**Report on the consequences of different design choices of the Bovine TB VIVA trial**

**Introduction**

Bovine Tuberculosis is an endemc disease in the Uk, causing..

Currently, the surveillance relies on a so-called Skin test,….

This means that vaccination can not be implemented

Recently, new DIVA tests have become available, that are able to…

These have only been evaluated in controlled conditions, necessitating a trial in realistic field conditions. This paper describes the effect that design choices, test charactreristics,

Modelling have indicated that a DIVA test would need to reach 99.85% specificity. The SICCT test have a reported specificity of ….

When evaluating a diagnostic test, the ideal way would be to use a Gold Standard test; a test that…

Unfortunately, in the BTB case, such a

Instead, this paper relies on a latent class analysis, following the approach pioneered by Hui Walter in …..

NIels Tofte have shown that….

**Methods**

**Data used**

-Three tests: 1,2,3

-Two populations: A,B

-Two vaccine statuses: +,-

-Sensitivity for each test, under positive and negative vaccination (reference for why this is needed?) (unknown, latent).

-Specificity for each test (unknown, latent).

-Prevalence of BTB for each population (unknown, latent)

-Number of vaccinated and unvaccinated animals in each population (known).

-Number of animals tested positive in each subpopulation for each test (measured)

-Number of animals tested negative in each subpopulation for each test

(measured)

This gives 3\*2\*2=12 measured counts, four known sizes, and 3\*2+2=8 unknowns. This should be an identifiable problem.

**Statistical Method**

Denote by the event that the first two tests, according to a specified ordering, are positive and the third is negative. Denote in a similar fashion the event of all three being positive (), the first and second test negative and the third positive () etcetera. Using this notation, we can write out the probability for a combined test result given population, vaccination status, and infection status, as:

For each triplet belonging to the set of permutations , we have

that :

and

**Considerations of identifiability**

If we assume that specificity of the standard test for vaccinated animals is 0.5, i.e completely unable to distinguish between negative and vaccinated animals, and you allow the sensitivity and specificity to range between 0 and 1, there is a degenerate solution for the above equations where the sensitivity of both the standard and the Viva test is zero, and they always show negative results for positive animals. A solution to this is to require that Sensitivity and Specificity both are above 0.5 (as otherwise flipping the sign would result in a better test) [though is this really the case?? Not sure when combining both Se and Sp…]

**Results**

We generated data assuming that the trial was run on four groups of 5000 individuals each: vaccinated and unvaccinated cattle , from either a high prevalence (modelled as a prevalence of 5%), or a low prevalence (modelled as 2%) population. During a sample run of this scenario, under the assumption that the true sensitivity of the VIVA test was 99.9%, the 95% posterior credible interval for the VIVA test specificity was borderline successful in proving that it was higher than the critical threshold value of 99.4%.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **lower** | **upper** | **True.value** |
| High prevalence pop | 0.0418 | 0.0629 | 0.0500 |
| Low prevalence pop | 0.0134 | 0.0247 | 0.0200 |
| SeStd vaccine pop | 0.6738 | 0.8264 | 0.7000 |
| SeStd nonvaccine pop | 0.6283 | 0.8542 | 0.7000 |
| SeViva vaccine pop | 0.5004 | 0.8329 | 0.7000 |
| SeViva nonvaccine pop | 0.5645 | 0.7569 | 0.7000 |
| SpStd vaccine pop | 0.5437 | 0.5645 | 0.5500 |
| SpStd nonvaccine pop | 0.9943 | 1.0000 | 0.9970 |
| SpViva vaccine pop | 0.9932 | 1.0000 | 0.9990 |
| SpViva nonvaccine pop | 0.9939 | 1.0000 | 0.9990 |

**Recommendations**

**Appendix**

**References**

**Refs to add**

**Btb vaccine**  Waters et al. 2012

Interferance with skin test (Whelan et al. 2011)

Eradication strategies Conlan etal 2012

DIVA tests (Vordermeier, Gordon, and Hewinson 2011; Jones et al. 2012)

SICCT test has a exceedingly high estimated specificity of > 99.99% (Goodchild and Clifton-Hadley 2001)

sensitivity relative to visible lesions with variable estimates of between 55.1%-95.5% (de la Rua-Domenech et al. 2006; Katerina Karolemeas et al. 2012).

currently viable DIVA tests are based on the gamma-interferon platform, which is known to have a considerably lower specificity than SICCT testing (Vordermeier, Gordon, and Hewinson 2011).

The SORI model is the more traditional view of bTB progression in cattle (Barlow et al. 1997; Kao et al.1997; Fischer et al. 2005)