Epidémiol. santé anim., 1997, 31-32

TESTING THE EFFECT OF INTERVENTIONS ON TRANSMISSION IN ANIMAL EXPERIMENTS AT LABORATORY SCALE

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Une description est donnée de la façon de réaliser des expériences de transmission et de les analyser ensuite sur le plan statistique. Le test d'hypothèse et l'estimation peuvent être faites très efficacement en utilisant un modèle stochastique.
Les méthodes statistiques sont décrites et expliquées à l'aide d'un exemple. La puissance statistique atteinte avec ces expériences de transmission est très élevée pour un nombre limité d'animaux et, par suite, ces méthodes sont utiles pour obtenir davantage de connaissance sur la transmission et sur l'évaluation pratique des mesures de contrôle.

INTRODUCTION

One of the main goals of epidemiology is to measure the reduction in disease or in number of infections after applying control measures or removing risk factors , i.e. after interventions. Traditionally, this epidemiological evaluation is done in the field under conditions under which the intervention would normally be applied. The advantage of such a field evaluation is that extrapolation to the practical application is relatively straightforward. One disadvantage is that spurious results can be obtained: the observed effect is not due to the treatment but occurs because of biases in the study design or is due to chance. Proper statistical methods should be used to keep these sources of error small. Another disadvantage is that if in the trial the intervention fails there is often little information from the trial data to improve the intervention.
Because of the disadvantages mentioned, all interventions are in the early stages of development tested under controlled circumstances in the laboratory. Only those intervention that are promising under laboratory conditions are tested in the field, because field experiments are often much more expensive than laboratory experiments.
Extrapolation of the laboratory experiments to the field is important to understand the reasons why particular interventions do or do not work in the field. If protection of the animal against clinical symptoms is the target of intervention intervention-challenge experiments are informative. Any discrepancy between field trails and laboratory experiments will provoke the development of more realistic challenge models and thus to a better understanding of the pathogenesis of the disease.
However, many interventions are used primarily to reduce the transmission of an infectious agent (De Jong, 1995) and in that case the intervention-challenge experiment is not very informative. Instead transmission experiments are needed (De Jong & Kimman, 1994). The transmission process leads to complicate dynamics because of the non-linearity and stochasticity (De Jong, 1995) and thus special statistical methods are needed to test and estimate the effect of intervention on transmission. Here we explain our approach which is an extension and improvement of earlier work by De Jong & Kimman (1994).

TRANSMISSION EXPERIMENT

The transmission experiment consists of (replicates of) two or more separate groups of animals: one or more treatment group(s) where all animals receive one particular intervention (vaccine, other housing) and a control group where none of the animals receive the intervention. All treatment groups and the control are housed in such a manner that the infectious agent is not transmitted from one group to the other. The experiments is started when half of the group is placed back with their own group after being some time earlier being inoculated with the agent. The period between inoculation and return to the groups is chosen so that the in-contact animals will not be infected by the inoculum. The statistical variable of interest is the nummer of in-contact animals that become infected.

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Figure 1
The p-value as function of R

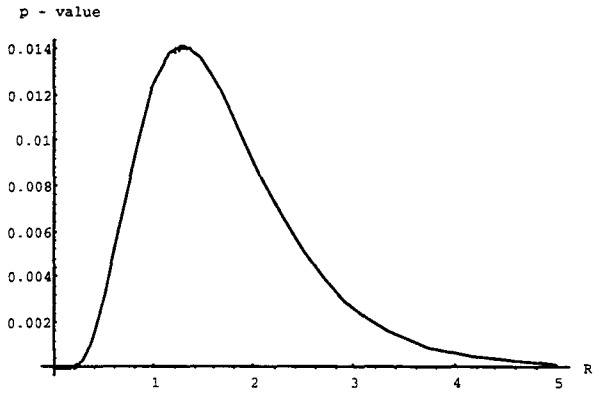
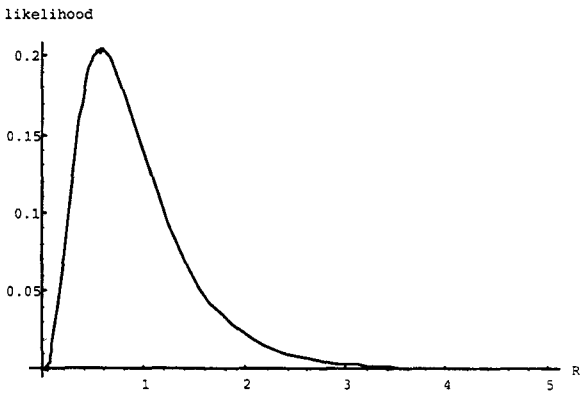


Figure 2
Likelihood function to estimate R



Example: One vaccine, two replicates and ten pigs per group. Thus, there are 4 separately housed groups each consisting of 10 pigs: 2 groups are vaccinated and 2 groups are not-treated and serve as control groups. Of each of the 4 groups 5 animals are inoculated with virus. The observed outcome is for the controls: 5 and 5 in-contact animals infected, and for the treatment: 2 and 1 in-contact animal infected.

Note that when actually doing this experiment an important part of the effort is the choice of the inoculation procedure and the definition and measurement of which animals are 'infected' (Bouma et al., 1996, 1997a,b). Here emphasis is on the statistical methods.

STOCHASTIC MODEL

Every statistical analysis necessitates a stochastic model describing the way fixed effects and chance effects can lead to the observed outcome. Here the stochastic model used is a model specific for the transmission process: the stochastic SIR model. As with all statistical methods validity of inferences is dependent on the validity of the model chosen. However, checks on the validity of the model are limited by the amount of data that can be collected (see discussion below).

Assuming identical animals at the start of the experiment within each (treatment) group each animal can be either 'susceptible' (S), infectious (I) or 'immune' (R from recovered). Note that 'susceptible' in terminology used may imply vaccinated but not yet been in contact with infectious agent. Two events can happen within the group: either an animal is infected (and becomes infectious) or an infectious animal recovers. Thus the stochastic SIR model is fully specified by the starting conditions (S_0 , I_0 and the population size N) and the rates at which the two events occur (Table I).

Table I
Model description for the stochastic SIR model

event	symbolic	rate	conditional probability
infection	(S,I) -> (S-1,I+1)	b SI / N	R*S / (R*S+N)
recovery	(S,I) -> (S,I-1)	aI	N / (R*S+N)

where N is the total number of animals in the group and R is the reproduction ratio (R=b/a).

For this model the probability distribution $Prob[X=x|R,S_0.I_0,N]$ of the observable stochastic variable X, i.e. the number of contact infected animals, can be numerically determined. It can be shown that this distribution depends only on R and not on b and a separately.

STATISTICAL ANALYSIS

First of all it has to be determined that there is a significant effect of the treatment:

$$H_0: R_{treatment} = R_{controle}$$
$$H_a: R_{treatment} < R_{controle}$$

The test statistic to be used is the difference (say Y) between the number of contact infections in the control group(s) and that in the group(s) that received any particular treatment. Given the initial conditions the distribution for Y is known from the distribution of X ($Prob[X=x|R,S_0.I_0,N]$) except for the value of R. Thus, the p-value for the test is the maximum of $Prob[Y^3y|R,S_0.I_0,N]$ where y is the observed value.

Example(continued): The observed difference is y=10-3=7. In Figure 1 the value of $p=Prob[Y^37|R,S_0.I_0,N]$ is plotted. The p-value is thus 0.014.

Yet another hypothesis test would test whether the R of the group after treatment is below one:

H_0: $R^3 1$

H_a: $R<1$

The test statistic here would be the total number of contact infections observed under the null hypothesis.

Example(continued): The observed number of contact infections is 3, p is thus p=Prob[Z£3|1,S_0.I_0,N] which is p=0.30 not significant.

Furthermore, the distribution may be used to obtain maximum likelihood estimates for R.

Example(continued): In Fig. 2 the likelihood is given with which the maximum likelihood estimation is done . This results in an estimated R=0.59 for the treatment group.

Optimality of experimental design in case of hypothesis testing is measured as maximal power. Numerical work showed that maximum power for a given number of animals is obtained when the groups are large and when about 50% of the animals in the group are inoculated.

CONCLUSIONS AND DISCUSSION

It was shown how transmission experiments can be analysed building on the earlier work by De Jong & Kimman, (1994). Furthermore, it was shown that considerable power can be obtained in transmission experiments under controlled conditions. Off course the conclusions are dependent on the assumptions that the particular model chosen for the analysis is valid. However, the model that was chosen is a model where the variation in number of infections caused by one individual varies much more than is probably true in reality. If this is the case, p-values are conservative and thus the high power is a realistic phenomenon.

Intuitively this can be understood as follows: all SIR models for transmission will lead to the qualitative behaviour that for R<1 there will be only minor outbreaks and for R>1 there will be both minor outbreaks and major outbreaks (see De Jong, 1995 and references therein). In this experimental setting the probability that a minor outbreak occurs when in fact R>1 is minimized because 50% of the experimental animals are inoculated. Thus, any outcome with small number of contact infections in the treatment group and all animals infected in the control group will be very unlikely and hence the large power.

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