COMPARISON OF TWO METHODS TO QUANTIFY TRANSMISSION FROM ONE-TO-ONE TRANSMISSION EXPERIMENTS.

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De Jong & Kimman[1] have reported on an experimental comparison and quantification of the transmission of a virus between pigs. Their approach was based on a method to calculate the probability of all feasible outcomes of a transmission experiment for a given transmission parameter. In their experiments the observed outcome was the total number of animals ever to be infected in the experimental group.

They were able to determine this number experimentally because there were good reasons to infer that the infectivity of individual animals is of short duration and that therefore the infection chain had stopped before the end of the experiment. For bacterial infections, the duration of infectivity cannot reasonably be assumed to be limited to a short period. Hence the experiment is often stopped when still both infectious and susceptible animals are present.

Thus, testing and estimation of transmission of a bacterial infection has to be based on the number of animals that were infected before an arbitrary stopping moment. To do this, the probability of all outcomes as a function of time has to be calculated. This can be done with a method following the general stochastic model developed by Bailey[2]. However, the implementation of this method is restricted to experiments with a limited number of animals and/or replicates, even though the formal analytical solution is available[3].

The question we want to answer is the following. If the method of De Jong & Kimman is used to quantify transmission from transmission experiments when actually the method of Bailey should be used, what error is to be expected? For simplicity and to understand the basic concept of the application of the algorithms used in the two methods, a one-to-one experiment is used for the comparison.

Material & Methods

In a one-to-one experiment one susceptible (S) is housed together with one infectious animal (I) in an isolation unit and both animals are monitored on the presence of the infectious agent. The population state is given by (S,I). Five combinations may occur: a starting state (S,I)=(1,1), two transient states (0,2) and (0,1), and two absorbing states (1,0) and (0,0).

Given that the population consists of one susceptible and one infectious animal, only two things can happen; first the susceptible animal can become infected and second the infectious animal can recover. The probability that the next change in the population is from an infection event is denoted by *p*. The probability that the next event is a recovery is *1-p*.

When an observed value of a response variable falls into two possible categories, it is called to be binary. The two categories in a one-to-one experiment are having one susceptible animal or having no susceptible animal on moment *t*, which depends on whether there has been an infection or not.

If *n* one-to-one experiments were carried out, all mutually independent, each experiment has the same success probability, *p*, of having an infection event. Then, the total number of infection events, *k*, is binomial distributed:

$$Q_{[y=k]} = \binom{n}{k} \cdot p^k \cdot (1-p)^{n-k}$$

The success probability *p* is a function of the transmission parameter *R*, which is derived from the SIR-model[4]. This transmission parameter *R* is also called the reproduction ratio, and is defined as the number of secondary cases caused by one typically infectious individual during its whole infectious period.

The difference between the two methods is a difference in the function *p*. According to the method of De Jong & Kimman, *p* is the following function with one parameter, *R*.

$$p = p_1 = \frac{R}{R+2}$$

According to the method of Bailey *p* is the following function with two parameters, *R*, and time, *t*, expressed as the number of infectious periods passed by.

$$p = p_2(t) = \frac{R}{R+2} - \frac{2}{R+2} \cdot e^{-\frac{2+R}{2} \cdot t}$$

Actually, p_1 is a special case of $p_2(t)$: p_1 equals the asymptotic value of $p_2(t)$ when *t* tends to infinity. This seems logical, because when time goes to infinity, the infection chain has had plenty of time to finish and will reach the final size of the outbreak. And reaching this final size was the assumption on which the method of De Jong & Kimman was based. Thus, the comparison of both methods can be done by looking at the differences in the estimates based on $p_2(¥)$ and $p_2(t<¥)$.

The most likely estimate of $p_2(t)$ is the observed proportion of successes, *k/n*. This proportion is known after having done multiple one-to-one experiments. So, the reproduction ratio, *R*, as a function of *t* can be estimated by equating $p_2(t)$ with *k/n*.

Results

An estimate of *R* alone does not imply a lot if there is no information about the precision of this estimate. This precision can be expressed by a confidence interval. The lower limit of the 95% confidence interval can be calculated by equating the summation of $Q_{[y=k]}$ from *k* to *n* with 0.025 and the upper limit can be calculated by equation summation of $Q_{[y=k]}$ from 0 to *k* with 0.025.

When using the method of De Jong & Kimman ($t=¥$) to derive an estimate of the R from experimental data, the R is always underestimated compared to when

using the method of Bailey ($t<¥$). This is illustrated in Figure 1, where the *R* was estimated from the example of 15 infection events were counted in 25 one-to-one experiments and plotted against *t*.

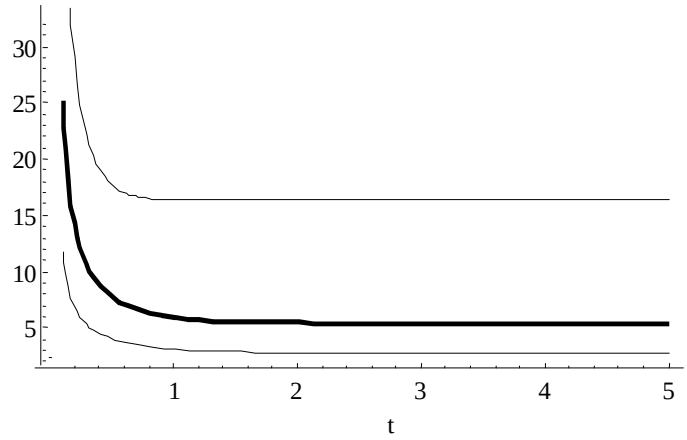

Figure 1: The estimated R and its 95% confidence interval in relation to the duration of the experiment (expressed as the number of infectious periods).

R has a threshold value one. When *R* is below this threshold, the infectious agent will be eradicated from the population. Thus, it is important to test whether *R* is smaller than 1 or not. To test this, the summation of $Q_{[y=k]}$ from 0 to k, with $p_2(t)$ and $R=1.0$ should be lower than the chosen critical value (0.05) in order to conclude that *R* is significantly smaller than 1.

When the duration of the experiment is very long compared to the duration of the infectious period and the method of De Jong & Kimman was used to test whether R<1, wrong conclusions can be drawn. So, in this case one should be cautious.

Transmission experiments are very often done to test the effect of an intervention on the transmission by exposing one group to an intervention (e.g. vaccination) and the other group not (control group). The difference in *R* between the two groups can be tested on significance according to a method described by De Jong & Kimman. It was proven by Velthuis & De Jong[5] that there is no difference between the two methods for testing a difference in *R*. So, if the main interest lies in testing for a difference in transmission between two treatments with data of one-to-one experiments, the two methods yield the same result.

References

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