Preventive Veterinary Medicine 111 (2013) 297–303

Contents lists available at SciVerse ScienceDirect

Preventive Veterinary Medicine

journal homepage: www.elsevier.com/locate/prevetmed

Estimating the power of a *Mycobacterium bovis* vaccine trial in Irish badgers

I. Aznar[a,b,*], S.J. More[a], K. Frankena[b], M.C.M. De Jong[b]

[a] *Centre for Veterinary Epidemiology and Risk Analysis, UCD School of Veterinary Medicine, University College Dublin, Belfield, Dublin 4, Ireland*

[b] *Quantitative Veterinary Epidemiology Group, Wageningen Institute of Animal Sciences, Wageningen University, P.O. Box 338, 6700 AH Wageningen, The Netherlands*

ARTICLE INFO

Article history:
Received 12 January 2012
Received in revised form 13 May 2013
Accepted 15 May 2013

Keywords:
Study power
Sample size
Vaccine Efficacy for Susceptibility
Vaccine Efficacy for Infectiousness
Group randomized trial

ABSTRACT

The aim of this study was to estimate the power, using simulation techniques, of a group randomized vaccine field trial designed to assess the effect of vaccination on *Mycobacterium bovis* transmission in badgers. The effects of sample size (recapture percentage), initial prevalence, sensitivity and specificity of the diagnostic test, transmission rate between unvaccinated badgers, Vaccine Efficacy for Susceptibility (VE_S) and Vaccine Efficacy for Infectiousness (VE_I), on study power were determined.

Sample size had a small effect on power. Study power increased with increasing transmission rate between non-vaccinated badgers. Changes in VE_S had a higher impact on power than changes in VE_I. However, the largest effect on study power was associated with changes in the specificity of the diagnostic test, within the range of input values that were used for all other modelled parameters. Specificity values below 99.4% yielded a study power below 50% even when sensitivity was 100% and, VE_I and VE_S were both equal to 80%. The effect of changes in sensitivity on study power was much lower.

The results from our study are in line with previous studies, as study power was dependent not only on sample size but on many other variables. In this study, additional variables were studied, i.e. test sensitivity and specificity. 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 maximize test specificity.

1. 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) will be highly unlikely without measures to prevent transmission between cattle and badgers and vice versa (More, 2009). In a recent Irish study, 36% of badgers were found to be infected with bTB (Murphy et al., 2010), with prevalence known to vary in areas of high (43.2%, Corner et al., 2012) and low (14.9%, Murphy et al., 2011) bTB prevalence in cattle. Focused badger culling is currently being used as a short-to-medium term strategy to limit transmission in areas of high bTB prevalence in cattle, with the expectation that culling will be replaced by badger vaccination once an effective bTB vaccine becomes available (Sheridan, 2011). 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

* Corresponding author at: Centre for Veterinary Epidemiology and Risk Analysis, UCD School of Veterinary Medicine, University College Dublin, Belfield, Dublin 4, Ireland. Tel.: +353 1 7166148; fax: +353 1 7166147.
E-mail address: inma.aznar@ucd.ie (I. Aznar).

0167-5877/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.prevetmed.2013.05.007

on a series of initial 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., 2007, 2008a,b, 2010). These pen-based studies were recently extended to the field, 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. This design is appropriate for non-communicable diseases because the probability that an individual will become infected depends only on their susceptibility. Individual randomized trials allow the estimation of vaccine effects that reduce the susceptibility of an individual to infection or Vaccine Efficacy for Susceptibility (VE_S), 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 (VE_I), and is the result of the indirect effects of the vaccination on vaccinated and non-vaccinated individuals, of which herd immunity is the most important. With infectious diseases, group randomized trials are the design of choice, allowing estimates of both the reduction in susceptibility (VE_S) and infectiveness (VE_I) (Riggs and Koopman, 2005). 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 VE_S and VE_I based on incidence data from three badger populations vaccinated with BCG at different levels of vaccination coverage: 100%, 50% and 0%. In such a trial, estimates of VE_I 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., 2008a). This trial design is similar to that outlined by Longini et al. (1998), who propose methodology, using unconditional parameters, to jointly estimate VE_S and VE_I from a trial conducted in only two populations. This approach, as used by Longini et al. (1998) and Aznar et al. (2011), has been defined by Hayes et al. (2000) as a hybrid of group and individually randomized trials.

As outlined by Charvat et al. (2009), power calculations based on the comparison of two independent binomials can largely overestimate study power if indirect effects are not taken into account. In recognition of this concern, there have been recent changes in both the design and analysis of vaccine trials to estimate sample size and power in these studies. In particular, computer simulation techniques are now frequently used to address study power issues (Walters, 2004; Barth-Jones et al., 2004).

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) examined some of these factors, including unit (group) size, contact rate, external force of infection and infection duration.

In this paper, we estimate the power, using simulation techniques, of a group randomized vaccine field trial designed to assess the effect of vaccination on *M. bovis* transmission in badgers. In this work, study power was defined as the proportion of simulations in which the null hypothesis (that the transmission parameter between vaccinated (β_{VV}) and non-vaccinated badgers (β_{UU}) was equal) was rejected at a 0.05 level of significance. Further, we assess the effects on study power of sample size (recapture percentage), initial prevalence, the sensitivity and specificity of the diagnostic test, transmission rate between badgers prior to the start of the trial, and VE_S and VE_I.

2. Materials and methods

2.1. Vaccine trial design

The vaccine trial area, covering approximately 750 km^2 in county Kilkenny, was divided into three zones (A, B and C) north to south, each 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 to achieve a north–south gradient in vaccination coverage. The middle zone (zone B) was vaccinated using a capture-tag-release protocol, to achieve and maintain 50% vaccination coverage throughout the trial period. In this zone, randomization was conducted at the level of the animal (Aznar et al., 2011). Zones A and C were randomly allocated to a 100% and 0% vaccination coverage.

The vaccination trial commenced in September 2009 and ran for 4 years. During each of the first 3 years, there were two trapping exercises over the entire trial area. At their first trapping, each badger was allocated to a vaccine/placebo treatment. A blood sample was taken at each capture during the trial period; however, treatment was repeated no more than once each year. During year 4, two trappings exercises were also conducted. At their first capture in year 4, a blood sample was collected, and each badger was either vaccinated or euthanased for detailed post mortem investigation. Data from the second trapping carried out in year 4 was not included in the analysis. Therefore, each badger could be captured, at most, on 7 separate occasions.

2.2. The model

The outcome from the vaccine trial will be of the form of a Bernoulli experiment. Data were collected about each badger at each trapping, including the infection status of each animal at the initial and each subsequent trapping.

Further to Aznar et al. (2011), the expected number of vaccinated $E(C_V)$ and non-vaccinated $E(C_U)$ badgers in each of the study zones that became infected with *M. bovis* between consecutive trappings can be estimated as:

$$E(C_V) = S_V * (1 - e^{-(K_0 + K_1 * Fvz) * PrevZ * \Delta t}) \text{ and}$$
$$E(C_U) = S_U * (1 - e^{-(k_0 + k_1 * Fvz) * PrevZ * \Delta t}), \text{ respectively.}$$

where $K_0 = \beta_{UV}$, $K_1 = (\beta_{VV} - \beta_{UV})$, $k_0 = \beta_{UU}$ and $k_1 = (\beta_{VU} - \beta_{UU})$.