DIVA test Se/Sp estimation using a Gold Standard test.

There is no real standard to define the numbers required to estimate sensitivity and specificity. We need to know the true sensitivity, and how precisely we need to estimate this figure.

From Andrew, original values from AHVLA for the test sensitivity and specificity are 64.4% and 99.4% respectively. More recent estimates are 77.3% and 99.5%. Using his target cutoff of 99.85 for the test specificity and the original ROC curve we can estimate the resulting sensitivity to be 41.1%. To bring us right up to date AHVLA claim that using 3 antigens they can attain a Sensitivity of 73.3% and Specificity of over 99.85%.

Table 1 details these values and the numbers needed for some accuracies. So, if we look at the first line: if the true sensitivity or specificity is 40% and we wish to be 95% certain that we'll get an estimate between 35% and 45% we would need to test 369 animals. For a given accuracy we need the largest number for a Se/Sp of 50%, with this decreasing as the Se/Sp approaches 100% (or 0%).

The 300 animals suggested for determining the Se suggests that this has been estimated for a value of 75% or thereabouts, with an accuracy of ±5%. It is harder to tell where the 1000 animals comes from, but it would appear to be assuming somewhere around 99.5% with an accuracy of about ±0.5%.

Andrew's modelling estimates that if we don't want a vaccination-DIVA policy to cost more than the present test-and-cull policy then we need a DIVA specificity of at least 99.85% To demonstrate this we would need a test with true specificity of 99.9% and 15,119 animals. Note that this just ensures that 95% of the time we would have a point estimate of over 99.85%, not that the 95% CI would be at, or above 99.85%. However, by symmetry, if the measured Sp was 99.9% the 95% CI would be above 99.85%. We would expect this to happen approximately 50% of the time.

However all this assumes that we have a “gold standard” test. That is: a test that perfectly corresponds to the true status of the animal. AHVLA appear to be suggesting the use of lesion identification and causal agent identification as a gold standard. Whilst this may have 100% specificity (although it depends on our case definition whether this is true or not), I am certain that it does not have anywhere near 100% sensitivity. It will miss early infections, and possibly later infections where the lesions are small.

There is also the issue of whether all animals ought to be vaccinated, or not. We probably ought to have 4 groups: vaccinated-negative, vaccinated-positive, unvaccinated-negative, unvaccinated-positive animals. This would give us two values for Sensitivity and two for Specificity.

In the absence of a gold standard we need to use a latent class analysis to get accurate and reliable estimates. For this we need at least two conditionally independent tests, and we were proposing the four populations above. It may be that using the three antigens can be considered as three conditionally independent tests. It is likely that we will need more animals than those suggested by the gold standard analysis, but we may be able to use a sub-population of the vaccination trial. It may be that we need to implement a presumed gold

standard approach to give initial estimates of Se/Sp, then use these as priors in the more extensive latent class analysis, performed as part of the vaccination trial.

Table 1: number of samples/animals required to obtain specified absolute accuracy at a number of different

True Se/Sp	Absolute accuracy	Number required	Comments
40%	±5%	369	
65%	±5%	350	
73%	±5%	303	Where the 300 come from?
77%	±5%	273	
99%	±5%	73	Really not precise enough
99.5%	±5%	3	Really not precise enough
99.85%	±5%	8	Really not precise enough
99.5%	±0.5%	764	
99.85%	±0.5%	231	
99.5%	±0.1%	18753	
99.9%	±0.1%	3823	
99.9%	±0.05%	15119	This is the only one that would enable us to demonstrate no cost disadvantage in vaccinating regimen