Risk assessment for tuberculosis in deer imported to Sweden

The Swedish Board of Agriculture (Jordbruksverket) has asked the National Veterinary Institute (SVA) to estimate the risk of importing tuberculosis infected deer under different testing requirements. Models of the Swedish tuberculosis control and status in wild and farmed game animals was also included in the request. The latter are under development, but will not be finalised until the first half of 2007.

This document contains background information on the tuberculin test and the data that form the basis for the import risk assessment, as well as the risk assessment itself. The assessment has been made based on the limited data available and due to time constraint the model is rather simple. It is possible that a more complex model would have been more realistic and if necessary such a model might be developed for future discussions. However, the simple model is transparent and should suffice as an initial basis for discussion.

It should be noted that all data, distributions and assumptions in this risk assessment model are based on data for other countries, as the issue concerns animals imported to Sweden under current import regulations. Therefore, none of the data should be extrapolated to Swedish deer, where the situation is sometimes very different, and where more detailed data are usually available.

Tuberculin testing

The tuberculin test may be applied either as a single intradermal injection of mammalian tuberculin or as a comparative test, using both mammalian and avian tuberculin. The test site most commonly used is the neck (i.e. the cervical site), but in some cases the tuberculin is applied in the caudal fold, the axillary region or the eyelid. Which method is used will affect the sensitivity of the test. The sensitivity of the tuberculin test is also known to vary with animal species, tuberculin potency (Bakker et al., 2005), age or genetic factors (affecting the ability to respond to tuberculin), environmental factors (e.g. cross-reactivity due to exposure to environmental mycobacteria), stage of the tuberculosis infection, presence of other diseases, and the skill and experience of the veterinarian performing the test (Wahlstrom, 2004). Moreover, recent tuberculin testing is known to affect the sensitivity of subsequent tests (Corrin *et al.*, 1987). In Sweden, an interval of at least 90 days is used for repeat tests.

Deer

In cervids, the cervical site is preferred. The reported sensitivity of the tuberculin test in deer varies between 76.5 % and 97% (Kollias *et.al.*, 1982; Corrin *et.al*., 1987; Stuart, 1988; Corrin *et.al*., 1993; Zomborsky *et.al*., 1995; Gaborick *et.al*., 1996; Palmer *et.al*., 2001; Wahlstrom, 2004; Bakker *et.al*., 2005). Some of the figures for the comparative test are lower than for the single test (using only mammalian tuberculin), ranging from 76.5% to 97% vs from 85% to 97%. Most of the cited reports use the comparative test, which may be the explanation for the wider range in sensitivity figures. However, a lower sensitivity would be expected for the comparative test, as this test is used to improve specificity, at the possible expense of sensitivity.

Reported figures for sensitivity are not truly comparable, since there are many variations in protocols for both testing and interpretation as well as in background factors that affect sensitivity. However, lacking more detailed and reliable data, the range of reported figures were used as a basis for the estimate of sensitivity in the risk assessment model below.

Post-mortem examination for tuberculosis in deer

Post-mortem examinations for tuberculosis include thorough necropsies as well as meat-inspection of slaughtered animals. The macroscopic examination of internal organs and lymph nodes usually determine whether further examinations by histology and bacteriology (culture or molecular detection methods) should be used, i.e. usually further investigations are only

made if visible lesions are detected. Visible lesions are expected to develop at a later stage of infection than the tuberculin reaction and this detection method would thus presumably be of lower overall sensitivity. However, this depends on the prevalence and expected stages of infection in the animal population investigated. A thorough necropsy would be expected to detect more lesions than the meat inspection procedure, as the latter is restricted to the main predilection sites for tuberculosis and is performed under more time constraint. Moreover, if samples from all lymph nodes and internal organs are examined by histology and bacteriology, bacteria and microscopic lesions that were undetectable by the naked eye may be revealed. O'Brien and co-workers (2004) estimated the sensitivity of sampling visible lesions in deer for further examinations, as compared to laboratory investigations of samples from all animals regardless of visible lesions, to about 75%. Corner and co-workers (1990), as well as Norby and co-workers (2004) reported that some 85% of all lesions in cattle identified by histology and bacteriology were detected by detailed necropsy. Most sensitivity figures for meat inspection are lower (de Kantor *et. al*., 1987, Corner *et. al*., 1990). Post-mortem examinations in wild deer are sometimes performed on material submitted by hunters, which would only include a limited amount of material, further reducing sensitivity (Palmer et al., 2000).
Overall, the reported estimates of sensitivity of post-mortem examinations vary between 36% and 85% (de Kantor *et. al*., 1987; Corner *et. al*., 1990; Palmer *et al*., 2000; Norby *et al*., 2004; O'Brien *et al.*, 2004).
When using post-mortem inspection to confirm or disprove a tuberculin reaction in a control programme for tuberculosis in farmed deer, this would presumably involve thorough necropsy and culture from all abdominal, thoracal, cervical and laryngeal lymph nodes regardless of visible appearance. The same applies to individual herds running a test programme for export of farmed deer. Therefore a higher estimate for sensitivity of post-mortem inspection of tuberculin reactors is used in the risk assessment model below.

Herd sensitivity vs sensitivity in individual animals.
The test sensitivity on herd level is usually higher than when the test is applied to a single animal. This is mainly because more than one infected animal may be present in an infected herd, and it is more likely that at least one of the tested animals will be in a stage of infection that is detectable by the test. Moreover, testing all animals in a herd means that not only is the sample size increased, but the probability of including the infected animal(s) increases to 1. Since tuberculosis is a slowly developing chronic disease, a newly infected animal from an infected herd may not be identified, but the infection may be revealed on herd-level.
Factors that affect herd-level sensitivity are: the sensitivity of the individual test, the number of animals tested and number of infected animals in the herd (within-herd prevalence). The herd-level sensitivity increases as within-herd prevalence increases, and with increasing numbers of tested animals.
When applying the tuberculin test in a control programme, reactor animals are usually culled and the result confirmed by post mortem investigations (see above). This requirement reduces the overall test sensitivity somewhat, since application of a serial interpretation (i.e. requiring both tests to be positive for the overall result to be positive) of the tuberculin test and post-mortem confirmation will produce an overall sensitivity on that particular animal that is lower than the sensitivity of the first test.
The herd level sensitivity of a test, when using the cut-off point of one positive animal as the definition of a positive herd can be estimated as $1-(1-AP)^n$, where AP is the apparent prevalence and n is the number of animals tested (Christensen *et al*., 2000). For tuberculosis in deer, one positive animal is enough to classify the herd as infected.

However, if all animals in a herd are tested, an estimate based on assumed within-herd prevalence and the combined sensitivities of the tuberculin test and post-mortem inspection might be more appropriate, especially if various testing regimens are to be compared. The estimate for a whole-herd test is then $1-(1-Se)^{no.\ inf.}$ (MacDiarmid, 1988), where Se, in this context, is the combined sensitivity of the tuberculin test and post-mortem confirmation of reactors, and no.inf. is the number of infected animals in the herd (calculated as the within-herd prevalence estimate * the estimated number of animals in a herd). This is the calculation used in the risk assessment below.
It should be remembered that most reported prevalence figures are probably an underestimation of the true prevalence, due to lack of sensitivity of the methods of detection (see post-mortem examination above).

Prevalence of tuberculosis in deer
There are large variations in the reported estimates of prevalence of tuberculosis in deer. Most reports include post-mortem surveys of wild animals. In such studies, the true prevalence will probably be underestimated, due to the fact that only animals with macroscopic lesions observed at slaughter or necropsy are included in the estimate (i.e. animals in earlier stages of infection will be missed). Moreover, for surveys based on hunted and slaughtered animals, a further reduction in sensitivity would be expected, since these include only apparently healthy animals. On the other hand, surveys based on animals found dead might give an overestimation of the prevalence, since such animals would be more likely to be infected with tuberculosis than healthy animals.
Most results from surveys of wild animals may be regarded as an estimate of within-herd prevalence (i.e. the proportion of an animal population that is infected), since they were conducted in a limited area on what could be expected to be a single animal population. However, some reports cover a more extensive region and the results may thus be regarded as an estimate of the overall prevalence on a regional or national basis.
As regards the few reports on farmed deer, most of them are based on post-mortem investigations, although a few include tuberculin testing of parts or the whole herd. However, confirmation of the diagnosis is made post mortem, so the prevalence figures mainly represent animals with macroscopic lesions detected at necropsy or slaughter. The majority of the results from reports on farmed deer represent within-herd prevalence. However, a few reports give figures for national (i.e. herd) prevalence. Unfortunately, the zoonoses reports from the EU member states rarely include figures for farmed deer. Only countries that aim to control tuberculosis in farmed deer report results for this animal species and, as expected, these figures are extremely low (0% for 2004, EFSA, 2006).
From wild deer, prevalence figures that may be regarded as estimates of within-herd prevalence range from 0 to 50% (Proud & Davis, 1998; O'Brien *et al*., 2004; Delahay *et al*., 2005; Miller & Kaneene, 2006; Vicente *et al*., 2006), and figures that may be regarded as representing overall prevalence range between 0 and 14% (Philip, 1989; Clausen & Korsholm, 1991; Jacques *et al*., 2003; Clifton-Hadley & Wilesmith, 2005; Lutze Wallace & Turcotte, 2005; Hermoso de Mendoza *et al*., 2006; Miller & Kaneene, 2006; Parra *et al.*, 2006; Vicente *et al*., 2006).
For farmed deer, estimates of within-herd prevalence range between 0 and 83% (Whiting & Tessaro, 1994; Kaneene *et al*., 2002) and estimates of herd prevalence range between 0 and 1% (Selwyn & Hathaway, 1990; Wyss *et al*., 2000; Kaneene *et al*. 2002; Griffin *et al.*, 2004). However, published data on herd prevalence (i.e. the proportion of infected deer farms in a country or region) are very limited and cannot be used as a reliable basis, therefore the overall prevalence estimate (see above) was used for herd prevalence in the risk assessment below.

Risk assessment
An attempt to estimate the risk of importing tuberculosis via farmed deer under various testing regimens is made below.

The testing regimens used for the 5 risk estimates were:

1) Only one comparative cervical tuberculin test (CCT) on each imported animal.
2) Two CCTs on each imported animal, 90 days apart.
3) Three CCTs on each imported animal, with 90 days between each test.
4) One CCT on all adult animals in the herd of origin.
5) Three CCTs on all adult animals in the herd of origin, with 90 days between each test.

The latter (5) is comparable to the requirements for trade of live deer within Sweden. The 90 day interval between tests is chosen to ensure no lingering effect from previous tests that might affect the results.

In all scenarios it is assumed that precautions are taken to ensure that the animal(s) or the herd are not infected after the testing regimen is introduced, such as isolation of single animals or restrictions on the introduction of live animals into the herd.

The exporting country is called “country X” in the models and is assumed to be any EU country from which deer might be imported.

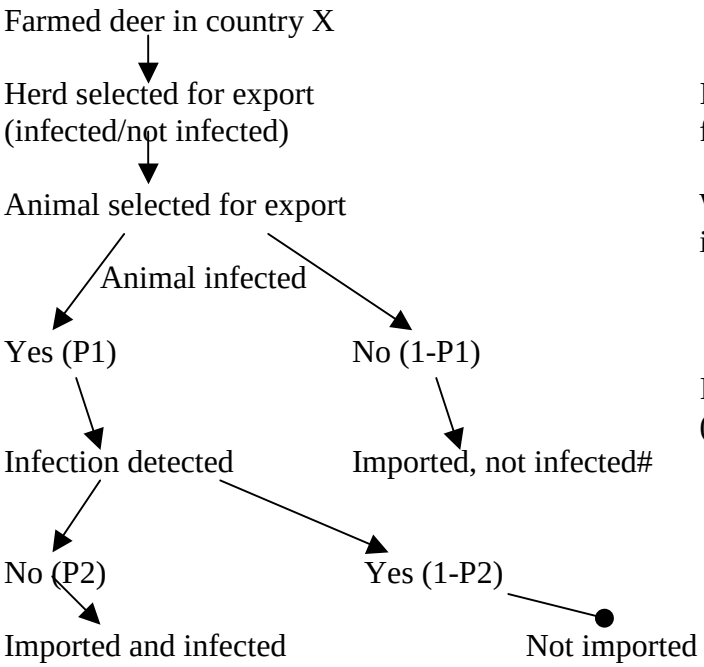
The **risk questions** were: What is the risk of importing a tuberculosis infected deer under the different testing regimens, expressed as the probability of any (i.e. an average) animal being infected and as the probability of importing at least one infected animal during a ten-year period. The latter assumes an average yearly import of 24 animals. This figure is based on actual import applications to Sweden during the past 10 years.

Input data for the maximum and minimum figures for prevalence and sensitivity of the tuberculin test were derived from the publications cited above. For minimum prevalence in an infected herd (the estimate used in the model assumes that the herd is infected, i.e. minimum prevalence >0), one infected animal was assumed, and the maximum value was derived from the publications cited above. For the most likely prevalence values, the expert opinion of Susanna Sternberg Lewerin and Helene Wahlström was used. The figures for sensitivity of PM inspection of tuberculin reactors were based on the expert opinion of Susanna Sternberg Lewerin, Helene Wahlström and Göran Bölske[1].

For the herd size figures, an attempt was made to estimate the sizes of herds exporting to Sweden during the last 10 years. However, these data were mostly unavailable apart from one very large Danish herd, which made the data very skewed. Instead, the average herd sizes in member countries of the Federation of European Deer Farmers’ Associations (www.fedfa.com) were used for minimum and most likely values, and the large Danish herd as the maximum value.

[1]Associate Professor Susanna Sternberg Lewerin, DVM, PhD and Dr Helene Wahlstrom, DVM, PhD, Department of Disease Control, and Dr Göran Bölske, DVM, PhD, head of TB laboratory, Department of Bacteriology, all in the National Veterinary Institute, Uppsala

A) Model framework (1-3)



Model inputs

Herd prevalence of tuberculosis in farmed deer in country X

Within-herd prevalence of tuberculosis in farmed deer

Individual sensitivity of tuberculin test (Se ind)

#For simplicity, lack of test specificity is not included, i.e. no false positive animals are assumed. This might lower the risk estimate slightly (due to a higher estimate of the denominator for R below), but is assumed of less consequence.

Calculations
P1 = estimate for herd prevalence * estimate for within-herd prevalence
(This is the probability that an individual farmed deer in country X is infected)

1-P1 is the probability that an individual farmed deer in country X is not infected. Such animals do not contribute to the risk. Some of them may test false positive and therefore not be imported, but this is not included in the calculations as it is not assumed to have a significant effect on the final estimate (see # above)

P2 = $(1\text{-Se ind})^{\text{times tested}}$
(This is the probability that an infected animal is not detected by the testing regimen)

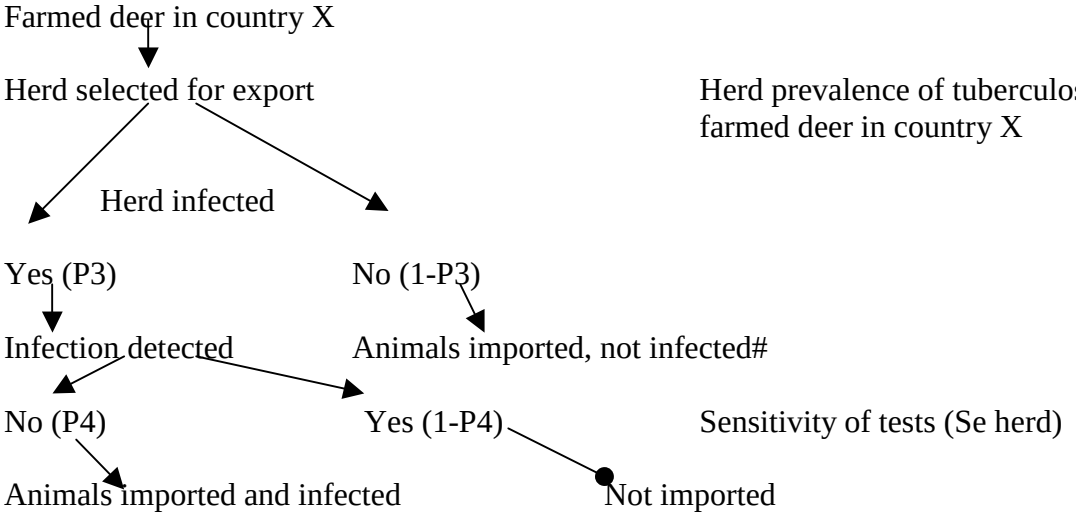
1-P2 is the probability that an infected animal is detected by the testing regimen. Such animals will not be eligible for import and do thus not contribute to the risk

Probability of one imported animal being infected = R(A)

R(A) = P1 * P2/((P1 * P2)+(1-P1))

Probability of importing at least one infected animal during a ten-year period assuming 240 imported animals during this period = $1- (1\text{-R(A)})^{240}$

B) Model framework (4-5) **Model inputs**



#For simplicity, lack of test specificity is not included, i.e. no false positive herds are assumed. This might lower the risk estimate slightly (due to a higher estimate of the denominator for R below), but is assumed of less consequence.

Calculations
P3 = Estimate for herd prevalence
(This is the probability that an individual deer farm in country X is infected)

1-P3 is the probability that an individual deer farm in country X is not infected. Animals from such farms do not contribute to the risk. Some of them may have animals that test false positive which would exclude the farm from export, but this is not included in the calculations as it is not assumed to have a significant effect on the final estimate (see # above).

P4 = $(1\text{-Se herd})^{\text{times tested}}$
(This is the probability that an infected herd is not detected by the testing regimen)

1-P4 is the probability that an infected deer farm is detected by the testing regimen. Animals from such farms will not be eligible for import and do thus not contribute to the risk.

Probability of one imported animal being infected = R(B)
Probability of selected export herd being infected but not detected= P3*P4/((P3*P4)+(1-P3))

R(B) = P3*P4/((P3*P4)+(1-P3))*within-herd prevalence
(This is the probability that one selected animal from the herd is infected)

Probability of importing at least one infected animal during a ten-year period assuming 240 imported animals during this period = $1- (1\text{-R(B)})^{240}$

Data and probability distributions for model inputs

Input	Data	Distribution
Herd prevalence of TB	Maximum, minimum and most likely figures for overall prevalence based on published reports and expert opinion	BetaPert (0, 0.02, 0.14)
Within-herd prevalence of TB	Maximum, minimum and most likely figures for prevalence based on published reports and expert opinion	BetaPert (1/n, 0.02, 0.8)
Individual sensitivity of tuberculin test (Se ind)	Maximum and minimum figures based on published reports	Uniform (0.765, 0.97)
Sensitivity of post-mortem inspection performed on tuberculin reactors (Se PM)	Maximum and minimum figures based on expert adjustment of data from published reports	Uniform (0.85, 0.95)
Sensitivity of herd testing in scenario 4 and 5 (Se herd)	$1- (1-(\text{Se ind} * \text{Se PM}))^{\text{no. inf.}}$	
Herd size in scenario 4 and 5 (n)	Average herd size in FEDFA member countries, and herd size of herds exporting to Sweden during the past 10 years	BetaPert (20, 80, 2000)
Expected number of infected animals in infected herds that would export to Sweden (no. inf.)	n * within-herd prevalence	

The model was built and run in @Risk (Palisade Co. Ithaca, USA), with 10 000 iterations.

Risk assessment results

The median values for the outcome of the model simulations are presented below. Figures within brackets represent the 5th and 95th percentile, respectively. CCT= comparative cervical tuberculin test.

Testing regimen	**Risk of one imported animal being infected**	**Risk of importing ≥ 1 infected animal during 10 years**
1 CCT on each imported animal	$4*10^{-4}$ ($3*10^{-5}$, $3*10^{-3}$)	$9*10^{-2}$ ($6*10^{-3}$, $46*10^{-2}$)
2 CCT on each imported animal (90 d apart)	$5*10^{-5}$ ($2*10^{-6}$, $5*10^{-4}$)	$2*10^{-2}$ ($4*10^{-4}$, $10*10^{-2}$)
3 CCT on each imported animal (90 d apart)	$6*10^{-6}$ ($1*10^{-7}$, $9*10^{-5}$)	$1*10^{-3}$ ($2*10^{-5}$, $2*10^{-2}$)
1 CCT on all adult animals in the herd of origin	0 (0 , $4*10^{-6}$)	0 (0 , $9*10^{-4}$)
3 CCT on all adult animals in the herd of origin (90 d apart)	0 (0 , $2*10^{-10}$)	0 (0 , $4*10^{-8}$)

In summary, the risk of importing tuberculosis infected deer (whether expressed as the median risk of importing one infected animal or the 10-year probability of importing at least one infected animal) is substantially larger when testing single animals as compared to the whole herd. The risk in an individual animal decreases about ten-fold with each tuberculin test. The median value of 0 for the whole herd testing schemes reflect the skewed distribution of the model outputs. The reason for using the median values were that due to the skewed distributions, medians were more stable than averages, and thus regarded as more representative.

The average, or expected values, of the model outputs are detailed below.

Testing regimen	**Risk of one imported animal being infected**	**Risk of importing ≥ 1 infected animal during 10 years**
1 CCT on each imported animal	$7*10^{-4}$	$14*10^{-2}$
2 CCT on each imported animal (90 d apart)	$1*10^{-4}$	$3*10^{-2}$
3 CCT on each imported animal (90 d apart)	$2*10^{-5}$	$5*10^{-3}$
1 CCT on all adult animals in the herd of origin	$2*10^{-6}$	$4*10^{-4}$
3 CCT on all adult animals in the herd of origin (90 d apart)	$3*10^{-8}$	$8*10^{-6}$

The results demonstrate that increasing the number of tests decreases the risk of introducing tuberculosis infected deer. Furthermore, testing the whole herd instead of single animals leads to a decreased risk.

Discussion

The results indicate that if 240 deer are imported with only one tuberculin test on each individual animal an average of $14*10^{-2}$ tuberculosis infected animals will be imported. During a 30 year period, with 720 imported animals, the expected number of imported infected animals would be 0.4. This seems realistic if compared with the recent history in

Sweden. During the 80s, about 600 deer were imported with only one test on each animal and tuberculosis was demonstrably introduced via these imports.

It should be emphasised that these estimates are based on very rough assumptions about biological data that cannot be truly estimated at present. However, it is not surprising that testing the whole herd lowers the risk (see discussion on herd-level sensitivity vs. individual sensitivity above).
Moreover, the calculations assume that all tuberculin tests are independent, which is not true. The estimates for these tests may thus be slightly exaggerated, and the risks underestimated. This applies to all tuberculin testing schemes in the model.

Due to the large differences in herd prevalence between various exporting countries, large variations in risk must be expected for different countries. Fixing the herd prevalence value at the maximum (14%) used in the model above increased the risk about 5-fold for the single animal testing schemes and 10-fold for the whole-herd testing schemes.
A simulation was also run imagining a “worst case scenario” with herd and within-herd prevalences fixed at maximum values (14% and 80%, respectively) and test sensitivities for the tuberculin test and post-mortem examination at minimum values (76.5% and 85%, respectively). This resulted in a 100-fold increase of the risk for the single animal testing schemes. As the results for the herd testing regimens depend on herd sensitivity and this sensitivity increases with increasing within-herd prevalence, this is not a “worst case scenario” for the herd testing schemes 4 and 5.

The number of imported animals is expected to have a large effect on the 10-year risk estimates. As no data on expected future import figures are available, this is hard to estimate. However, the restrictive import policy during the past 10 years may have resulted in a smaller number of import applications than would be the case should this policy be changed. During the 1980s, when the Swedish import requirements were less stringent, a total of 608 farmed deer were imported to the country. A larger number of imported deer would inevitably result in a larger estimated risk of importing tuberculosis.

The estimates include a large amount of uncertainty, both due to lack of data and due to inherent variability in the variables included in the model. More reliable data may thus reduce some of the uncertainty in the estimates, but they will always remain rough estimates of the true risks.

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