ANALYSIS OF EU HORIZONTAL TRANSMISSION EXPERIMENTS

Klinkenberg D[1], Bouma A, De Jong MCM

Section of Quantitative Veterinary Epidemiology, Department of Immunology Pathobiology and Epidemiology, ID-Lelystad, P.O.Box 65, 8200 AB Lelystad, The Netherlands

Mathematical modelling is a useful tool in addressing questions in veterinary epidemiology. It can be used to evaluate measures taken to stop transmission of infection[1] or to predict what possible measures would do[2]. One of these possible measures to stop transmission of Classical Swine Fever Virus (CSFV) is vaccination. Vaccination often results in reduction of clinical symptoms[3], but in order to be a successful measure in fighting an epidemic it should be able to reduce transmission of the virus as well. An important tool in testing effectiveness of a vaccine (or possible other measures) is the transmission experiment.

Transmission experiments are experiments in which some individual animals in a group of animals are infected. Subsequently it is measured how many of the non-infected animals get infected during the experiment. In the spring of 1999 transmission experiments have been done with CSFV, in order to evaluate effectiveness of two different marker vaccines in reducing transmission of the virus between pigs[4]. The vaccines tested will in this presentation be called Bayer and Intervet, after their producers. Marker vaccines are vaccines with an accompanying test, which can discriminate between vaccinated and infected animals. In this presentation, the analysis of these experiments will be presented: it is statistically tested whether the vaccine works and additionally the basic reproduction ratio R_0 in time after vaccination is estimated.

Testing vaccine effectiveness

In order to test vaccine effectiveness, each of two marker vaccines has been tested in 8 transmission experiments, and additionally 3 control experiments (without vaccine) have been done. Each experiment consisted of a group of ten conventional (non-SPF) pigs. Five of these pigs were inoculated with CSFV, either 7, 10, 14 or 21 days after vaccination of the whole group or without vaccination (control groups). Each time interval was tested twice per vaccine. Subsequently, every two or three days blood samples were taken to test whether the animals were viraemic or seropositive.

With these tests the so-called final sizes were obtained: the number of animals per experiment ultimately infected. With these final sizes it was possible to test whether an experimental group (e.g. Intervet after 7 days) differed significantly from the control group. This was done by testing the null-hypothesis: $R_V = R_C$; R_0 in the vaccinated group = R_0 in the control group[5,6]. If the probability for the observed difference in number of contact infections between the experimental group and the control group is smaller than 0.05, the null-hypothesis is rejected and it is concluded that the vaccine works.

[1] The first author acknowledges financial support from STW, Utrecht, The Netherlands

In table 1 the p-values belonging to H_0 ($R_C = R_V$) are listed for all experiments. From this analysis it can be concluded that both vaccines are able to reduce transmission. For the Bayer vaccine that was showed for inoculation from 14 days after vaccination; for the Intervet vaccine for inoculation from 21 days after vaccination.

Time interval	*p-value Bayer*	*p-value Intervet*
7 days	0.0279*	0.151
10 days	0.151	0.292
14 days	0.0122*	1
21 days	0.00684*	0.0279*

Table 1: p-values for the null-hypothesis $R_C = R_V$.
*: vaccine significantly reduces transmission

Estimating the Reproduction Ratios R_0

Now that it is known that the vaccines do reduce transmission, it is important to know what R_0 becomes after vaccination. That makes it possible to make predictions on the spread of the disease if an area would be vaccinated. For that purpose we made use of the maximum likelihood estimation method, as explained in Klinkenberg *et al.*[7]. With that method, a separate estimation is done for β (transmission rate: expected number of new infections per infectious individual per day in a susceptible population) and α (recovery rate). R_0 then is calculated from these estimations: $R_0 = \beta/\alpha$.

Estimating R_0 over all experiments together
With both vaccines different time intervals between vaccination and inoculation have been tested. In our analyses we have assumed that R_0 changes over time from vaccination day until some day that maximal protection is achieved. This change is the same in all groups, no matter when inoculation has taken place. That means that, for instance, if an animal gets infected 18 days after vaccination, this was due to the same infection rate per infectious individual whether that happened in the 7 days groups or in the 14 days group. Therefore, after subdividing each

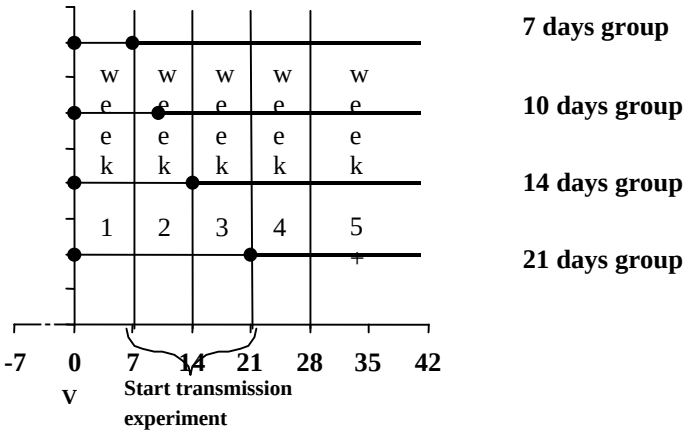

Figure 1. Schematic overview of the transmission experiments per vaccine. Although the transmission experiments did not start at the same time, for some part they did overlap. For estimation of R_0 over time, infection and recovery data have been pooled per week after vaccination (V). On x-axis time in days.

separate experiment into time intervals[6], we pooled all time intervals per week after vaccination over all experiments (figure 1).

With these data we first estimated R_0 per week after vaccination to get an idea of R_0 in time (table 2a). These estimations lead to the conclusion that after 21 days both vaccines reached their maximum protection level. Assuming that R_0 did not change after 21 days, we re-estimated R_0 in two time periods after vaccination: before 21 days and after 21 days. These estimations with accompanying 95% confidence intervals are listed in table 2b. With both vaccines R_0 is significantly decreased from 21 days after vaccination. R_0 is then estimated below 1 and although this is a statistically non-significant result, even with an R_0 of 1.2 no more than about 31% of a herd will ultimately be infected.

	Bayer	*Intervet*
Time	**R_0**	**R_0**
0 days	**6.8**	**6.8**
7-14 days	**--**	**9.1**
14-21 days	**2.1**	**2.3**
21-28 days	**0.28**	**0.51**
28+ days	**0.41**	**0.46**

(a)

	Bayer			*Intervet*		
Time	**R_0**	lower	upper	**R_0**	lower	upper
0 days	**6.8**	3.6	13	**6.8**	3.6	13
-21 days	**2.4**	0.91	6.3	**3.3**	1.3	8.2
21+ days	**0.36**	0.11	1.2	**0.47**	0.18	1.2

(b)

Table 2. Estimations of R_0. (a) Estimations per week after vaccination; 0 days is control group. (b) Estimations in two periods after vaccination, with lower and upper level of the 95% confidence interval

Acknowledgements

The authors thank the EU Commission for financing the project; Bayer AG, Leverkusen, Germany and Intervet BV, Boxmeer, the Netherlands for supplying the vaccines; and ID-Lelystad, the Netherlands and Bommeli, Switzerland for supplying the Ceditest and Chekit ELISA tests.

References

1. Stegeman JA, Elbers ARW, Smak JA, De Jong MCM. Quantification of the transmission of classical swine fever virus between herds during the 1997-1998 epidemic in The Netherlands. Prev. Vet. Med. 1999; 42: 219-234.

2. Graat EAM, De Jong MCM, Frankena K, Franken P. Modelling the effect of surveillance programmes on spread of bovine herpesvirus 1 between certified cattle herds. Prev. Vet. Med. *submitted*

3. Bouma A, De Smit AJ, De Kluijver EP, Terpstra C, Moormann RJM. Efficacy and stability of a subunit vaccine based on glycoprotein E2 of classical swine fever virus. Vet. Microbiol. 1999; 66(2): 101-114.

4. Uttental Å, *et al. In prep.*

5. De Jong MCM, Kimman TG. Experimental quantification of vaccine-induced reduction in virus transmission. Vaccine 1994; 12: 761-766.

6. Kroese AH, De Jong MCM. Testing and estimation for experimental data on transmission. *In prep.*

7. Klinkenberg D, De Bree J, De Jong MCM. R_0 estimation from horizontal transmission experiments. in Proceedings. ISVEE 2000: