SUMMARY

The aim of this study was to estimate the power of a badger vaccine field trial using simulation techniques. The effects of sample size, sensitivity and specificity of the diagnostic test, transmission rate between unvaccinated badgers, Vaccine Efficacy for Susceptibility (VES) and Vaccine Efficacy for Infectiousness (VEI) on study power were determined.

The most striking result was the large effect of the specificity of the diagnostic test on study power. Sample size had a small effect on power. Study power increased with increasing transmission rate between non-vaccinated badgers. Changes in VES had a higher impact on power than changes in VEI.

In summary, study power in group randomized trials depends not only on sample size but on many other parameters. In the current vaccine trial, power was highly dependent on the specificity of the diagnostic test. Therefore, it is critical that the diagnostic test used in the badger vaccine trial is optimized to maximise test specificity.

INTRODUCTION

Badgers (Meles meles) are an important reservoir of Mycobacterium bovis for cattle in Ireland and the United Kingdom and as a result, eradication of bovine tuberculosis (bTB) becomes likely impossible without measures to prevent cattle-to-badger transmission (More, 2009). In a recent Irish study, 36% of badgers were found to be infected with bTB (Murphy et al., 2010). In 2001, Ireland initiated a 10-year work programme investigating the use of Bacillus Calmette-Guerin (BCG) vaccine in badgers as a medium-long term strategy to assist with national bTB control and eradication (Corner et al., 2007; Lesellier et al., 2009). Based on a series of initial experimental studies in captive badgers, BCG vaccination in badgers was associated with a reduction in both the number and size of gross histological lesions (Corner et al., 2008*, Corner et al., 2010). These pen-based studies are currently being extended, with the design and implementation of a field trial in Ireland to evaluate vaccine efficacy in wild badger populations (Aznar et al., 2011).

In traditional vaccine field trials, individuals are randomly allocated (individual randomization) to either a vaccine or a placebo treatment and the relative risk of acquiring infection is determined by comparing infection rates in vaccinated and non-vaccinated individuals.
individuals. This design is appropriate for non-communicable diseases because the probability that an individual will become infected only depends on their susceptibility. Individual randomized trials allow the estimation of vaccine effects that reduce the susceptibility of an individual to infection or VES (Vaccine Efficacy for Susceptibility). This is also known as the direct effect of vaccination (Halloran et al., 1999). When dealing with infectious diseases, however, the likelihood that an individual will become infected depends not only on its susceptibility but also on the infectivity of surrounding individuals. The reduction in infectivity achieved by vaccination is known as Vaccine Efficacy for Infectiousness, (VEI) and is the result of the indirect effects of the vaccination in vaccinated and non-vaccinated individuals. With infectious diseases, group randomized trials are the design of choice, allowing estimates of both the reduction in susceptibility (VES) and infectiveness (VEI) (Riggs and Koopman, 2005), with herd immunity being the most important indirect effect. In a field trial to evaluate BCG vaccine efficacy in badgers, Aznar et al. (2011) outlined the use of group randomization to provide estimates of both VES and VEI based on incidence data from three badger populations vaccinated with BCG at different levels of vaccination coverage: 100%, 50% and 0%. VEI can be estimated using this design by varying the proportion of susceptible individuals across populations (Longini et al., 1998). In the badger vaccine trial, estimates of VEI may be particularly important, given the reported reduction in gross histological lesions (and, potentially, reduced infectiousness) in vaccinated badgers (Hayes et al., 2000, Corner et al., 2008). Aznar et al. (2011) have previously outlined how the combined effects of VES and VEI can be summarized using the Basic Reproduction Ratio (R0) estimated as a function of vaccination coverage (R(p)).

It is essential to estimate study power to determine whether a vaccine field trial design is sufficient to detect a difference in outcome of a particular size or larger between the vaccinated and non-vaccinated group (Riggs and Koopman, 2004). As outlined by Charvat et al. (2009), power calculations based on the comparison of two independent binomials in which indirect effects are not taken into account, can largely overestimate study power. The same study refers to these calculations as ‘naive’. In recognition of this concern, there have been recent changes both to trial design and to methodologies that are used to estimate sample size and power in these studies. In group randomized trials, where direct and indirect vaccine effects are each important, power depends on a range of factors. Riggs and Koopman (2004, 2005) looked at some of these factors including unit size (size of the groups), contact rate, external force of infection and infection duration. Computer simulation techniques are now frequently used to address study power estimation (Joines et al., 2000; Walters, 2004).

The aim of this paper is to estimate the power of a group randomized badger vaccine field trial designed to assess the effect of vaccination on M. bovis transmission in badgers using simulation techniques. The vaccine trial started in September 2009 and it will run for four years. The effects of sample size, sensitivity and specificity of the diagnostic test, transmission rate between badgers prior to the start of the trial, VES and VEI on study power are determined. Although sample size was determined prior to the start of the study based on logistical issues without potential for further expansion, power calculations are still relevant as other parameters affecting power, such as Se and Sp of the diagnostic test, could potentially be adjusted to optimize study power.
MATERIALS AND METHODS

Vaccine trial design

The vaccine trial area comprised about 750 square kilometres and it was divided into three zones North to South: A, B and C with similar characteristics in terms of size, number of main badger setts, cattle herds, cattle and land classification type. Three vaccination levels: 100%, 50% and 0% were allocated to zones A, B and C in a way that a gradient of vaccination coverage North to South was achieved. The vaccination trial started in September 2009 and three trappings have been already carried out in the trial area. The middle zone (Zone B) has been vaccinated at 50% coverage, while Zones A and C were randomly allocated to a 100% and 0% vaccination coverage. Vaccination within Zone B has and will be done randomly at an individual level (Aznar et al., 2011). Badgers have been trapped twice a year since the beginning of the trial. The first time badgers are trapped, they are allocated to a vaccine/placebo treatment. The treatment will be repeated on a yearly basis and the trial will run for four years since the start in 2009.

The model

The total number of expected newly infected vaccinated and non-vaccinated badgers (E(C)) at the end of every time interval (Δt or time between two subsequent trappings) were simulated using the cumulative binomial distribution with parameters (s, p), where s is the total number of susceptible badgers caught in each of the trial zones at the beginning of each time interval Δt, and p is the probability that each of these badgers will become infected during that time interval. E(C) was simulated by drawing a random number (between 0 and 1) from a uniform distribution and next, using the random number, s and p, the smallest integer E(C) is determined such that the binomial cumulative distribution function evaluated at E(C) is equal to or exceeds that random number (this is implemented as the BIN.INV function in Excel 2010 and as the CRITBINOM function in earlier versions). This procedure assures a random draw from a binomial distribution with parameters s and p. The probability of each of the badgers becoming infected (p) was dependent on the transmission parameter β, the fraction of infected vaccinated badgers (Fv) and the prevalence (Prev) of infection in the area where each badger was located during each time interval (Aznar et al., 2011).

Model parameterisation was determined based on expert opinion and/or data available at the time of model construction (see Table 1), as follows:

- Three hundred badgers were used in the simulation model including 120, 60 and 120 in zones A, B and C, respectively, based on the figures obtained during the first trapping exercise (120, 64 and 115 in zones A, B and C, respectively).
- The percentage of badgers re-trapped was set at 70%. No data was available at the time of the start of the study on re-trapping as only one trapping exercise had been carried out in the vaccine trial area. The figure of 70% was based on expert opinion based on previous trappings in other areas.
The initial prevalence for the three trial zones was set at 30%. In zone A, where no vaccination will be implemented, the prevalence was assumed to remain constant until the end of the trial. In zone B, where 50% vaccination will occur, prevalence was expected to reduce to 20% at the 7th and 8th trapping. In zone C, where we assumed all animals were vaccinated, prevalence was set to 20% at the second trapping, and to 10% and 5% at the fourth and seventh trappings, respectively.

The fraction of susceptible and infected badgers vaccinated was set to 0% in zone A. In zone B, this fraction was increased from 30% to 40% at the 5th trapping. In zone C, this fraction was increased from 60% to 70% in the 5th trapping, and then to 80% in the 6th and subsequent trappings.

Based on the simulated dataset and using the methodology described by Aznar et al. (2011) to estimate the four transmission parameters, $\beta_{UU}$, $\beta_{VV}$, $\beta_{UV}$ and $\beta_{VU}$, the transmission rate between non-vaccinated badgers was estimated to be $\beta_{UU}=0.1$.

Table 1. Table showing simulated dataset consisting on: trapping exercise number, zone of the vaccine trial, fraction of susceptible vaccinated badgers (fs), fraction of infected vaccinated badgers (fi) and prevalence used during the model simulations.

<table>
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<th>Trapping</th>
<th>Zone</th>
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<th>fi**</th>
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The simulation process

The badger vaccine trial was designed to run for four years with two trapping exercises per year. Therefore, a dataset of 42 records was generated (7 subsequent trappings x 3 trial zones x 2 vaccine status), comprising the total number of newly infected vaccinated and non-vaccinated badgers in each of the three trial zones at the end of each subsequent trapping. The final dataset was read into SAS (SAS 9.1, SAS Institute Inc., 2005) and a simulation process was set up by means of a macro. We performed 1,000 simulations for each set of conditions (see following section). In each simulation, a new random number was drawn and a t-test was used to test for the null hypothesis of the transmission parameters between vaccinated ($\beta_{VV}$) and non-vaccinated badgers ($\beta_{UU}$) being equal. The power of the study was then estimated as the fraction of simulations in which the null hypothesis was rejected at a 0.05 level of significance.

The scenarios tested

Se and Sp of the diagnostic test: The power of the study was estimated for all combinations of sensitivity (Se) between 0 and 100%, and specificity (Sp) between 98 and 100% at increments of 5% and 0.2%, respectively, assuming an initial transmission between non-vaccinated badgers of $\beta_{UU}=0.1$ and a vaccine effect on susceptibility (VES) and infectivity (VEI) of 80%. The same simulations were repeated assuming VES and VEI were each 40%.

Sample size: The study sample size was determined by both the expected number of trapped badgers and by re-trapping percentages. We explored the effects of sample size on study power by modifying both parameters so that the total number of re-trapped badgers varied from 10% to 100% of the expected number of badgers (120/60/120). We assumed an initial transmission between non-vaccinated badgers of $\beta_{UU}=0.1$(this is the figure obtained based on the simulated data), a Se of 40% and a Sp of 99.9%. Vaccine effect on susceptibility (VES) and infectivity (VEI) was set at 80% (we assumed that vaccination conferred protection against the infection to 80% of the vaccinated badgers and infectiousness of vaccinated badgers was reduced by 80%). The same simulations were repeated assuming VES and VEI
equal to 40%. To investigate the decrease in power observed for larger samples sizes, the same simulations were run assuming a perfect test with 100% Se and 100% Sp.

Initial transmission: We estimated power using a fixed Se and Sp of 40% and 99.9%, respectively, for vaccine effects (VE₁ and VE₅) of 80% and 40%, and for β₁ values of 0.3, 0.2, 0.1, 0.005 and 0.025. We aimed to see the effect of variations in the β₁=0.1 obtained from the simulated data on study power.

Vaccine effects on susceptibility and infectivity: Using a Se of 40% and a Sp of 99.9% and fixing VE₁ at 80%, power was estimated for different β₁ values (0.3, 0.2, 0.1, 0.005 and 0.025) and two values of Vaccine Efficacy for Susceptibility: VE₅=80% and VE₅=40%. The same simulations were done but in this case we fixed VE₅ at 80% and looked at the effect of modifying VE₁ from 40% to 80% on study power when β₁ values varied from 0.025 to 0.3.

Outputs

Two dimensional graphs were built using the software Mathematica® 6.0 (Wolfram Research, Champaign, IL). To obtain the function that best fitted our data, we used Stata® version 10 (Stata Corp, College Station, TX, USA) to fit a generalized linear model (GLM) with different links of the binomial family. The link with the lowest AIC was selected. Line graphs were built using Microsoft Excel 2003 (Microsoft Corporation, Redmond, WA, USA).

RESULTS

Study power for different sensitivity and specificity of the diagnostic test

The study power for different Se and Sp values of the diagnostic test are shown in Figures 1 and 2. A decrease in Sp has much bigger impact on power than a decrease in Se. In Figure 1 it can be seen that the power of the study decreases sharply to around 5% when the Sp is 98.0% independently of the Se of the test. The effect of the Se on study power is much lower and given a Sp of 98.8 remains above 50% even when the Se is 40%. A VE₅ and VE₁ of 80% were assumed in this graph. Similar results were obtained when we assumed a VE₅ and VE₁ of 40%. This is shown in Figure 2 where for a Sp of 99.8% and a Se of 40%, study power was 45%.
Study power for variations in sample size
The effect of a decrease in the expected number of total badgers re-trapped (120/60/120) is presented in Figure 3. Assuming a Se of 40%, a Sp of 99.9% and a transmission parameter for non-vaccinated badgers $\beta_{UU}=0.1$, the study power was determined for two scenarios: both VE$_S$ and VE$_I$ equal to 40% and 80%, respectively, when the percentage of total badgers re-trapped varied from 10% to 100%. Figure 3 shows an increase in study power as sample size increases from 10% to 30% and then a slow and small decrease as sample increases up to 100%.

To investigate reasons for the slow decrease in the study power observed as sample size increases, the same simulations were repeated using a perfect diagnostic test with 100% Se and 100% Sp. Then, it is shown that study power increases when sample size rises from 10% to 20% and remains constant up to 100% of the expected sample size (Figure 4). Assuming a perfect test, the study power varied from 79.8% to 85.9% when sample size increased from 30 to 300 badgers and VE$_S$ and VE$_I$ were equal to 40%. When VE$_S$ and VE$_I$ were equal to 80%, the study power varied from 91.2% to 95.8% as sample size went from 30 to 300 badgers.

![Graph showing the study power as function of the total percentage of badgers re-trapped and variation in vaccine efficacy. $\beta_{UU}$ was set at 0.1, VE$_I$ and VE$_S$ to 80% (or 40%), Se at 40% and Sp at 99.9%.](image-url)
Study power for variations in the initial transmission

A transmission value of 0.1 was used in all previous calculations of study power. In order to see the effect of deviations from this value on study power, we ran our macro keeping all other parameters fixed except $\beta_{UU}$. Figure 5 illustrates how the transmission rate between badgers prior to the start of the vaccine trial ($\beta_{UU}$) affects study power. Assuming $Se=40\%$, $Sp=99.9\%$ and $VE_S$ and $VE_I=80\%$, the study power increases from 77\% to 80\% when $\beta_{UU}$ increases from 0.1 to 0.3 and decreases to 0.63 when transmission is four times smaller (0.025). Under the same conditions but assuming a $VE_S$ and $VE_I$ of 40\%, power varies from 0.57 to 0.70 when $\beta_{UU}$ goes from 0.025 to 0.3. The power obtained when assuming an 80\% reduction in susceptibility and infectivity due to vaccination were on average 73.4\% versus an average of 63.4\% when the vaccine effects reduction was 40\%. In both cases, the power decreases as the transmission rate between non-vaccinated badgers decreases.
Fig. 5 Graph showing the power of the badger vaccine trial by transmission rate between non-vaccinated badgers (βuu) assuming a sensitivity and specificity of the diagnostic test of Se=40% and Sp=99.9%.

Study power for different vaccine effects on susceptibility and infectivity

To illustrate whether changes in the vaccine effect on susceptibility had higher, lower or equal impact on power than changes in the vaccine effect on infectivity, we ran our simulation process for the same range of βuu values as in the previous section but keeping VE_I =80% (Figure 6) or VE_S =80% (Figure 7) while varying the opposite vaccine effect. Both graphs then show the study power when VE_S and VE_I both equal 80% in a dark blue line (solid triangles) compared to the study power values when only one of the vaccine effects is 80% and the other is set at 40% (green line with solid squares).

The average study power when VE_I is 80% and VE_S is 40% is 65% (green line with solid squares in Figure 6) compared to an average of 72.2% (showed by a green line with solid squares in Figure 7) when VE_I is 40% and VE_S is 80%. If we compare these two averages with the average obtained when both vaccine effects are set to 80% (average power=73.4%), we can see then that changes in VE_S have a much higher impact on power than changes in VE_I. This is also observed by looking at the proximity of both lines in Figure 7 compared to Figure 6.
Fig. 6 Graph showing the power of the badger vaccine trial by transmission rate between non-vaccinated badgers ($\beta_{UU}$) assuming a sensitivity and specificity of the diagnostic test of Se=40% and Sp=99.9% and an effect of vaccination in infectivity of 80%; % and 40%, respectively.
DISCUSSION

Scientific evidence obtained from vaccine field trials has played an important role in public health, helping governments to plan successful vaccination programs. Estimating statistical power in a vaccine trial is of great importance. If done \textit{a priori} (before the trial starts), the optimal sample size to be used in the trial can be estimated. Using this sample size can give assurance of having sufficient statistical power to detect a pre-determined vaccine effect if it does indeed exist, whilst avoiding any unnecessary waste of resources. In the badger vaccine trial the maximum sample size was determined based on logistical issues without potential for further expansion of the vaccine trial area. Nonetheless, power calculations were still relevant as other parameters affecting power, such as Se and Sp of the diagnostic test, could potentially be adjusted to optimize study power.

A simulation approach was used to estimate the power of the trial where the following assumptions were made:

- The contact function is frequency rather than density-dependent. Riggs and Koopman (2004) show how in density-dependent models sample size has a much higher impact on study power than in frequency-dependent models. This is in agreement with the results obtained in our simulations. Power remained relatively constant, varying from 70\% to 87\% when sample size increased from 30 to 300 badgers (assuming a perfect
diagnostic test). De Jong et al. (1995) explain how for most animal diseases, a frequency-dependent contact rate function fits the data better than a density-dependent function. Therefore, our assumption seems reasonable.

- The badger prevalence in the trial area was assumed to be 30%. A recent study carried out in Ireland, where comprehensive bacteriological culture methods had been used, detected a prevalence of 36.3% in badgers (Murphy et al., 2010).
- The expected number of badgers being trapped in each trapping exercise was set to 120, 60 and 120 for zones A, B and C, respectively. Although the three zones in the vaccine trial area were selected to have a similar number of main badger setts, trappings conducted prior to the start of the trial revealed a lower number of badgers in Zone B compared to zones A and C.
- Data on the re-trapping percentage and the fraction of susceptible (fs) and infected (fi) vaccinated badgers were based on expert opinion. Although a sensitivity analysis was carried out to see the effect of changes on the re-trapping percentage, slower or faster changes in fs and fi were not explored.

The most striking result obtained during the simulations was the large effect of the specificity of the diagnostic test on study power. The minimum specificity required to achieve a power above 60% was 99.8%. The effect of the sensitivity on power was much smaller. Assuming both $VE_S$ and $VE_I=80\%$ and given a specificity of 99.8\%, the power remained above 50\% even when the sensitivity was 40\%. These results have substantial implications in terms of the optimization of the diagnostic test to be used in the vaccine trial, showing that although specificity needs to be very high, there is some degree of flexibility in terms of the sensitivity of the diagnostic test. The effect of sample size on study power was deemed to be very small. The small decrease observed on power as sample size increased (Fig. 3) disappeared when a 100\% Se and Sp test was assumed (Fig. 4). The decrease in power observed was proven to be an artefact.

Decreasing $VE_S$ and $VE_I$ both had a negative effect on power, but changes in $VE_S$ had a larger impact on power than changes in $VE_I$. For a $B_{UU}=0.1$, a reduction in $VE_I$ of 50\% (from 80\% to 40\%) resulted in a reduction in power from 77\% to 73\%, while the same reduction in $VE_S$ led to a higher reduction in power, going from 77\% to 62\%. The reduction in power is not considered high in either case, nonetheless the effect of $VE_S$ in power is something to consider because of the uncertainty around the biological mechanisms in which BCG vaccine works in badgers. Using BCG vaccine by the subcutaneous or mucosal routes in badgers, Corner et al. (2008) demonstrated a reduction in histological lesions in vaccinated badgers compared to non-vaccinated badgers but did not show individual protection against infection. This lack of protection has to be interpreted with caution as the challenging doses used during the experiments might not be representative of the natural infection dose. However, if the results obtained in the study are indicative of the real $VE_S$, study power could be somewhat compromised.

In summary, it can be concluded that study power in group randomized trials depends not only on sample size but on many other parameters. In the current vaccine trial, power was highly dependent on the specificity of the diagnostic test. Therefore, it is critical that the diagnostic test used in the badger vaccine trial is optimized to maximise test specificity.
ACKNOWLEDGEMENTS

I want to thank the Irish Department of Agriculture, Fisheries and Food (DAFF) for funding this project which is part of my PhD. I also want to thank James O’Keeffe for his expert contribution to data parameterisation.

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