} are costs to train temporary vaccinators, C_{ic} are costs of the information campaign and C_{cc} are the capital costs.

$$C_{va} = n_{vd} \times (p_{va} + t_{va}) \qquad (5)$$

Costs of vaccine (C_{va}) are conducted of the amount of vaccinated dogs (n_{vd}), which depends on the vaccination coverage, the price of vaccination per dose (p_{va}) and costs of transportation of the vaccine from manufacturer to each regency (t_{va}).

$$C_{ma} = n_{vd} \times (p_{sn} + p_{ib}/n_{capv} + p_{ds}) \qquad (6)$$

Costs for consumables (C_{ma}) are conducted of number of vaccinated dogs (n_{vd}), price of syringes and needles (p_{sn}), price of ice bars (p_{ib}), vaccination capacity (n_{capv}) and price of disinfectant swabs (p_{ds}).

$$C_{vt} = C_{tv} + C_{sv} \qquad (7)$$

Costs of vaccinators (C_{vt}) are conducted of costs for temporary vaccinators (C_{tv}) and costs for supervisors (C_{sv}).

$$C_{tv} = n_{vd} \times (s_{tv} + f_{cm}/n_{capv}) \qquad (8)$$

Costs of temporary vaccinators (C_{tv}) are conducted of number of vaccinated dogs (n_{vd}), salary of temporary vaccinator (s_{tv}), transportation cost of vaccinator (f_{cm}) and vaccination capacity (n_{capv}).

$$C_{sv} = n_{vdays} \times (C_{ps} + f_{cm}) \quad (9)$$

Costs of supervisor (C_{sv}) are conducted of number of vaccination days (n_{vdays}), cost of public servant (C_{ps}) and transportation costs of vaccinator (f_{cm}).

$$n_{capv} = n_{vd}/n_{capv} \times 1/n_{vs} \quad (10)$$

Number of vaccination days (n_{vdays}) is conducted of number of vaccination days (n_{vd}), vaccination capacity (n_{capv}) and the number of temporary vaccinators that can by supervised by one supervisor (n_{vs}).

$$C_{cc} = ((n_{cb} \times p_{cb} + n_{mc} \times p_{mc} + n_{rf} \times p_{rf})/(l_{cmr} \times n_{dy}) + (n_{mz} \times p_{mz})/(l_{mz} \times n_{dy})) \times n_{vdays} \quad (11)$$

Capital costs (C_{cc}) are conducted of number of cool bags (n_{cb}), price of cool bags (p_{cb}), number of motor cycles (n_{mc}), price of a motorcycle (p_{mc}), number of refrigerators (n_{rf}), price of a refrigerator (p_{rf}), life years of capital goods (l_{cmr}), number of days in one year (n_{dy}), number of muzzles (n_{mz}), price of muzzles (p_{mz}), life years of muzzles (l_{mz}) and number of vaccination days (n_{vdays}).

Costs to train temporary vaccinators (C_{mt}) and costs of the information campaign (C_{ic}) are fixed values which are presented in Table 3.

Double costs for local vaccine

Because the local vaccines need to be applied twice to be effective, some costs need to be accounted for 2 times within one vaccination campaign. This concerns the costs of vaccine (C_{va}), costs for consumables (C_{ma}), cost of temporary vaccinators (C_{tv}) and the number of vaccination days (N_{vdays}), hereby indirectly accounting capital costs (C_{cc}) twice. Because the number of vaccination days (N_{vdays}) will be counted twice, the costs of supervisor (C_{sv}) will be automatically be doubled, because it multiplies number of vaccination days with labour costs and vaccination costs of the supervisor.

Opportunity costs

In the original paper by Wera *et al.* (33), opportunity costs of the dog owner were also included.

$$C_{do} = O_{do} \times n_{vd} \quad (12)$$

Opportunity costs (C_{do}) are conducted of the dog owner's time to catch and restrain the dog (O_{do}) and the number of vaccinated dogs (n_{vd}).

$$O_{do} = w_{hl} \times d_w/n_{hw} \quad (13)$$

The dog owner's time to catch and restrain the dog (O_{do}) are conducted of working hours lost for the dog owner (w_{hl}), daily wage (d_w) and number of hours work (n_{hw}).

In this research it is chosen not to take these opportunity costs into account, since these costs concerns the community and not the government. This choice was made to come to a result, which is directly adaptable to the field of the authorities.

Table 3. Input values for economic analysis (33)

Description	Variable	Value	Unit
Price of vaccine			
- local	p_{valoc}	0.29	US$/dose
- import	p_{vaimp}	1.50	US$/dose
Transportation costs of vaccine from manufacturer to each regency	t_{va}	0.15	US$/dose
Price of syringes and needles	p_{sn}	0.19	US$/dog
Ice bars	p_{ib}	0.33	US$/cool bag/day
Vaccination capacity	n_{capv}	25	Dogs/vaccinator/day
Disinfectant swabs for cleaning dogs skin	p_{ds}	0.02	US$/dog
Salary of temporary vaccinator	s_{tv}	0.28	US$/vaccinated dog
Transportation cost for people involved in the rabies control	f_{cm}	1.00	US$/person/day
Cost of public servant	c_{ps}	10.06	US$/person/day
The number of vaccinators that can be supervised by one public servant	n_{vs}	10	Vaccinator/supervisor
Costs of training and meeting	c_{mt}	851.30	US$/year
Campaign costs	c_{ic}	13,267	US$/year
Cool bags	n_{cb}	27	Pieces
Price cool bag	p_{cb}	27.99	US$/piece
Motorcycles	n_{mc}	16	Pieces
Price motor cycle	p_{mc}	1,669	US$/piece
Refrigerator	n_{rf}	8	Pieces
Price refrigerator	p_{rf}	174.68	US$/piece
Muzzles	n_{mz}	27	Pieces
Prize of muzzle	p_{mz}	5.53	US$/piece
Life years of capital goods (cool bags, refrigerators and motorcycles)	l_{cmr}	5	Years
Life years of muzzles	l_{mz}	2	Years
Number of days in one year	n_{dy}	365	Days
Working hours lost for a dog owner	w_{hl}	2	Hours/vaccinated dog
Daily wage	d_w	4.31	US$/day
Numbers hours work	n_{hw}	8	Hours/day

3.2.5 Mass vaccination scenarios evaluated

Three different scenarios were evaluated by considering different planning horizons. Within these three scenarios, a distinction was made for the different types of vaccine. The first type of vaccine is local vaccine without booster, as applied in the current situation on Flores, where duration of immunity (1/v) is 0.775 years as was calculated before. The second type of vaccine is local vaccine with booster, where there is certainty assumed about the dogs coming back for their second (and thus booster) vaccination, duration of immunity equals then 1.5 years. The last type of vaccine is the import vaccine with a duration of immunity of 3 years. In all scenarios the parameter setting on death rate and population growth are fixed, after the previous determined values (Table 2).

Scenario 1; Yearly application

In the first scenario, costs and effectiveness are evaluated on a yearly basis (12 months' time), based on the assumption that an annual vaccination is conducted, which is the standard approach on Flores.

Varying in vaccination coverage from 0 until 100 percent, with steps of 5 percent, the immunity coverage's are calculated and compared. Hereafter the according costs and cost effectiveness ratio are presented.

Scenario 2; Application based on 55% coverage rate and a minimal immunity rate of 20% in a year
Overall, the vaccination coverage rate against dog rabies on Flores was relatively low for the past years. On average 53% of the dog owners participated in the vaccination campaign (33). Considering an equally distributed dog population among the dog owners, a vaccination coverage rae of 55% was considered representative for the current situation of mass vaccination on Flores Island, Aim was to have a minimal immunity coverage over time of 20%. In this scenario the frequency is determined to maintain an immunity coverage rate of at least 20% during a period of one year. For the three different types of vaccine, the costs were evaluated for one year time and a cost effectiveness ratio will be presented later.

Scenario 3; Application at a minimal immunity rate of 20% over a period of 10 years
In the third scenario, costs and effectiveness for a time period of 10 years are evaluated. It is assumed that after a time period of 10 years, the rabies virus will be eliminated from the island, when conducting mass vaccination effectively. For varying vaccination coverage (0-100%) the frequency of vaccination is calculated, taking a minimum immunity coverage of 20% into account. From this frequency, total costs over the time span of 10 years were calculated and presented.
After these results, a cost effectiveness ratio is calculated.

Sensitivity analysis
Besides the defined scenarios a sensitivity analysis has been conducted to evaluate the influence of the duration of immunity (1/v), population growth ratio (r) and death rate (d). The setting of these variables could have a strong influence on the outcome of the effectiveness of the vaccine and eventually the immunity coverage after a year. The values of *1/v* will vary between 0.5 and 10 years. Values of *r* and *d* will vary from 0 until 1, with steps of 0.1.

4. Results

The results for effectiveness and costs are presented according to the defined mass vaccination scenarios as they were described in materials and methods In each scenario, a distinction was made between the application of the local or imported vaccine. Within the local vaccine, a distinction was made between application with and without the booster.

4.1 Scenario 1: yearly vaccination

Annual vaccination is currently the standard routine on Flores Island. Therefore, the first scenario focuses at the immunity coverage obtained within a period of a year time and the costs related to this yearly approach. First, the results for vaccinating with the local vaccine as carried out in practice (without booster) will be presented, followed by the results obtained from local vaccination in combination with a booster application and then the results based on the use of the imported vaccine.

4.1.1 Local vaccine: 'current situation – without booster'

First analysis that was performed was vaccination with the local vaccine and without providing the booster, which represents the current situation on Flores Island. In this situation the average duration of immunity = 0.775 year (1/v)). A very high vaccination coverage rate is required to maintain a best as possible immunity coverage. However, even with a vaccination coverage rate of one hundred percent (meaning that all dogs present on Flores Island are vaccinated) an immunity coverage of at least 20% will not be maintained after a period of one year (Figure 4 and Table 4). In the situation of 50% vaccination coverage, the immunity coverage rate is already below 20% after a period of 6 months after vaccination.

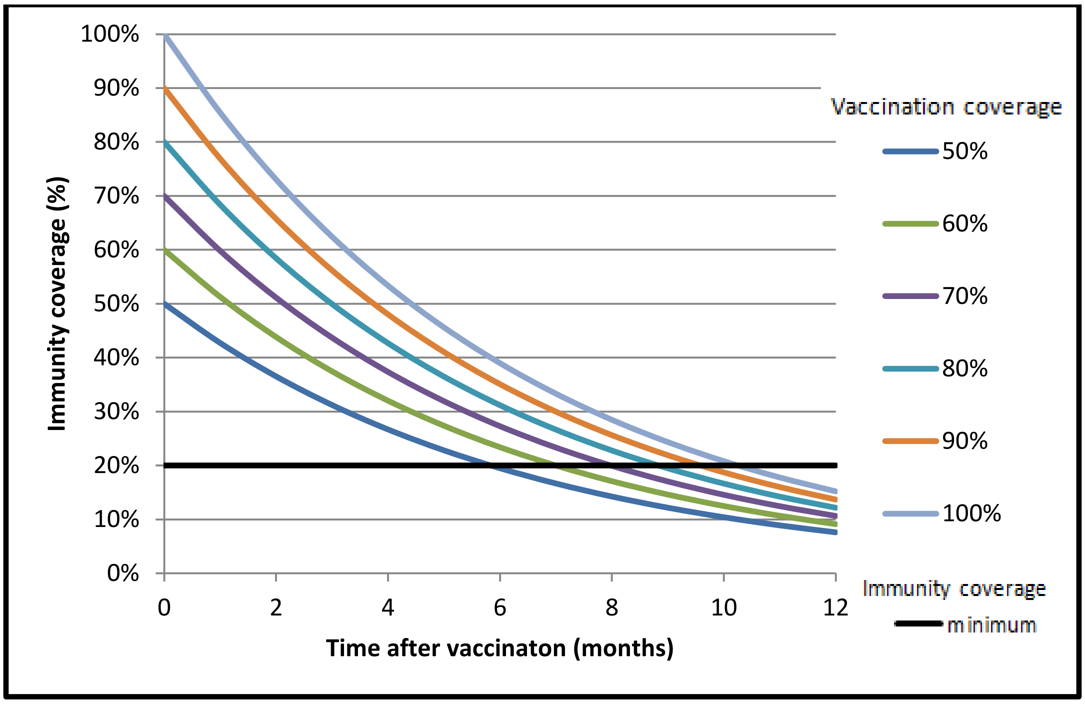

Figure 4. Immunity coverage in time after vaccination by local vaccination without booster, varying in vaccination coverage rates at time =0 (50-100%).

Table 4. Immunity coverage in time after vaccination by local vaccination with varying vaccination coverage (50-100%)

Time after vaccination (months)	**Vaccination coverage (%)**					
	50%	**60%**	**70%**	**80%**	**90%**	**100%**
0	50.00%	60.00%	70.00%	80.00%	90.00%	100.00%
1	42.73%	51.28%	59.83%	68.37%	76.92%	85.47%
2	36.52%	43.83%	51.13%	58.44%	65.74%	73.05%
3	31.22%	37.46%	43.70%	49.95%	56.19%	62.43%
4	26.68%	32.02%	37.35%	42.69%	48.02%	53.36%
5	22.80%	27.36%	31.92%	36.48%	41.05%	45.61%
6	19.49%	23.39%	27.28%	31.18%	35.08%	38.98%
7	16.66%	19.99%	23.32%	26.65%	29.98%	33.31%
8	14.24%	17.08%	19.93%	22.78%	25.63%	28.47%
9	12.17%	14.60%	17.03%	19.47%	21.90%	24.34%
10	10.40%	12.48%	14.56%	16.64%	18.72%	20.80%
11	8.89%	10.67%	12.44%	14.22%	16.00%	17.78%
12	7.60%	9.12%	10.64%	12.15%	13.67%	15.19%

Costs for 50 to 100% vaccination of the dogs on Flores Island are according to Table 5.
The total vaccination costs increase with a rise of vaccination coverage, but costs per dog become less with increasing vaccination coverage. The cost effectiveness ratio of total costs divided by the percentage of induced immunity degressively decreases with increasing vaccination coverage.

Table 5. Costs of local vaccination without booster, varying in vaccination coverage (50-100%)

Vaccination coverage (%)	**Total costs**	**Costs/dog**	**Costs/km²**	**Immunity coverage**	**Total costs / % Immunity coverage**
50	$181,873	$1.18	$1,272	7.60%	$23,941
60	$215,423	$0.99	$1,506	9.12%	$23,632
70	$248,974	$0.85	$1,741	10.64%	$23,410
80	$282,525	$0.74	$1,976	12.15%	$23,244
90	$316,076	$0.66	$2,210	13.67%	$23,115
100	$349,627	$0.59	$2,445	15.19%	$23,012

4.1.2 Local vaccine: 'vaccination with booster'

If the local vaccination is carried out with the booster application it was assumed that the dogs that were still alive and were vaccinated in the previous year, received their second vaccination within 6 months after the first vaccination.

Figure 5 and Table 6 indicate the obtained immunity coverage rates over time, based on varying coverage rates. When accounting for a yearly vaccination scheme, a vaccination coverage of 75% turns out to be sufficient to maintain an immunity coverage rate of at least 20% after one year.

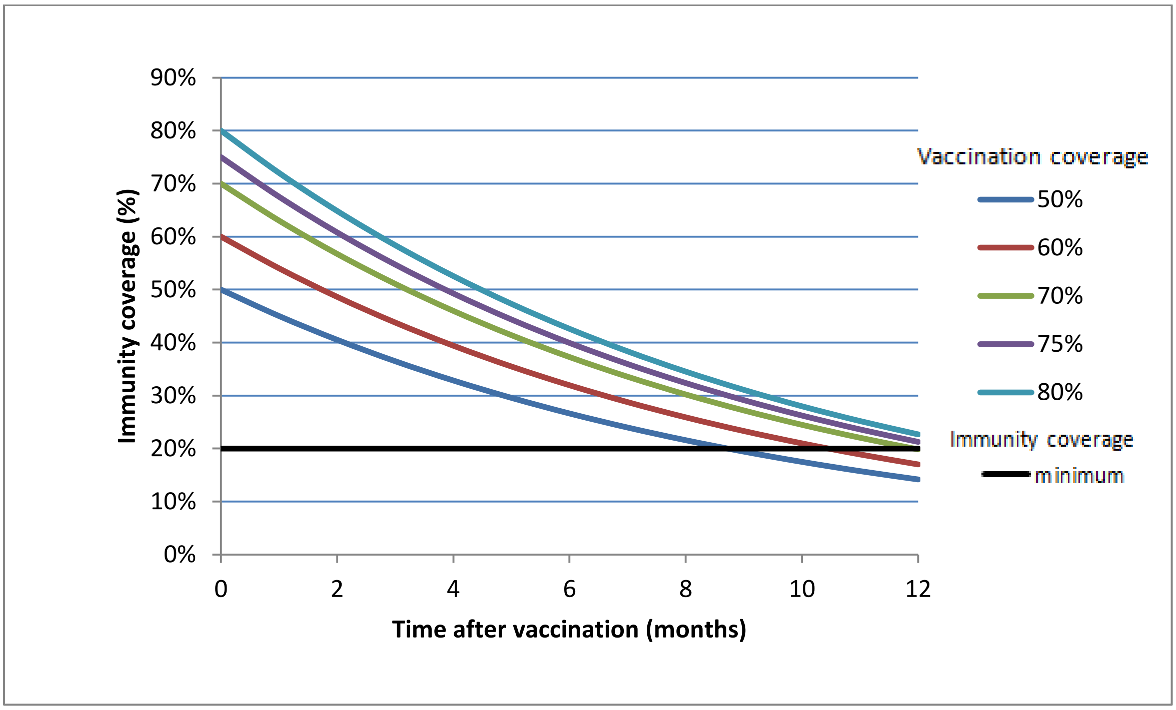

Figure 5. Immunity coverage in time after vaccination by local vaccination with booster, varying in vaccination coverage rates at time =0 (50-80%).

Table 6. Immunity coverage in time by local vaccination with booster, with varying vaccination coverage (50-80%)

Time after vaccination (months)	**Vaccination**	**coverage**	**(%)**		
	50%	**60%**	**70%**	**75%**	**80%**
0	50.00%	60.00%	70.00%	75.00%	80.00%
1	45.01%	54.02%	63.02%	67.52%	72.02%
2	40.52%	48.63%	56.73%	60.79%	64.84%
3	36.48%	43.78%	51.08%	54.73%	58.37%
4	32.85%	39.41%	45.98%	49.27%	52.55%
5	29.57%	35.48%	41.40%	44.35%	47.31%
6	26.62%	31.94%	37.27%	39.93%	42.59%
7	23.97%	28.76%	33.55%	35.95%	38.35%
8	21.58%	25.89%	30.21%	32.36%	34.52%
9	19.42%	23.31%	27.19%	29.14%	31.08%
10	17.49%	20.98%	24.48%	26.23%	27.98%
11	15.74%	18.89%	22.04%	23.61%	25.19%
12	14.17%	17.01%	19.84%	21.26%	22.68%

The costs will differ from the adaptation without booster of the local vaccine, because some costs will be accounted for twice (see materials and methods), due to the booster that is required for the vaccine to work properly for a year after the first vaccination. Costs for local vaccination with booster applied to vaccination coverage rates varying from 50-80% will then become according to Table 7. Similar to the results based on a local vaccination scheme without booster, costs per dog decreases with increasing vaccination coverage, however to a lesser extent. The cost effectiveness ratio of total costs divided by percentage of immunity decreases with increasing vaccination coverage.

The cost effectiveness ratio of total costs divided by percentage of immunity decreases with increasing vaccination coverage.

Table 7. Costs of local vaccination with booster, varying in vaccination coverage (50-80%)

Vaccination coverage (%)	Total costs	Costs/dog	Costs/km²	Immunity coverage (%)	Total costs/%Immunity coverage
50	$349,626	$2.27	$2,445	14.17%	$24,668
60	$416,728	$2.26	$2,914	17.01%	$24,502
70	$483,830	$2.25	$3,383	19.84%	$24,383
75	$517,381	$2.24	$3,618	21.26%	$24,336
80	$550,932	$2.24	$3,853	22.68%	$24,295

4.1.3 Import vaccine

The import vaccine promises an immunisation time of 3 years. However, due to waning of immunity and a high dog population turnover, this immunity coverage will decrease within these 3 years. With a minimum vaccination coverage of 55%, the threshold of 20% immunity coverage can be maintained at yearly vaccination with the import vaccine (Figure 6 and Table 8).

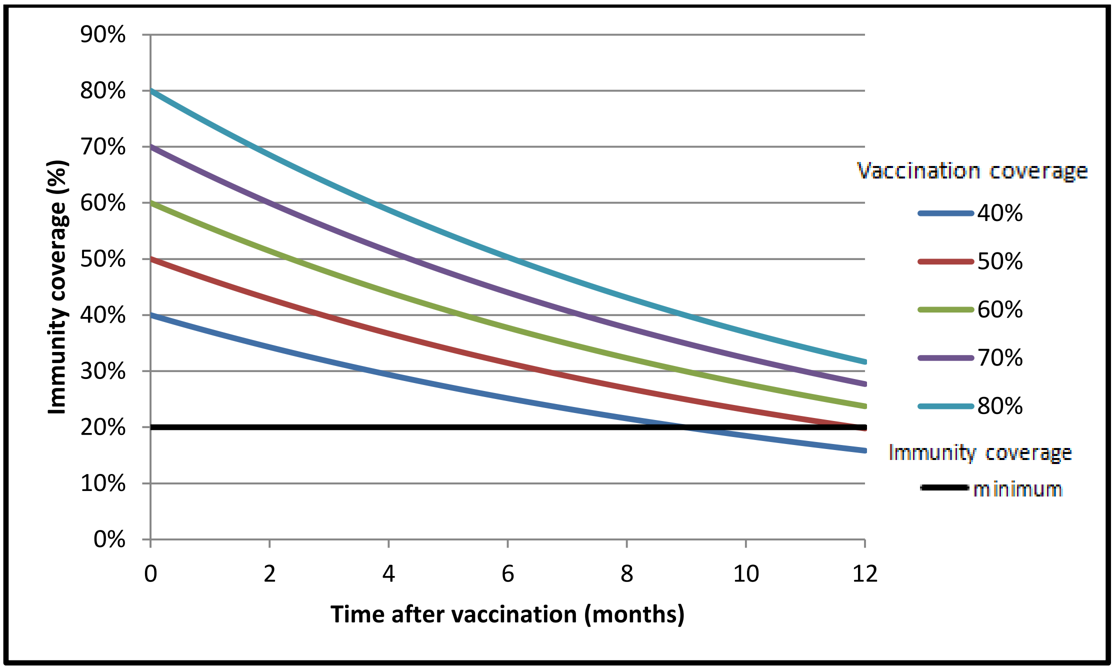

Figure 6. Immunity coverage in time after vaccination by import vaccination, varying in vaccination coverage rates at time =0 (40-80%).

Table 8. Immunity coverage in time by import vaccine with varying vaccination coverage (40-80%)

Time after vaccination (months)	Vaccination Coverage (%)					
	40%	**50%**	**55%**	**60%**	**70%**	**80%**
0	40.00%	50.00%	55.00%	60.00%	70.00%	80.00%
1	37.03%	46.28%	50.91%	55.54%	64.79%	74.05%
2	34.27%	42.84%	47.12%	51.41%	59.98%	68.54%
3	31.72%	39.65%	43.62%	47.58%	55.52%	63.45%
4	29.36%	36.70%	40.38%	44.05%	51.39%	58.73%

5	27.18%	33.98%	37.37%	40.77%	47.57%	54.36%
6	25.16%	31.45%	34.59%	37.74%	44.03%	50.32%
7	23.29%	29.11%	32.02%	34.93%	40.75%	46.58%
8	21.56%	26.95%	29.64%	32.33%	37.72%	43.11%
9	19.95%	24.94%	27.44%	29.93%	34.92%	39.91%
10	18.47%	23.09%	25.40%	27.70%	32.32%	36.94%
11	17.10%	21.37%	23.51%	25.64%	29.92%	34.19%
12	15.82%	19.78%	21.76%	23.74%	27.69%	31.65%

Costs for vaccination with import vaccine annually, varying in vaccination coverage from 40-80%, are according to Table 9. Total costs increase with increasing vaccination coverage and costs per dog decreases. Costs per square kilometre increase with increasing vaccination coverage. The costs of annual vaccination with the import vaccine increases linear with percentage of immunity coverage. The cost effective ratio decreases with increasing vaccination coverage.

Table 10. Costs of import vaccination, varying in vaccination coverage (40-80%)

Vaccination coverage (%)	Total costs	Costs/dog	Costs/km^2	Immunity coverage (%)	Total costs/%Immunity coverage
40	$297,094	$2.42	$2,077	15.82%	$18,775
50	$367,838	$2.39	$2,572	19.78%	$18,596
55	$403,210	$2.39	$2,819	21.76%	$18,531
60	$438,582	$2.38	$3,067	23.74%	$18,477
70	$509,326	$2.37	$3,562	27.69%	$18,392
80	$580,070	$2.36	$4,056	31.65%	$18,328

4.2 Scenario 2: 55% vaccination coverage and minimal 20% immunity coverage

In this second scenario the frequency is determined to maintain an immunity coverage rate of at least 20% during a period of one year, based on a vaccination coverage rate of 55%. Figure 7 and Table 10 indicate the change in immunity coverage over time after one vaccination round for the three different vaccines (local without booster, local with booster and import)

When vaccinating with the local vaccine without booster, the threshold value of 20% immunity coverage is reached in six months of time. Therefore, with this strategy, vaccination needs to be carried out at least twice per year. Vaccination based on the local vaccine with the booster application means per definition vaccinating twice per year. Despite the booster effect, the minimum value of 20% for immunity coverage is reached in 9 months' time; indicating on average the need for a 3/12 additional vaccination round per year (3 months left after 9 months). When vaccinating with import vaccine, the minimum value of 20% for immunity coverage remains above the threshold value. So yearly vaccination with import vaccine at 55% coverage is an effective strategy.

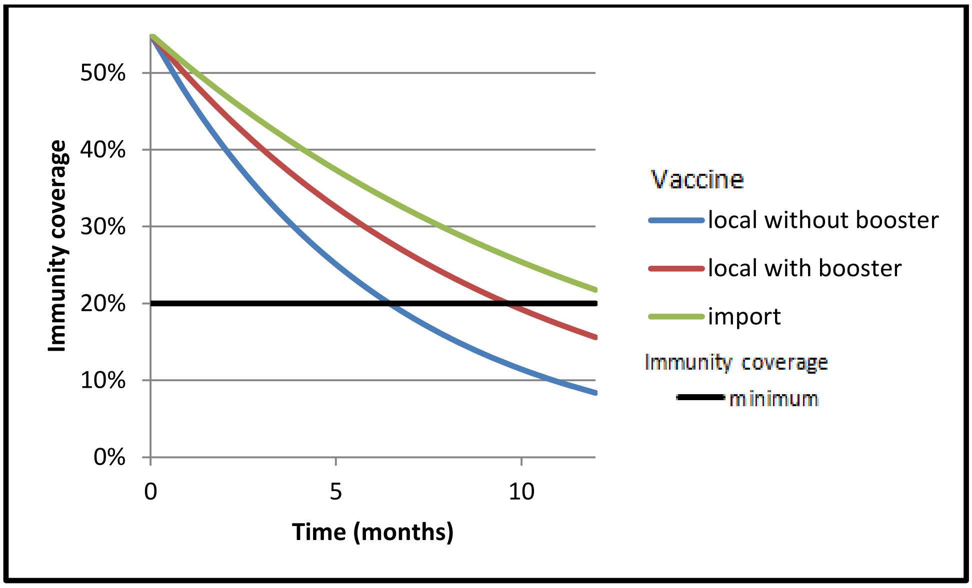

Figure 7. Immunity coverage for set value of vaccination coverage (55%) for different vaccination strategies over time (months), based on one vaccine application.

Table 10. Immunity coverage of local current, local with booster and import vaccines at a vaccination coverage of 55%, varying in time (months)

Time (months)	**Immunity coverage (%)**		
	Local without booster (1/v=0.775)	**Local with booster (1/v=1.5)**	**Import**
0	55.00%	55.00%	55.00%
1	47.01%	49.52%	50.91%
2	40.18%	44.58%	47.12%
3	34.34%	40.13%	43.62%
4	29.35%	36.13%	40.38%
5	25.08%	32.53%	37.37%
6	**21.44%**	29.28%	34.59%
7	18.32%	26.36%	32.02%
8	15.66%	23.73%	29.64%
9	13.38%	**21.37%**	27.44%
10	11.44%	19.24%	25.40%
11	9.78%	17.32%	23.51%
12	8.36%	15.59%	**21.76%**

In Table 12, the annual frequencies for application of the different vaccines are presented. Local vaccine without booster needs to be applied for every six months. Therefore the frequency becomes 2 rounds (=12/6) a year. Local vaccine with booster needs to applied for every nine months, therefore the annual frequency becomes 1.33 (12/9), but within this campaign a booster is applied. Therefore the annual frequency becomes doubled (2.66). however, the costs will be multiplied with 1.33, because the double costs are already accounted for in the costs of the campaign for local vaccine with booster.

Import vaccine can be applied once, for the immunity coverage to stay above the minimum value of 20%, therefore the annual frequency is 1.

Despite the highest required frequency of application, annual costs are the lowest for the scheme based on local vaccine without booster, compared to the schemes based on local vaccine with booster or the import vaccine (Table 11). Looking at the cost effectiveness ratio of total costs divided by percentage immunity coverage, the ratio for the vaccination based on local vaccination without booster is almost equal to the ratio for vaccination with import vaccine. Costs for the booster strategy are the highest as well as the cost effectiveness.

Table 11. Costs of vaccinating at vaccination coverage of 55%, varying in type of vaccine; local without booster, local with booster and import vaccine

Vaccination type	Duration of immunity (1/v)	Immunity coverage (%)	Annual vaccination frequency	Costs of annual campaign	Total costs / year	Total costs/%Immunity coverage
Local without booster	0.775	21.44%	2	$198,648	$397,296	$18,532
Local with booster	1.5	21.37%	2.66*	$383,178	$510,904	$23,911
Import	3	21.76%	1	$403,210	$403,210	$18,531

**this is including the booster, so the annual frequency for the total campaign is 1,33, but within this campaign a booster is applied. Therefore the annual frequency becomes doubled (2,66), but the costs will be multiplied with 1.33 (as stated before).*

4.3 Scenario 3: 10 year time span of minimal 20% immunity coverage

It is assumed that in the time span of 10 years, dog rabies can be under control and eventually eliminated from Flores Island. Therefore, in scenario 3, for the three different vaccine schemes the frequency of vaccination application per vaccination coverage level is evaluated over the time span of 10 years, during which the immunity coverage was required to stay above the effective value of 20%.

The frequency in which the vaccination campaigns need to be conducted, decreases with increasing vaccination coverage (Figure 8). With an increasing vaccination coverage the required frequency of vaccination decreases rapidly, independent on the vaccination scheme. However, this decrease becomes less severe when vaccination coverage takes on higher levels. The costs per vaccination round increase evenly for every 5% increase in vaccination coverage, while the costs saved by a decrease in required frequency degressively reduces per step of 5% increase in vaccination coverage (see Tables 12, 13 and 14). At a certain point, the costs saved by the decrease in frequency are not enough to compensate the linear increase in costs due to the increase in vaccination coverage. From this break-even point on, the total costs for the total time of 10 years will increase instead of decrease with increasing vaccination coverage (see Tables 12 -14 + Figure 9).

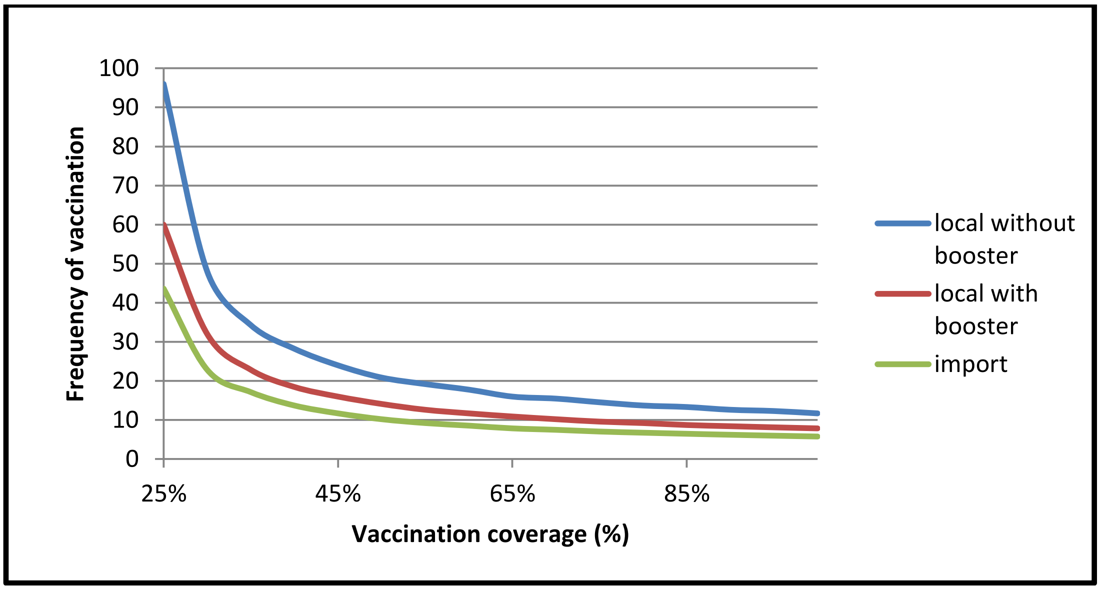

Figure 8. Frequency of vaccination with 3 different types of vaccination within time span of 10 years, varying vaccination coverage (25-100%).

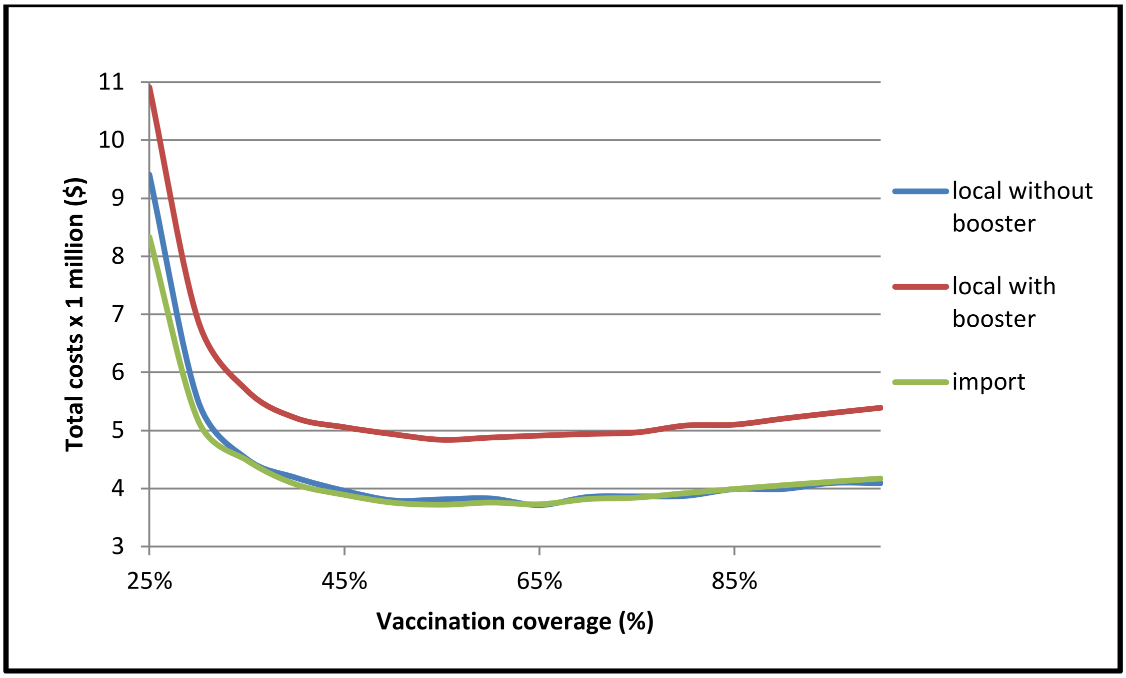

Figure 9. Total costs of 3 different types of vaccines over 10 years' time in which immunity coverage > 20%, varying in vaccination coverage (25-100%).

When looking at the total costs of an application of the local vaccine without booster, evaluating a time period of 10 years, a scheme in which 65% vaccination coverage is applied with a frequency of 20.9 vaccination?? during this time period is required. Costs for this will be 3.7 million dollars (Table 12).

Lowest cost-effectiveness ratio is obtained at a scheme based on 60%; equalling $184,222. The difference for the required vaccination coverage between total costs and cost-effectiveness ratio is due to the fact that the immunity coverage differs and thus the moment of vaccinating differs between the two. On a monthly base, the immunity coverage is evaluated and required to remain above the value of 20%. The total costs are for instance for 60% vaccination coverage lower than for 55 or 65%. This is because vaccination needs to be conducted relatively late in the situation of a vaccination coverage of 50% and allows immunity coverage to reduce to a level of 20.27%, compared to immunity coverage for 55 and 65% vaccination coverage, which have an immunity coverage of 20.6 and 20.8% respectively. This explains why the lowest ratio can be found at vaccination coverage of 60%.

The same explanation holds true for the difference in required vaccination coverage between total cost and cost-effectiveness ratio for local with booster (Table 13).

Table 12. Frequency, costs and cost-effectiveness of local vaccination without booster over 10 years in which immunity coverage >20%, varying in vaccination coverage (25-100%)

Vaccination coverage (%)	**Frequency/10 years**	**Immunity coverage**	**Costs/vaccination round**	**Total costs (10 years)**	**Total costs/%Immunity coverage**
25%	96.00	20.54%	\$97,995	\$9,407,562	\$457,912
30%	48.00	20.26%	\$114,770	\$5,509,001	\$271,920
35%	34.29	20.20%	\$131,546	\$4,510,158	\$223,259
40%	28.24	20.52%	\$148,322	\$4,187,907	\$204,066
45%	24.00	20.52%	\$165,097	\$3,962,331	\$193,071
50%	20.87	20.27%	\$181,873	\$3,795,601	\$187,257
55%	19.20	20.61%	\$198,648	\$3,814,042	\$185,032
60%	17.78	20.79%	\$215,423	\$3,829,750	**\$184,222**
65%	16.00	20.02%	\$232,199	**\$3,715,182**	\$185,582
70%	15.48	20.73%	\$248,974	\$3,855,086	\$185,975
75%	14.55	20.53%	\$265,750	\$3,865,450	\$188,259
80%	13.71	20.25%	\$282,525	\$3,874,630	\$191,361
85%	13.33	20.69%	\$299,301	\$3,990,674	\$192,926
90%	12.63	20.25%	\$316,076	\$3,992,539	\$197,182
95%	12.31	20.55%	\$332,851	\$4,096,633	\$199,349
100%	11.71	20.00%	\$349,627	\$4,093,192	\$204,678

For local vaccine with booster, a vaccination coverage of 55% is sufficient and the frequency of vaccinations will be 12.63 times per 10 years. Total costs will be 4.8 million dollars (Table 13), resulting in a cost-effectiveness ratio of \$239,000.

Table 13. Frequency, costs and cost-effectiveness of local vaccination with booster over 10 years in which immunity coverage >20%, varying in vaccination coverage (25-100%)

Vaccination coverage (%)	**Frequency/10 years**	**Immunity coverage (%)**	**Costs/vaccination round**	**Total costs (10 years)**	**Total costs/%immunity coverage**
25%	60.00	20.26%	\$181,873	\$10,912,354	\$538,553
30%	32.00	20.23%	\$215,423	\$6,893,550	\$340,734
35%	22.86	20.16%	\$248,974	\$5,690,840	\$282,254
40%	18.46	20.21%	\$282,525	\$5,215,849	\$258,124
45%	16.00	20.47%	\$316,076	\$5,057,216	\$247,108
50%	14.12	20.47%	\$349,627	\$4,935,908	\$241,107
55%	12.63	20.27%	\$383,178	**\$4,840,139**	\$238,744
60%	11.71	20.44%	\$416,729	\$4,878,773	**\$238,680**
65%	10.91	20.47%	\$450,279	\$4,912,139	\$240,012
70%	10.21	20.37%	\$483,830	\$4,941,245	\$242,568
75%	9.60	20.17%	\$517,381	\$4,966,859	\$246,226

80%	9.23	20.42%	$550,932	$5,085,526	$249,099
85%	8.73	20.05%	$584,483	$5,100,941	$254,434
90%	8.42	20.14%	$618,033	$5,204,490	$258,400
95%	8.14	20.17%	$651,585	$5,301,027	$262,788
100%	7.87	20.15%	$685,135	$5,391,229	$267,590

The import vaccine requires a vaccination coverage of 55% and a frequency of 9.23 within 10 years. Total costs will be 3.7 million dollars at a cost effectiveness ratio of $185,000 (Table 14).

Table 14. Frequency, costs and cost-effectiveness of import vaccination over 10 years in which immunity coverage >20%, varying in vaccination coverage (25-100%)

Vaccination coverage (%)	**Frequency/10 years**	**Immunity coverage (%)**	**Costs/vaccination round**	**Total costs (10 years)**	**Total costs/%immunity coverage**
25%	43.64	20.21%	$190,978	$8,333,595	$412,274
30%	22.86	20.00%	$226,350	$5,173,719	$258,749
35%	17.14	20.38%	$261,722	$4,486,666	$220,184
40%	13.71	20.34%	$297,094	$4,074,434	$200,294
45%	11.71	20.38%	$332,466	$3,892,287	$190,983
50%	10.21	20.17%	$367,838	$3,756,645	$186,284
55%	9.23	20.14%	$403,210	**$3,721,940**	**$184,801**
60%	8.57	20.34%	$438,582	$3,759,275	$184,847
65%	7.87	20.00%	$473,954	$3,729,475	$186,442
70%	7.50	20.33%	$509,326	$3,819,946	$187,906
75%	7.06	20.16%	$544,698	$3,844,927	$190,708
80%	6.76	20.29%	$580,070	$3,921,600	$193,235
85%	6.49	20.35%	$615,442	$3,992,056	$196,183
90%	6.23	20.33%	$650,814	$4,057,022	$199,535
95%	6.00	20.25%	$686,186	$4,117,116	$203,281
100%	5.78	20.12%	$721,558	$4,172,865	$207,411

So even though the costs for the local vaccine are lower than for the import vaccine ($0.29 vs. $1.50), looking at a time span of 10 years and the decrease in vaccination frequency when applying import vaccine, it seems that the costs for local vaccine without booster and import vaccine are approximately the same over 10 years of time. Since the import vaccine has the lowest cost-effectiveness ratio at the break-even point for total costs, this is the most cost-effective type of vaccine, looking at a time span of 10 years.

4.4 Sensitivity analysis

A sensitivity analysis was conducted on duration of immunity of the vaccine (1/v), population growth rate (r) and death rate of dogs (d). These sensitivity analyses gave insight in the impact of different variables on the results obtained in scenario 1. In scenario 1 a time span of one year was considered as planning horizon, reflecting the current situation on Flores Island .

The results of the sensitivity analysis show the increase or decrease in immunity coverage obtained one year after vaccination for altering values on the duration of immunity, population growth rate or death rate. Duration of immunity can directly be influenced by the selection on the type of vaccine. However, population growth rate and death rate cannot be influenced directly; decision makers have to deal with uncertainty about the expected values of these variables. This uncertainty in variation of values for *r* and *d* will be reflected by the change in vaccination costs compared to the default settings of r=0.144 and d=0.45.

4.4.1 Duration of immunity (1/v)

The duration of immunity differs between different vaccines. In the previous analyses, three values for different types of vaccines have been used, reflecting 1/v values of 0.775 (local without booster), 1.5 (local with booster) and 3 (import). In this sensitivity analysis the impact of variation in duration of immunity of vaccines will become visible (Table 15 and Figure 10).

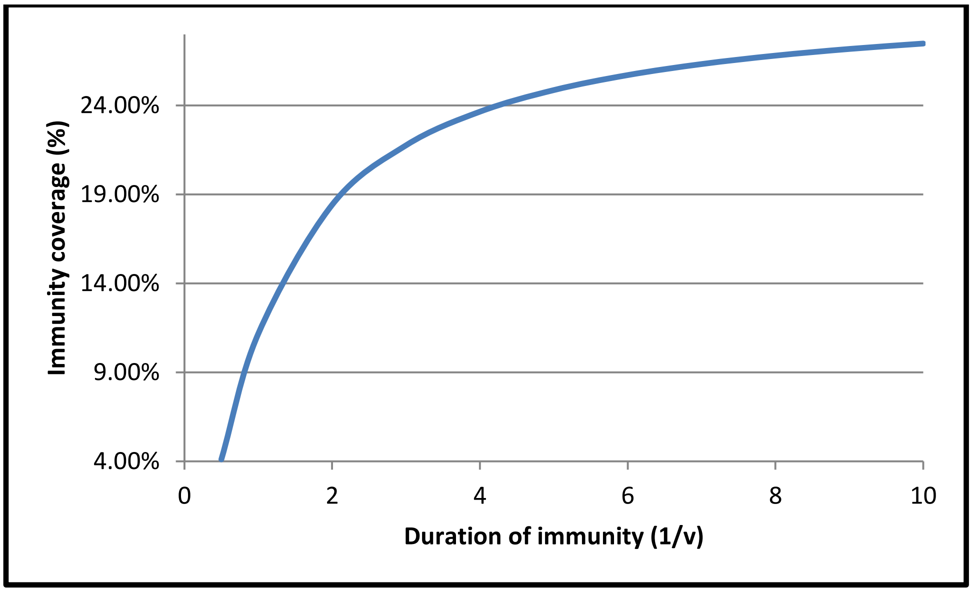

Figure 10. Variations in duration of immunity (1/v) and the according immunity coverage for a vaccination coverage rate of 55%.

The immunity coverage after one year of vaccine application increases very fast for values of 1/v until approximately an immunity duration of 3 years. After this value of 1/v, the line of increase becomes less steep, but immunity coverage still increases with increasing duration of immunity (Figure 10).

Table 15. Immunity coverage (%) of varying duration of immunity;1/v (0.5, 1, 2,…,10) for annual vaccination by varying vaccination coverage. Values with minimum immunity coverage of 20% are presented in bold.

	Duration of immunity (1/v)												
Vaccination coverage	**0.5**	**0.775**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
5	0.37	0.76	1.02	1.42	1.67	1.98	2.15	2.26	2.34	2.39	2.44	2.47	2.50
10	0.75	1.52	2.03	2.83	3.35	3.96	4.30	4.52	4.67	4.79	4.87	4.94	5.00
15	1.12	2.28	3.05	4.25	5.02	5.93	6.45	6.78	7.01	7.18	7.31	7.41	7.49
20	1.49	3.04	4.06	5.67	6.70	7.91	8.60	9.04	9.35	9.57	9.74	9.88	9.99
25	1.87	3.80	5.08	7.09	8.37	9.89	10.75	11.30	11.68	11.97	12.18	12.35	12.49
30	2.24	4.56	6.09	8.50	10.05	11.87	12.90	13.56	14.02	14.36	14.62	14.82	14.99
35	2.62	5.32	7.11	9.92	11.72	13.85	15.05	15.82	16.36	16.75	17.05	17.29	17.49
40	2.99	6.08	8.12	11.34	13.39	15.82	17.20	18.08	18.69	19.14	19.49	19.76	19.98
45	3.36	6.84	9.14	12.76	15.07	17.80	19.35	**20.34**	**21.03**	**21.54**	**21.93**	**22.23**	**22.48**
50	3.74	7.60	10.16	14.17	16.74	19.78	**21.50**	22.60	23.37	23.93	24.36	24.70	24.98
55	4.11	8.36	11.17	15.59	18.42	**21.76**	23.65	24.86	25.70	26.32	26.80	27.17	27.48
60	4.48	9.12	12.19	17.01	**20.09**	23.74	25.80	27.12	28.04	28.72	29.23	29.64	29.97
65	4.86	9.88	13.20	18.43	21.77	25.71	27.95	29.38	30.38	31.11	31.67	32.11	32.47
70	5.23	10.64	14.22	19.84	23.44	27.69	30.10	31.64	32.71	33.50	34.11	34.58	34.97
75	5.60	11.39	15.23	**21.26**	25.12	29.67	32.25	33.90	35.05	35.90	36.54	37.05	37.47
80	5.98	12.15	16.25	22.68	26.79	31.65	34.40	36.16	37.39	38.29	38.98	39.52	39.97
85	6.35	12.91	17.26	24.09	28.46	33.63	36.55	38.42	39.73	40.68	41.42	41.99	42.46
90	6.72	13.67	18.28	25.51	30.14	35.60	38.70	40.68	42.06	43.08	43.85	44.46	44.96
95	7.10	14.43	19.30	26.93	31.81	37.58	40.85	42.94	44.40	45.47	46.29	46.94	47.46
100	7.47	15.19	**20.31**	28.35	33.49	39.56	43.00	45.20	46.74	47.86	48.72	49.41	49.96

By reducing the vaccination coverage, with increasing duration of immunity (1/v), the gain will be a decrease in total costs, because less dogs have to be vaccinated. The highest reachable gain is a gain from 55% to 45% vaccination coverage, reached with a vaccine with *1/v* of 5. For higher values of *1/v*, vaccination coverage does not go down, but stagnates (Table 15).
By increasing *1/v* from the value of 3 (= default import vaccine) to a level of 5, the largest reduction in vaccination costs can be reached. For these values of *1/v* the lowest possible vaccination coverage can be applied, at which the immunity coverage remains above the minimum value of 20% after one year.

Vaccines with higher vaccination duration are generally more expensive. When considering the total vaccination costs of the import vaccine scheme (1/v = 3) as the maximum of financial resources available, the maximum price for the vaccine with a duration of 4 and 5 years can be estimated to result in the same total vaccination campaign costs (see Table 16a).

Table 16a. Maximum costs of vaccines with varying duration of immunity (3-5) and according cost-effectiveness ratio (total costs/%immunity coverage) obtained by total costs

Duration of immunity (1/v)	**Vaccination coverage**	**Immunity coverage**	**Max. total costs**	**Max. price of vaccine**	**Total costs/%Immunity coverage**
3	55%	21.76%	$403,210*	$1.50*	$18,530
4	50%	21.50%	$403,210	$1.73	$18,754
5	45%	20.34%	$403,210	$2.01	$19,824

**actual costs of import vaccine with annual vaccination (scenario 1)*

However, when accounting for a comparable cost-effectiveness ratio as obtained by the import vaccine with a duration of 3 years, maximum prices for the vaccines with longer durations equal the values in Table 16b. In these cases, the cost-effectiveness ratio should stay under or equal to the value of cost-effectiveness ratio of the import vaccine, in order for the new vaccines with new 1/v to stay cost effective.

Table 16b. Maximum costs of vaccines with varying duration of immunity (3-5) and according cost-effectiveness ratio (total costs/%immunity coverage) obtained by cost-effectiveness ratio

Duration of immunity (1/v)	**Vaccination coverage (%)**	**Immunity coverage (%)**	**Max. total costs**	**Max. price of vaccine**	**Total costs/%Immunity coverage**
3	55%	21.76%	$403,210*	$1.50*	$18,530
4	50%	21.50%	$398,392	$1.85	$18,530
5	45%	20.34%	$376,898	$1.97	$18,530

**actual costs of import vaccine with annual vaccination (scenario 1)*

4.4.2 Population growth rate (r)

The population growth rate of the dog population on Flores was set at a default value of 0.144, as stated before. Since the value of population growth rate cannot directly be influenced, there is uncertainty for this value. A change in the value of growth rate can possibly have a big impact on the results of the previously presented results. Therefore it is interesting to look at the impact of a change in population growth rate (r), around the assumed value of 0.144.

Immunity coverage decreases with increasing population growth rate for all 3 types of vaccines (Table 17). Therefore it is not desirable for the growth rate to increase, because in that case the vaccination coverage requires a higher immunity coverage in order to stay above the minimum value of 20% and consequently the costs will increase. Values with minimum immunity coverage of 20% are presented in bold.

Table 17. Immunity coverage (%) of varying growth rate ;r (0, 0.1, 0.144, 0.2, 0.3) for annual vaccination with 3 different types of vaccine. Values with minimum immunity coverage of 20% are presented in bold.

	r	**Local**	**without**	**booster**		**r**	**Local**	**with**	**booster**		**r**	**Import**			
Vaccination coverage (%)	**0**	**0.1**	**0.144**	**0.2**	**0.3**	**0**	**0.1**	**0.144**	**0.2**	**0.3**	**0**	**0.1**	**0.144**	**0.2**	**0.3**
5	0.88	0.79	0.76	0.72	0.65	1.64	1.48	1.42	1.34	1.21	2.28	2.07	1.98	1.87	1.69
10	1.75	1.59	1.52	1.44	1.30	3.27	2.96	2.83	2.68	2.43	4.57	4.13	3.96	3.74	3.38
15	2.63	2.38	2.28	2.15	1.95	4.91	4.44	4.25	4.02	3.64	6.85	6.20	5.93	5.61	5.08
20	3.51	3.18	3.04	2.87	2.60	6.55	5.92	5.67	5.36	4.85	9.14	8.27	7.91	7.48	6.77
25	4.39	3.97	3.80	3.59	3.25	8.18	7.41	7.09	6.70	6.06	11.42	10.34	9.89	9.35	8.46
30	5.26	4.76	4.56	4.31	3.90	9.82	8.89	8.50	8.04	7.28	13.71	12.40	11.87	11.22	10.15
35	6.14	5.56	5.32	5.03	4.55	11.46	10.37	9.92	9.38	8.49	15.99	14.47	13.85	13.09	11.85
40	7.02	6.35	6.08	5.75	5.20	13.09	11.85	11.34	10.72	9.70	18.28	16.54	15.82	14.96	13.54
45	7.90	7.14	6.84	6.46	5.85	14.73	13.33	12.76	12.06	10.91	**20.56**	18.60	17.80	16.83	15.23
50	8.77	7.94	7.60	7.18	6.50	16.37	14.81	14.17	13.40	12.13	22.84	**20.67**	19.78	18.70	16.92
55	9.65	8.73	8.36	7.90	7.15	18.01	16.29	15.59	14.74	13.34	25.13	22.74	**21.76**	**20.57**	18.62
60	10.53	9.53	9.12	8.62	7.80	19.64	17.77	17.01	16.08	14.55	27.41	24.80	23.74	22.44	**20.31**
65	11.41	10.32	9.88	9.34	8.45	**21.28**	19.25	18.43	17.42	15.76	29.70	26.87	25.71	24.31	22.00
70	12.28	11.11	10.64	10.06	9.10	22.92	**20.74**	19.84	18.76	16.98	31.98	28.94	27.69	26.18	23.69
75	13.16	11.91	11.39	10.77	9.75	24.55	22.22	**21.26**	**20.10**	18.19	34.27	31.01	29.67	28.05	25.38
80	14.04	12.70	12.15	11.49	10.40	26.19	23.70	22.68	21.44	19.40	36.55	33.07	31.65	29.92	27.08
85	14.91	13.50	12.91	12.21	11.05	27.83	25.18	24.09	22.78	**20.61**	38.83	35.14	33.63	31.80	28.77
90	15.79	14.29	13.67	12.93	11.70	29.46	26.66	25.51	24.12	21.83	41.12	37.21	35.60	33.67	30.46
95	16.67	15.08	14.43	13.65	12.35	31.10	28.14	26.93	25.46	23.04	43.40	39.27	37.58	35.54	32.15
100	17.55	15.88	15.19	14.37	13.00	32.74	29.62	28.35	26.80	24.25	45.69	41.34	39.56	37.41	33.85

Local without booster

The variation in immunity coverage for local vaccine without booster is 2.5%, looking at values of *r*, varying from 0-0.3, at vaccination coverage of 55% (Table 17). For no value of population growth rate (r), immunity coverage reaches the minimum value of 20%, for local vaccine without booster.

Since for no value of population growth rate, the minimum value of 20% for immunity coverage is reached, the costs will be evaluated for the maximum vaccination coverage, so the best case scenario. The cost effectiveness ratio will increase with increasing growth rate (Table 18).

Table 18. Costs of varying growth rate (0-0.3) for annual vaccination with local vaccine without booster and according cost-effectiveness ratio (total costs/%immunity coverage)

Growth rate (r)	Vaccination coverage (%)	Immunity coverage (%)	Total costs	Total costs/%Immunity coverage
0	100%	17.55%*	$349,627	$19,922
0,1	100%	15.88%*	$349,627	$22,017
0,144	100%	15.19%*	$349,627	$23,017
0,2	100%	14.37%*	$349,627	$24,330
0,3	100%	13.00%*	$349,627	$26,894

**minimum value of 20% for immunity coverage not reached; not cost-effective*

Local with booster

The variation in immunity coverage for local vaccine with booster is 4.67% (immunity coverage ranging from 13.34 to 18.01), looking at values of *r*, varying from 0-0.3, at vaccination coverage of 55% (Table 17). Required vaccination coverage to obtain the minimum immunity coverage of 20% after one year varies from 65% in a situation without population growth (r=0) to 85% for a situation in which the dog population grows with a rate of 0.3. Given these required vaccination rates, the variation in costs is expressed as the difference in total costs compared to the costs based on the default growth rate of 0.144. The highest cost variation is $67,102 when *r* is 0 or 0.3 (Table 19).

When the government on Flores is uncertain about the population growth rate and wants to secure an effective immunity coverage, it is recommended to vaccinate a higher number of dogs (vaccination coverage of 85%). Considering a safety margin of 2 times the default setting on r this would mean that the government should invest $67,102 extra in the vaccination program, when vaccinating with local vaccine with booster.

The value for the variation in costs of $0.00 for *r* is 0.2 is caused to the fact that the minimum vaccination coverage does not decrease with increasing growth rate between r=0.2 and the default value of r=1.44? (Table 19). Corresponding cost effectiveness ratios, however, vary with an increase in ratio for the growth rate of 0.2.

Table 19. Costs of varying growth rate (0-0.3) for annual vaccination with local vaccine with booster, according cost-effectiveness ratio (total costs/%immunity coverage) and variation in costs($)

Growth rate (r)	Vaccination coverage (%)	Immunity coverage (%)	Total costs	Total costs/%Immunity coverage	Variation in costs
0	65%	21.28%	$450,279	$21,160	-$67,102
0,1	70%	20.74%	$483,830	$23,328	-$33,551
0,144	75%	21.26%	$517,381	$24,336	-
0,2	75%	20.10%	$517,381	$25,740	$0.00
0,3	85%	20.61%	$584,483	$28,359	$67,102

Import
The variation in immunity coverage for import vaccine is 6.51%, looking at values of *r* varying from 0-0.3, at vaccination coverage of 55% (Table 17). The required vaccination coverage to obtain the minimum immunity coverage of 20% after one year varies from 45% in a situation without population growth (r=0) to 60% for a situation in which the dog population grows with a rate of 0.3. Given these required vaccination rates, costs variations around the assumed value of 0.144 for population growth rate are presented in Table 20. The variation in costs around the assumed value of 0.144 for growth rate, with a range of approximately 0.15 is $50,718 ($228.230 versus $278,948) less costs for decreasing and $25,359 ($278,948 versus $304,307) more costs for increasing values of growth rate (Table 20).

When the government on Flores is uncertain about the population growth rate and wants to secure an effective immunity coverage, it should vaccinate more dogs (vaccination coverage of 60%). Considering a safety margin of 2 times the default setting on r this would mean that the government should invest $25,359 extra in the vaccination program, when vaccinating with import vaccine.

The value for variation in costs of $0,00 for the value of 0,2 for growth rate is due to the fact that the minimum vaccination coverage does not decrease with increasing growth rate between this value and the default value. (Table 20). Corresponding cost-effectiveness ratios, however, vary with an increase in ratio for the growth rate of 0.2.

Table 20. Costs of varying growth rate (0-0.3) for annual vaccination with import vaccine, according cost-effectiveness ratio (total costs/%immunity coverage) and variation in costs($)

Growth rate (r)	Vaccination coverage (%)	Immunity coverage (%)	Total costs	Total costs/%Immunity coverage	Variation in costs
0	45%	20.56%	$228,230	$11,101	-$50,718
0,1	50%	20.67%	$253,589	$12,268	-$25,359
0,144	55%	21.76%	$278,948	$12,819	-
0,2	55%	20.57%	$278,948	$13,561	$0.00
0,3	60%	20.31%	$304,307	$14,983	$25,359

4.4.3 Death rate (d)

The death of dogs on Flores has a default value of 0.45. Just as population growth, death is only partly under control of the decision maker. There is uncertainty about the true value of death rate. A change in the value of death rate could potentially have a big impact on the results of the previously presented results. Therefore it is interesting to look at the impact of a change in death rate (d) around the assumed value of 0.45.

Immunity coverage decreases with increasing death rate for all 3 types of vaccines (Table 21).
Therefore it is not desirable for the death rate to increase, because in this case the vaccination coverage requires to be higher for the immunity coverage to stay above the minimum value of 20% and hereby the costs will increase.

Table 21. Immunity coverage(%) of varying death rate ;r (0, 0.3,0.4,0.45,0.5,0.6) for annual vaccination with local vaccine with booster. Values with minimum immunity coverage of 20% are presented in bold.

	d	**Local**	**without**	**booster**		**d**	**Local**	**with**	**booster**		**d**	**Import**			
vaccination coverage (%)	**0.3**	**0.4**	**0.45**	**0.5**	**0.6**	**0.3**	**0.4**	**0.45**	**0.5**	**0.6**	**0.3**	**0.4**	**0.45**	**0.5**	**0.6**
5	0.88	0.80	0.76	0.72	0.65	1.65	1.49	1.42	1.35	1.22	2.30	2.08	1.98	1.88	1.70
10	1.77	1.60	1.52	1.45	1.31	3.29	2.98	2.83	2.70	2.44	4.60	4.16	3.96	3.76	3.41
15	2.65	2.40	2.28	2.17	1.96	4.94	4.47	4.25	4.04	3.66	6.89	6.24	5.93	5.64	5.11
20	3.53	3.19	3.04	2.89	2.62	6.59	5.96	5.67	5.39	4.88	9.19	8.32	7.91	7.53	6.81
25	4.41	3.99	3.80	3.61	3.27	8.23	7.45	7.09	6.74	6.10	11.49	10.40	9.89	9.41	8.51
30	5.30	4.79	4.56	4.34	3.92	9.88	8.94	8.50	8.09	7.32	13.79	12.48	11.87	11.29	10.22
35	6.18	5.59	5.32	5.06	4.58	11.53	10.43	9.92	9.44	8.54	16.09	14.56	13.85	13.17	11.92
40	7.06	6.39	6.08	5.78	5.23	13.17	11.92	11.34	10.79	9.76	18.39	16.64	15.82	15.05	13.62
45	7.94	7.19	6.84	6.50	5.88	14.82	13.41	12.76	12.13	10.98	**20.68**	18.72	17.80	16.93	15.32
50	8.83	7.99	7.60	7.23	6.54	16.47	14.90	14.17	13.48	12.20	22.98	**20.79**	19.78	18.82	17.03
55	9.71	8.78	8.36	7.95	7.19	18.11	16.39	15.59	14.83	13.42	25.28	22.87	**21.76**	**20.70**	18.73
60	10.59	9.58	9.12	8.67	7.85	19.76	17.88	17.01	16.18	14.64	27.58	24.95	23.74	22.58	**20.43**
65	11.47	10.38	9.88	9.39	8.50	**21.41**	19.37	18.43	17.53	15.86	29.88	27.03	25.71	24.46	22.13
70	12.36	11.18	10.64	10.12	9.15	23.05	**20.86**	19.84	18.87	17.08	32.17	29.11	27.69	26.34	23.84
75	13.24	11.98	11.39	10.84	9.81	24.70	22.35	**21.26**	**20.22**	18.30	34.47	31.19	29.67	28.22	25.54
80	14.12	12.78	12.15	11.56	10.46	26.35	23.84	22.68	21.57	19.52	36.77	33.27	31.65	30.11	27.24
85	15.00	13.58	12.91	12.28	11.12	27.99	25.33	24.09	22.92	**20.74**	39.07	35.35	33.63	31.99	28.94
90	15.89	14.37	13.67	13.01	11.77	29.64	26.82	25.51	24.27	21.96	41.37	37.43	35.60	33.87	30.65
95	16.77	15.17	14.43	13.73	12.42	31.29	28.31	26.93	25.62	23.18	43.66	39.51	37.58	35.75	32.35
100	17.65	15.97	15.19	14.45	13.08	32.93	29.80	28.35	26.96	24.40	45.96	41.59	39.56	37.63	34.05

Local without booster

The variation in immunity coverage for local vaccine without booster is 2.52%, looking at values of *d*, varying from 0.3-0.6, at vaccination coverage of 55% (Table 21). For no value of death rate (r), immunity coverage reaches the minimum value of 20%, for local vaccine without booster.

Since for no value of death rate, the minimum value of 20% for immunity coverage is reached, the costs will be evaluated for the maximum vaccination coverage, so the best case scenario. The cost effectiveness ratio will increase with increasing death rate (Table 22).

Table 22. Costs of varying death rate (0,3-0,6) for annual vaccination with local vaccine without booster and according cost-effectiveness ratio (total costs/%immunity coverage)

Death rate (d)	Minimum vaccination Coverage (%)	Immunity coverage (%)	Total costs	Total costs/%Immunity coverage
0.3	100%	17.65%	$135,248	$7,663
0.4	100%	15.97%	$135,248	$8,469
0.45	100%	15.19%	$135,248	$8,903
0.5	100%	14.45%	$135,248	$9,360
0.6	100%	13.08%	$135,248	$10,340

Local with booster

The variation in immunity coverage for local vaccine with booster is 4.69%, looking at values of *d*, varying from 0-0.3, at vaccination coverage of 55% (Table 21). Required vaccination coverage to obtain the minimum immunity coverage of 20% after one year varies from 65% in a situation with a death rate of 0.3, to 85% for a situation in which the death rate is 0.6. Given these required vaccination rates, the variation in costs is expressed as the difference in total costs compared to the costs based on the default death rate of 0.45. The highest variation in costs is $67,102 when *d* is 0.6 (Table 23).

When the government on Flores is uncertain about the death rate and wants to secure an effective immunity coverage , it should vaccinate more dogs (vaccination coverage of 85%). Considering a safety margin of 2 times the default setting on *d* this would mean that the government should invest $67,102 extra in the vaccination program, when vaccinating with local vaccine with booster.

The value for the variation in costs of $0.00 for *d* =0.5, is due to the fact that the minimum vaccination coverage does not decrease with increasing death rate between this value and the default value (Table 23). Corresponding cost effectiveness ratios, however, vary with an increase in ratio for the death rate of 0.5.

Table 23. Costs of varying death rate (0,3-0,6) for annual vaccination with local vaccine with booster, according cost-effectiveness ratio (total costs/%immunity coverage) and uncertainty ($)

Death rate (d)	Minimum vaccination coverage (%)	Immunity coverage (%)	Total costs	Total costs/%Immunity coverage	Variation in costs
0.3	65%	21.41%	$450,279	$21,031	-$67,102
0.4	70%	20.86%	$483,830	$23,194	-$33,551
0.45	75%	21.26%	$517,381	$24,336	-
0.5	75%	20.22%	$517,381	$25,588	$0.00
0.6	85%	20.74%	$584,483	$28,181	$67,102

Import

The variation in immunity coverage for import vaccine is 6.55%, looking at values of *d*, varying from 0.3-0.6, at vaccination coverage of 55% (Table 21). The required vaccination coverage to obtain the minimum immunity coverage of 20% after one year varies from 45% in a situation where death rate is 0.3 to 60% for a situation in which the death rate is 0.6. Given these required vaccination rates, costs for variations around the assumed value of 0.45 for death rate are presented in Table 24. The variation in costs around the assumed value of 0.45 for death rate, with a range of approximately 0.3 is $50,717.88 less costs for decreasing and $25,358.94 more costs for increasing values of death rate (d).

When the government on Flores is uncertain about the death rate and wants to secure an effective immunity coverage, it should vaccinate more dogs (vaccination coverage of 60%). Considering a safety margin of 2 times the default setting on *d* this would mean that the government should invest $25,359 extra in the vaccination program, when vaccinating with import vaccine.

The value for variation in costs of $0,00 for the value of 0.5 for death rate is due to the fact that the minimum vaccination coverage does not decrease with increasing death rate between this value and the default value. (Table 24). Corresponding cost-effectiveness ratios, however, vary with an increase in ratio for the death rate of 0.5.

Table 24. Costs of varying death rate (0,3-0,6) for annual vaccination with import vaccine, according cost-effectiveness ratio (total costs/%immunity coverage) and uncertainty ($)

Death rate (d)	Minimum vaccination coverage (%)	Immunity coverage (%)	Total costs	Total costs/%Immunity coverage	Variation in costs
0.3	45%	20.68%	$228,230	$11,036	-$50,718
0.4	50%	20.79%	$253,589	$12,198	-$25,359
0.45	55%	21.76%	$278,948	$12,819	-
0.5	55%	20.70%	$278,948	$13,476	$0.00
0.6	60%	20.43%	$304,307	$14,895	$25,359

5. Discussion

The objective of this study was to evaluate the cost-effectiveness of different vaccination scenario's for Flores Island (Indonesia). This has been done by gathering more insight in the rabies problem to contribute to the future decision making process regarding the control of rabies on Flores.

5.1 Results

Given the current policy on Flores, where dogs are vaccinated annually (scenario 1) and the local vaccine is applied without the needed boost vaccine, has shown to be ineffective.. Even a 100% coverage rate of all dogs will not result in an immunity coverage of 20% or more after one year. When the local vaccine is combined with the required booster a vaccination coverage of 75% is sufficient to meet the minimum level of 20% immunity. However, due to previous stated factors a coverage rate of 75% appears to be unfeasible on Flores. A switch from local to the import vaccine would mean that an immunity coverage of almost 22% will be reached after a year of vaccination, when applying the vaccine at a vaccination coverage of 55%. The costs for this strategy will be 400 thousand dollars and on a yearly base.

Because there is a limitation to the vaccination coverage of 55%, in scenario 2 a set value for coverage rate is taken into account. Furthermore it was shown that in this case annual vaccination with local vaccine without booster is insufficient and the local vaccine without booster should be applied every 6 months for the immunity coverage to remain above the effective value of 20%. This will cost approximately 400 thousand dollars a year. The local vaccine with booster should be applied every 9 months, with annual costs of approximately 500 thousand dollars. The import vaccine is effective enough when applied once for every 12 months, resulting in annual costs of approximately 400 thousand dollars per year. The cost-effectiveness ratios for local vaccine without booster and import vaccine in scenario 2 are both approximately 18 thousand dollars per percentage of immunity coverage. Taking into account the fact that annual vaccination is the standard procedure on Flores application of import vaccine is preferable. The low frequency of vaccinations as well as the low level of obtained immunity coverage will form a problem when using the local vaccine, since not all dogs will receive the second necessary vaccination.

It is assumed that dog rabies will be under control and eventually eliminated when vaccination campaigns will be effectively conducted (immunity coverage ≥20%) over a time span of 10 years (scenario 3). Since there are no restrictions when it comes to the vaccination plan, progress can be made annually. Therefore, when a vaccine is found to be effective after the year had passed, no further campaign needs to be conducted.

The required vaccination coverages for local vaccine without booster, local vaccine with booster and import vaccine over a 10 year period of time are resp. 65, 55 and 55%. The costs associated with these methods are in total3.7, 4.8 and 3.7 million dollars respectively. The import vaccine and local vaccine without booster are equal in costs, but because of its higher duration of immunity the import vaccine needs to be applied less frequently. Therefore it is possible for import vaccine to be more cost-effective at higher vaccine coverage than the local vaccine. So, looking over 10 years of time, application of the import vaccine at vaccination coverage of 55% will be the most cost-effective strategy in scenario 3.

A sensitivity analysis was performed to show the costs for different scenarios in which uncertainties in the duration of immunity (1/v), death rate (d) and population growth rate (r) are taken into account.

The required vaccination coverage rate needed in order to maintain the minimum of 20% for immunity coverage decreases in a degressive manner with an increase in immunity duration (Figure 10). Therefore, it can be very rewarding to look at longer lasting vaccines, with a duration of immunity up to 4 years. However, values of duration of immunity above this 5 years are not rewarding anymore, because the lowest level of vaccination coverage is reached (Table 15).

An increase in the population growth (r) or death rate (d) results in a maximum variation in the costs of vaccinating with the local vaccine plus booster of 76 thousand dollar. For a local vaccine plus booster vaccination campaign with a 55% vaccine coverage the total costs are 383 thousand dollar. Therefore the variation in costs is 17.5% of the total costs of this campaign.
For the import vaccine, the maximum variation in costs for an shift in population growth rate or death rate is 25 thousand dollar. The total costs of a vaccination campaign with import vaccine and vaccination coverage of 55% and annual vaccination application are 403 thousand dollar. In this case, the variation in costs is 6.29% of the total costs of the vaccination campaign.
So both for population growth rate (r) and death rate (d), the import vaccine is less sensitive for fluctuations than the local vaccine and is therefore the most preferable vaccine when aiming to reduce the risk of having to make more costs, while conducting an annual vaccination campaign.

5.2 Limitations

The dog population on Flores exists of a large amount of young dogs which are younger than 3 months of age. This is due to the high turnover in dog population. Because of this large group of young dogs, vaccination coverage is reduced, since vaccination only can be applied after the dogs are 3 months of age. However, young dogs can be infected by the rabies virus and consequently they form a serious threat in disease transmission.
Research by Wera (2014) showed that only 55% of the dogs on Flores island can be reached for vaccination. There are several reasons for this. First of all the large amount of dogs younger than 3 months of age. Other factors are owners that do not come to the vaccination because of the long distance between their house and the vaccination point, the poor infrastructure on the island, poor notification or the difficulty to catch and restrain the free-roaming dogs when the vaccination teams arrive (37).
This is inconvenient, since the WHO states that 70% of the total dog population needs to be vaccinated in order to control and eliminate the rabies virus (14,23). It appears that this high vaccination coverage rate cannot be reached on Flores. However, since rabies has a relatively low reproductive number (R_0) it was found that an immunity coverage of 20-40% after one year would be sufficient.

The effectiveness in the results given above might be a slightly overestimation. This has several reasons. First, the way dogs are kept on Flores Island contributes to a high death rate. The immune system of the animals is weak and therefore it is doubted whether the vaccine will work in every dog Furthermore, the climate in Indonesia is very warm, especially in the spring and summer. Some towns are that remote that they cannot be reached by common roads. Transporting the vaccines to these towns involves the vaccines being out of a refrigerator for a significant amount of time and this results in a lower effectiveness and hence duration of immunity caused by the vaccine. As was shown in the results section of this report, the immunity coverage decreases dramatically for decreasing durations of immunity (*1/v)* (Figure 10). Therefore, the vaccine with the highest value for *1/v* should be used in order to minimize the consequences of the transportation. With a duration of immunity of 3 years the import vaccine is therefore best suitable.

In the results of scenario 2 it was shown that the local vaccine needs to be applied twice a year in order for the immunity coverage to remain above the boundary of 20%. It was assumed that all dogs that came for the first vaccination also received their second vaccination. However, this does not hold true in practice. Reasons for this can be insufficient awareness of the importance of the second vaccination or the owner having different priorities, for example work.   Therefore, the estimation of the immunity coverage is an overestimation. Consequently, the true vaccination coverage when vaccinating 55% of all dogs on Flores will be lower. Vaccination programmes should therefore aim for a higher vaccination coverage.

Because registration is poor on Flores island, it is questionable whether the data on the number of dogs on the island was estimated correctly. It was estimated that the number of dogs registered during the vaccination campaign in 2012 should be increased by 30% in order to receive the actual number of dogs on the island. This is an educated guess, it is possible that even this last calculation results in an underestimation of reality. The government of Flores Island should enhance its registration systems in order to find the proper method of rabies control (8).

5.3 Opportunity costs of dog owners

The opportunity costs of dog owners consist of the income lost, due to the loss in time which the dog owner has to spend on participating with the vaccination campaign with its dog, instead of performing labour. These opportunity costs are not taken into account in the calculation of the costs for the different vaccines. Even though the government does not have to make these costs, these costs are made by the community. The value of the opportunity costs with annual vaccination campaign with minimum immunity coverage of 20% (when possible) are shown in Table 25.

Table 25. opportunity costs of annual campaigns with minimum immunity coverage of 20% for different vaccines*

Type of vaccine	Duration of immunity (1/v)	Vaccination coverage (%)	Immunity coverage (%)	Opportunity costs	Total costs incl. opportunity costs	% of total costs
local without booster	0.775	100%	15.19%*	$331,203	$680,830	48.65%
local with booster	1.5	75%	21.26%	$248,402	$1,014,186	48.99%
import	3	55%	21.76%	$182,162	$585,372	31.12%

*minimum value of 20% for immunity coverage not reached; not cost-effective

For the local vaccine with booster, the opportunity costs are twice as high as the other two vaccines. This is caused by the fact that the vaccination needs to be carried out twice a year.
Opportunity costs make up a large percentage of the total costs of a vaccination program and it is therefore important keep them in mind. These opportunity costs could be an additional reason why dog owners decide not to come to the vaccination. In this study it is assumed that every dog will come for their second vaccination, but in practice this is unrealistic.

5.4 Comparing costs with other study

In the study of Wera, the costs for mass vaccination were also estimated. The annual value of these costs was $273,600 on average for the years 2000 to 2011 (33). These costs are lower than the costs calculated in this study. A reason for this is that Wera used costs obtained in practice. Here the vaccination coverage and hence the costs are relatively low.
Furthermore, the vaccination was applied on a yearly base with the local vaccine, so without the additional booster after 6 months.
On the other hand Wera took the opportunity costs into account. As stated before these costs are responsible for a large amount of the total costs of mass vaccination. Therefore, the actual costs made by the government will be slightly lower than $273,600. Even though the opportunity costs will be made by the community.

In a comparison of results found in this study with the results found by Wera it was shown that in this study for the local vaccine without booster the costs (excluding opportunity costs) at a vaccination coverage of 55% are $198,648.Including the opportunity costs, the total costs will be $380,810. This is over $100,000 more than the findings of Wera. Reason for this difference might be the fact that the number of vaccinated dogs in Wera's study is an averaged number since the vaccination coverage varied between years. In some years the animal health authority only vaccinated 23% of the dog population while in another year 53% was reached.

In this study, total costs including opportunity costs for annual vaccination with the local vaccine without the boost with a vaccination coverage of 25% were calculated to be $180,796. The average value of total costs, given the costs of a strategy on 25% and 55% vaccination coverage is $280,803, This value is similar to the costs of $273,600 calculated by Wera (33).

5.5 Future

This study shows that there are cost-effective methods to vaccinate against dog rabies on Flores island. However, there is room for improvement, for example by adopting an effective vaccination campaign with proper timing and a vaccination type with a long duration of immunity.

Applying oral vaccination besides the parenteral vaccination could contribute to an increase in vaccination coverage, resulting in an increased effectiveness of the vaccination campaigns and even increasing the rate of controlling and elimination of rabies.
In a study conducted by Faizah *et al.* (9) the efficacy of an oral vaccine was compared to two types of parenteral vaccines. The local vaccine on Flores was used as one of the compared parenteral vaccines. In the study it was found that the antibody response generated by the oral vaccine raised more slowly than the response of the local vaccine. However, it persisted longer (Appendix I). Therefore, it was concluded that the oral vaccine is a safe alternative for parenteral vaccination and was recommended as method to control rabies in Indonesia (9).

Costs of oral vaccination do not only consist of the costs for the vaccine itself. The cost of bait delivery is also an important factor, because the vaccines need to be distributed (1). The total costs of oral vaccination are generally high (26,29).
Oral vaccination seems promising but has not been applied as vaccination against dog rabies. As mentioned before, the social acceptance of the inhabitants of Flores is very low, because people are afraid that their children will become contaminated by rabies by picking up a bait. Fortunately, other methods to distribute oral vaccines are available, for example door to door distribution. The owners of the dog receive a bait and make sure that their free-roaming dog receives the bait. In this case, the risk of human contamination minimalizes (26).
The free roaming dogs are usually not available for parenteral vaccination, because they are difficult to catch. It seems unlikely that the costs of the vaccination programme decrease when oral vaccination of free-roaming dogs is applied next to parental mass vaccination. It will, however, increase the coverage rate which is with a current level of 55% relatively low. In this way oral vaccination increases the rate of rabies elimination.

When, in the future, rabies will be eliminated it is important to take measures to forestall a second outbreak of the disease. Many rabies free countries, in for example Europe, demand that animals traveling towards the country are vaccinated against rabies to make sure that the disease is not reintroduced. So even after rabies will be controlled or even eliminated from Flores, it is recommended to continue vaccination programmes.
In the Netherlands dog owners need to pay for the vaccination of their own pets. If this would be the case on Flores Island it is not likely that dogs will be vaccinated annually since due to the bare economic situation of many inhabitants they have other priorities than to invest money in their animals. Here lies another challenge for the Flores' government.

To study the impact of dog rabies on human health, a “One health” approach is necessary. This approach makes use of an integrated dog-human epidemiological model to estimate the impact of dog vaccination on human health and thus the amount of PET treatments and human deaths. At this moment, such an integrated model is not available to reflect the situation on Flores and therefore further research is necessary to develop a one-health approach, applicable for Flores, and being able to predict the impact of dog rabies on human health.

6. Conclusion

Currently, dog rabies is a problem on Flores island (Indonesia). Annual vaccination campaigns are being carried out, but circumstances are not ideal. The currently applied vaccination strategies on Flores island are not cost-effective, since the minimum immunity coverage of 20% cannot be maintained until the end of the vaccination period.

If Flores island continues using the short term planning, which includes vaccinating on an annual base, the only cost-effective strategy will be vaccinating with the import vaccine at a minimum vaccination coverage of 55%. This is a large investment for Flores, since this switch in strategy will cost the government $204,500 per year. However, the result will be an effective vaccination campaign.

Looking over a long term planning horizon (10 year timespan), the lowest costs can be found in the strategies of vaccination with the local vaccine without booster and with the import vaccine. The cost-effectiveness ratio is lower for the import vaccine than for the local vaccine without booster and hence vaccination with the import vaccine is in the long term the most cost –effective strategy.

Concluding, Flores Island should replace its local vaccine by the import vaccine. No differences can be found between the short and long term approach since 12 months is the exact amount of time the import vaccine will stay effective (immunity coverage ≥20%). Because governments mostly make their plans per year, this makes the execution very practical for the government of Flores island.

7. Acknowledgments

The author gratefully acknowledges the support of supervisor Dr. Ir. M. Mourits and the chair group Business Economics of Wageningen University for making this project possible. The author would also like to thank Ewaldus Wera for providing information on his practical experience with vaccination programs, the culture and citizens of Flores Island, Indonesia. Finally, my dear friend and fellow student, Laura Pouwels is acknowledged for her help with language corrections on this paper.

8. References

1) Aubert M.F.A. (1999) Costs and benefits of rabies control in wildlife in France. Rev. sci. tech. Off. int. Epiz., 18(2), 533-543
2) Bingham J (2001) Rabies on Flores Island, Indonesia: is eradication possible in the near future? In: Doddet, B., Meslin, F.X., 2001. Rabies Control in Asia John Libbey eurotext Paris.
3) Bögel K. and Meslin F.X. (1990) Economics of human and canine rabies elimination: guidelines for programme orientation. Bulletin of the World Health Organization, 66 (3): 281-291
4) Choosing Interventions That Are Cost-Effective (WHO-CHOICE). Geneva: World Health Organization; 2010. Accessed at www.who.int/choice/en on 1 April 2014.1
5) Cliquet et al. (2007) The safety and efficacy of the oral rabies vaccine SAG2 in Indian stray dogs. Vaccine 25: 3409–3418
6) Coleman P.G. and Dye C. (1996) Immunization coverage required to prevent outbreaks of dog rabies. Vaccine, Vol. 14, No. 3, pp. 185-186
7) Cost-Effectiveness Analysis. Accessed at: http://ec.europa.eu/europeaid/evaluation/methodology/examples/too_cef_res_en.pdf on 23 June 2014
8) Davlin S.L. and Vonville H.M. (2012) Canine Rabies vaccination and domestic dog population characteristics in the developing world: A systematic review. Vaccine 30: 3492-3502
9) Faizah, Mantik-Astawa IN, Putra AAG, Suwarno (2012) The humoral immunity response of dog vaccinated with oral SAG2 and parenteral Rabisin and Rabivet Supra92. Indonesia journal of biomedical science 6: 26-29.
10) Fekadu et al. (1996) Immunogenicity, efficacy and safety of an oral rabies vaccine (SAG-2) in dogs. Vaccine, Vol. 14, No. 6, pp. 465-468.
11) Fitzpatrick et al. (2014) Cost-Effectiveness of Rabies Vaccination in Tanzania. Ann Intern Med; 160:91-100
12) Hampson et al. (2009) Transmission Dynamics and Prospects for the Elimination of Canine Rabies. PLoS Biol 7(3): e1000053. doi:10.1371/journal.pbio.1000053
13) Hampson K, Dushoff J, Cleaveland S, Haydon DT, Kaare M, et al. (2009) Transmission dynamics and prospects for the elimination of canine rabies. PLoS Biol 7(3): e1000053. doi:10.1371/journal.pbio.1000053
14) Häsler et al. (2012) Economic analysis of rabies control in Bali, Indonesia. WSPA, UK.7
15) King AA, Turner GS (1993) RABIES - A REVIEW. Journal of Comparative Pathology 108: 1-39.
16) Knobel, D.L., Lembo, T., Morters, M., Townsend, S.E., Cleaveland, S., & Hampson, K. (In press) Dog rabies and its control. In *Rabies: Scientific basis of the disease and its control*, 3rd editions (A.C. Jackson, ed). Elsevier
17) Knobel D and Hiby E (2009) Bali rabies control report and recommendations. WSPA
18) Manning et al. (2008) Human rabies prevention–United States, 2008: recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep 2008, 57(RR-3):1-28.
19) Mossong J. and Muller C.P. (2000) Estimation of the Basic Reproduction Number of Measles during an Outbreak in a PartiallyVaccinated Population. Epidemiology and Infection, Vol. 124, No. 2: pp. 273-278
20) OneHealth Tool. Accessed at: http://www.who.int/choice/onehealthtool/en/ on 13 may 2014
21) Putra AAG, Hampson K, Girardi J, Hiby E, Knobel D, et al. (2013) Response to a rabies epidemic, Bali, Indonesia, 2008–2011. Emerging Infectious Diseases 19: 648–651.
22) Rabies. Accessed at http://www.who.int/rabies/en/ on 7 April 2014
23) Rabies: About Rabies. Accessed at http://www.who.int/rabies/about/en/ on 2 April 2014

24) Rabies: Essential rabies maps. Accessed at http://www.who.int/rabies/rabies_maps/en/ on 7 April 2014
25) Robinson R (1993) Cost-Effectiveness analysis. BMJ volume 307
26) Schumacher, C. L. & Aubert, A. (1995). The oral delivery of rabies vaccine to dogs. In Proceedings of the third international conference of the southern and eastern African rabies group: 150–158.
27) Siko, M.M. (2011) DINAMIKA POPULASI ANJING DAN PENGARUHNYA TERHADAP CAKUPAN VAKSINASI RABIES DI RURAL DAN URBAN KABUPATEN SIKKA PADA BULAN OKTOBER 2009 - APRIL 2010. PhD Universitas Gadjah Mada
28) Sterner et al. (2008) Skunk Rabies in California (1992–2003)—Implications for Oral Rabies Vaccination. Journal of Wildlife Diseases, 44(4): 1008-1013
29) Sterner et al. (2009) Tactics and Economics of Wildlife Oral Rabies Vaccination, Canada and the United States. Emerging infectious diseases, Vol. 15, No. 8, 1176-1184
30) Sudhi Ranjan Garg (2014) Vaccines and Other Biologicals: Animal Vaccines. In: Veterinary Public Health & Epidemiology, Lala Lajpat Rai University of Veterinary and Animal Sciences, Hisar, Haryana, India. *Rabies in Man and Animals.* Springer India.
31) Sureau P (1992) Contribution to rabies prevention. Vaccine, Vol. 10, Issue 13
32) Susilawathi et al.(2012) Epidemiological and clinical features of human rabies cases in Bali 2008-2010. BMC Infectious Diseases 12: 81
33) Wera E, Velthuis AGJ, Geong M, Hogeveen H (2013) Costs of Rabies Control: An Economic Calculation Method Applied to Flores Island. PLoS ONE 8(12): e83654. doi:10.1371/journal.pone.0083654
34) WHO Expert Consultation on Rabies, second report (2013). WHO Technical Report Series. http://apps.who.int/iris/bitstream/10665/85346/1/9789240690943_eng.pdf
35) Windiyaningsih C, Wilde H, Meslin FX, Suroso T, Widarso HS (2004) The rabies epidemic on Flores Island, Indonesia (1998-2003). Journal of the Medical Association of Thailand 87: 1389-1393.
36) Zinsstag et al. (2009) Transmission dynamics and economics of rabies control in dogs and humans in an African city. PNAS, Vol. 6. No. 35: 14996–15001
37) Wera E, Mourits MCM, Hogeveen H (2014) Adoption of rabies control measures by dog owners in Flores Island"; submitted to PLOS Neglected Tropical Diseases.

9. Appendix I

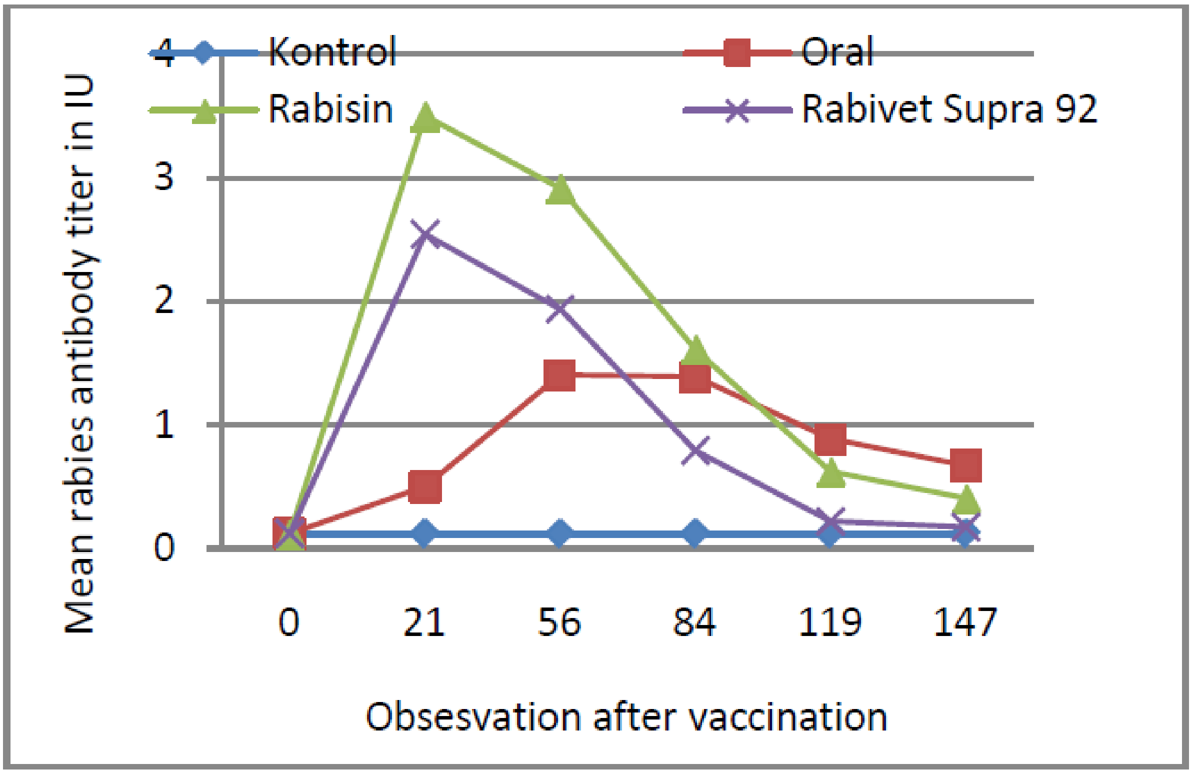

Figure 12. Comparing antibody titers in days of oral vaccination with parenteral Rabisin and Rabivet supra 92 (9)