**ADVISORY COMMITTEE ON THE MICROBIOLOGICAL SAFETY OF FOOD**

**INFORMATION PAPER**

# Risk assessment for the use of *Mycobacterium bovis* BCG Danish Strain 1331 in Cattle: Risks to public health

This paper a): informs Members on current work being funded by Defra and the Welsh Government to develop a CattleBCG vaccine that will contribute to the TB eradication programme, b): provides an outline of a risk assessment being conducted at AHVLA Weybridge to assess the risks to public health for certain milk and meat products from vaccinated cattle entering the food chain and, c): to flag that ACMSF will be asked to comment on the risk assessment when it is completed later this year.

## Background

1. Defra and the Welsh Government have funded a research and development programme to develop a BCG cattle vaccine against bovine TB. The vaccine has been shown to provide a degree of protection to cattle in both experimental and a field environment with a high infection pressure. However, there is currently an EU-wide ban on its use, primarily because BCG vaccination in cattle causes the animals to react to the current tuberculin-based tests, therefore hindering disease control programmes based on test and slaughter. To overcome this issue, the research programme has also developed a diagnostic test to Differentiate between Infected and Vaccinated Animals (DIVA), the most developed of which is based on the interferon-gamma platform.

2. In January 2013, the European Commission set out a tentative timeline[1] of the steps to take to be able to deploy a cattle BCG vaccine and associated DIVA test. These steps include large-scale, long-lasting (2-5yr) field trials of the vaccine and DIVA test.

3. The ultimate step in this process is the licensing of the vaccine. In January 2012 AHVLA submitted an application for a Marketing Authorisation (MA) for a BCG cattle TB vaccine (CattleBCG) to the UK Veterinary Medicines competent authority, the Veterinary Medicines Directorate (VMD) for assessment. During the course of their assessment, the VMD identified data gaps in the application some of which are concerned with the lack of opportunity (to date) to conduct field trials in the UK. The VMD assessment and list of data gaps were ratified by the Veterinary Products Committee (VPC), the independent scientific committee which advises VMD and also outlined the issues which would need to be resolved in order to conduct a field trial in the UK. Field trials, if agreed with the European Commission, could be conducted in GB providing sufficient information is provided to the VMD to allow grant of an Animal Test Certificate (ATC)

4. The European Commission requested an opinion from EFSA on the components for field trials for the use of a BCG vaccine against bovine TB and an associated DIVA test. This was published in December 2013[2] and included advice on how a trial might

[1] Letter from European Commissioner for Health and Consumer Protection to the Secretary of State for Environment, Food and Rural Affairs, 14 January 2013 https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/183229/bovinetb-letter-paterson.pdf

[2] http://www.efsa.europa.eu/en/efsajournal/doc/3475.pdf

address validation of a DIVA test (sensitivity and specificity), and how vaccine efficacy and safety might be assessed, including the application of modelling studies to optimise the design of the trials.

5. Aims of the field trials:

    a. Help gain international acceptance for use of the vaccine and DIVA diagnostic test

    b. Help to gain buy-in / acceptance from farmers and private veterinary surgeons for BCG vaccination of cattle

    c. Help to support an application for a UK Marketing Authorisation by addressing the data gaps that can only be assessed in the field

    d. Allow the impact of use of BCG and the DIVA test on the UK TB disease situation and surveillance programme to be assessed

    e. To inform work on the costs and benefits of vaccine deployment

6. Following a recent open-tender exercise, an interdisciplinary team, led by Triveritas Ltd, was awarded funding to carry out the design of the field trials.

7. Work is on-going at AHVLA to address some of the data gaps identified by the VMD and this includes a quantitative (where data allows) risk assessment on the safety of certain milk and meat products from vaccinated cattle entering the food chain.

8. This work links into previous risk assessments carried out by the ACMSF to assess the risk of *Mycobacterium bovis* infection via meat, raw milk and milk products. It is therefore important that ACMSF be made aware of this piece of work. The VMD has identified a quantitative risk assessment as a data gap which would need to be addressed in order for a MA to be granted and in order to conduct a field trial in the UK. An outline of the study and AHVLA planned scope of work is at Annex A.

9. ACMSF will be asked to comment on the final report of the risk assessment when this is completed.

## Annex A

## CattleBCG Risk Assessment – Scope of Work - REVISED

28 October 2013

This document provides further details of the risk assessment work that is proposed in order to address VMD's comments relating to the Application of a new Marketing Authorisation (MA) for the CattleBCG vaccination (Application no: 01817/2011).

The VMD originally requested quantitative risk assessments. However, analysis of the data so far has identified that there are severe data gaps in some areas of the literature. Namely, data is lacking on the survival of the CattleBCG and wild-type *M. bovis* within different products and environmental settings and dose-response. Indeed, it is our conclusion that a meaningful quantitative risk assessment is not possible at this point in time. It is therefore suggested that a qualitative approach is undertaken. This could be reasonably undertaken using one of two approaches (or elements of both):

(1) Develop a stand-alone farm-to-consumption risk assessment to assess the absolute risk for consumption of products potentially contaminated with CattleBCG (see Figure 1) or

(2) Develop a risk assessment that compares the relative risk of infection of CattleBCG to wild-type *M. bovis*, by the estimation of whether the BCG strain poses a greater risk than *M. bovis* for several key decision criteria (see Figure 2).

The first option is in theory the ideal solution, but the data gaps precluding a quantitative risk assessment also affect our ability to assess the qualitative risks. As such, a relative risk assessment, where it is assumed that the risk of natural *M. bovis* infection via milk or beef is considered broadly acceptable at current levels, allows us to target only those elements of the risk pathway that are likely to change given the difference between natural *M. bovis* and BCG strains (and hence to relieve some of the burden required of scarce data to complete the risk assessment). Examples of a similar relative risk methodology have been accepted by the FSA for comparison of meat inspection techniques (Hill et al, 2013a; Hill et al 2013b). Either approach to a qualitative risk assessment would rely heavily on the information available from the existing qualitative risk assessments and reviews for *M. bovis* in milk/beef products that were carried out by ACMSF (ACMSF 2010a-d; ACMSF 2011a-b).

It is highly possible that within the risk assessment, a worse-case scenario quantitative model will be developed utilising the experimental work that is currently underway. Due to the lack of data, the quantitative models may be simpler than originally intended (although still capable of providing information on the potential risk to humans). The resulting models may be deterministic (describing the average or worse-case risk) rather than stochastic (allows the uncertainty and/or variability associated with the input data to be mathematically described). For example, there is reasonable data availability for CattleBCG in unpasteurised milk up to the point of human exposure due to the additional experimental work on dissemination of CattleBCG that will be carried out by AHVLA and ADAS in a parallel project. Even if the experiments yield negative results, it may still be possible to produce a quantitative model as information on the

level of detection is also being produced, which will allow us to consider different scenarios including worse-case scenarios.

**Therefore it is our intention that we produce a qualitative risk assessment but, where data allows, quantitative models will be developed.**

Two risk assessments will be undertaken:

1. Qualitative risk assessment to assess the risk of infection with the CattleBCG *M. bovis* strain due to the consumption of milk and milk products.

2. Qualitative risk assessment to assess the risk of infection with the CattleBCG *M. bovis* strain due to the consumption of beef products.

The results of the quantitative models will be presented, but can also be converted into qualitative estimates and therefore utilised within the qualitative risk assessment. The risk assessments will utilise data from the trials being carried out by the AHVLA and also existing scientific literature. Data gaps/deficiencies will be identified by this process.

In the ideal world, many of the elements described in the previous Scope of Work will remain the same. It is still our intention to adopt as much as possible a farm-to-consumption process, allowing the factors that impact the probability of the commodity being infected/contaminated and also the level of the organism present (Figure 1) to be considered. For example, factors such as cross-contamination, survival and growth under different temperatures, storage and cooking practices will ideally be taken into consideration. However, as noted above, it is likely that data availability will be an issue here and hence may preclude our ability to assess the risk in this way. The final qualitative risk estimates will be derived from considering the level of likely (individual) exposure given consumption of beef and milk products, the likelihood of infection given exposure; an estimate for population risk can also be derived given appropriate information on the level of consumption of the chosen products. The probability of infection, given exposure, is most often estimated using a dose-response relationship. This will be a major area of uncertainty within the risk assessment as there will be no data for either a dose-response function for *M. bovis*, or for the probability of infection, given exposure, for the CattleBCG *M. bovis* strain. Therefore other data (if available) will be used as a surrogate organism, e.g. *M. tuberculosis*. Adopting a qualitative approach will mean that inferences on dose-response from epidemiological studies/outbreaks of *M. bovis* may be of use and can therefore be included within the risk assessment.

It should be noted at this point in time that it will probably not be possible to assess the risk for immunocompromised or pre-exposed people as this type of data does not exist (feeding trials, which are now not permissible on ethical grounds, will have used healthy volunteers). However the impact of susceptibility to infection could be assessed by the adoption of a worse-case scenario.

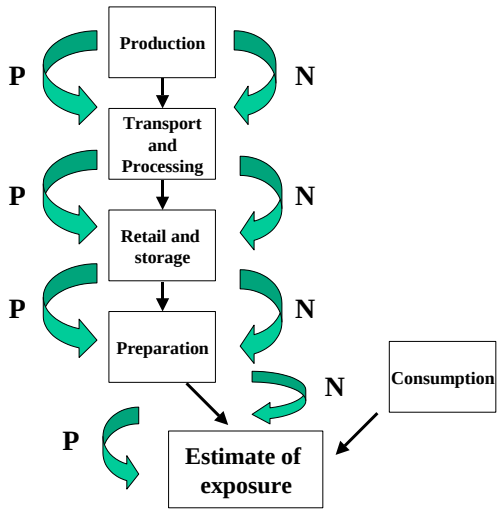


**Figure 1:** Farm-to-consumption exposure pathway. (P = probability of contamination; N = number of organisms)

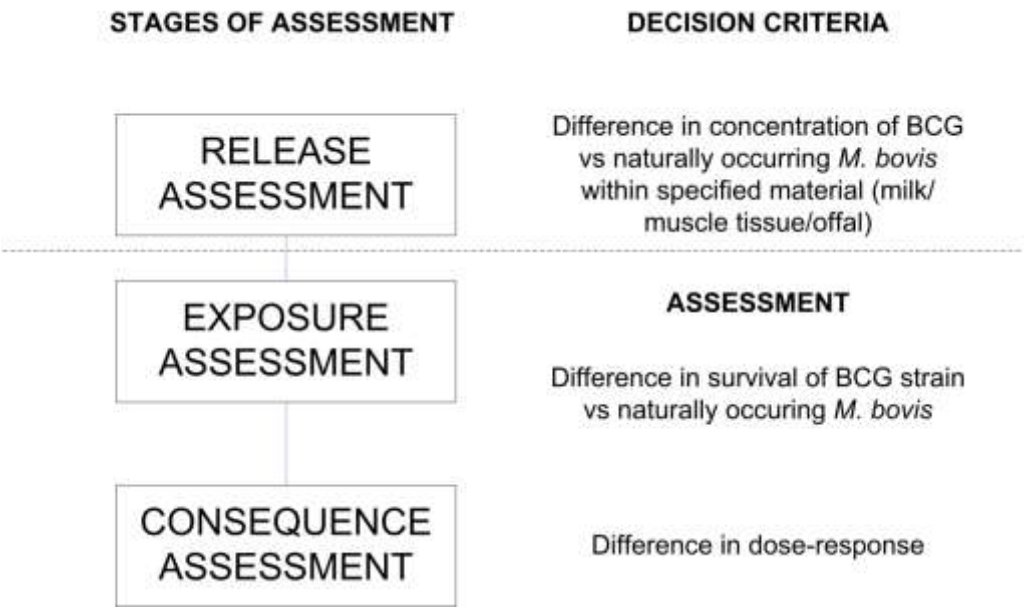


Figure 2: risk assessment framework that compares the relative risk of infection of CattleBCG to wild-type *M. bovis*, by the estimation of whether the BCG strain poses a greater risk than *M. bovis* for several key decision criteria.

As previously stated, all assumptions, data and any mathematical methodologies employed will be fully documented in order to provide a transparent description of the risk assessment.

**Qualitative risk assessment to assess the risk of infection with the CattleBCG *M. bovis* strain due to the consumption of milk and milk products.**

*Proposed Risk Question: What is the risk of human infection with the CattleBCG due to the consumption of a typical serving of milk and milk products?*

A qualitative risk assessment will be developed that assesses the probability of infection with the CattleBCG vaccine strain due to the consumption of milk and milk products. As described above, this could be either a stand-alone risk assessment for CattleBCG or a risk assessment that assesses the risks relative to wild-type *M. bovis*. Where possible, quantitative models will be included in the assessment and, where appropriate, may include methodology similar to that used for a VTEC in pasteurised milk risk assessment (Clough *et al.* 2009). For this risk assessment, the following milk products will be included: milk, soft cheese and hard cheese (see Table 1). These were selected after a review of available data against three set criteria: (1) CattleBCG present in the raw material; (2) CattleBCG survives any processes the product may be subjected to; (3) amount of product consumed.

Both unpasteurised and pasteurised milk will be included as pasteurised milk may be a viable risk management strategy if the risks are considered to be too high from unpasteurised milk. Cheeses made from pasteurised milk are not included as it is recognised that milk will be the worse-case scenario and therefore these additional risk assessments are not required. There is some variability in the production processes, particularly for cheese and therefore both a soft and hard unpasteurised cheese was selected representing a best case and worse case.

**Table 1:** Combinations to be included in the Milk & Milk Products Risk Assessment

| Product | Pasteurised | Unpasteurised |
|---|---|---|
| Milk | ✓ | ✓ |
| Soft cheese | × | ✓ |
| Hard cheese | × | ✓ |

**Qualitative risk assessment to assess the risk of infection with the CattleBCG *M. bovis* strain due to the consumption of beef products.**

*Proposed Risk Question: What is the risk of human infection with the CattleBCG due to the consumption of a typical serving of beef products?*

As above, a qualitative risk assessment will be developed for beef products however, where data are available, quantitative models will also form part of the assessment. Depending on the level of detail required it may be possible to utilise elements from the existing AHVLA quantitative risk assessment for VTEC 0157 in beef (Kosmider et al., 2010). As above, products have been selected based on three set criteria and, following this, it is proposed that the risk assessment will focus on mince and offal (see Table 2). Mince has been selected because this is a product that is likely to contain a number of parts of the carcass, including the neck meat, which is the location of the injection site. Consequently, contamination of mince is thought to be greater than in other beef products, such as steak. The risk assessment for mince will reflect the possibility of the lymph node being incised during removal and hence subsequent contamination occurring and also the possibility of lymph node not being removed. It will also be able to consider the impact of any

faecal contamination on the carcass on public health, if deemed relevant from the experimental work. This risk assessment will also consider the destination of the tissue surrounding the injection site within the food chain and include this product. The meat risk assessment will assess the impact of any potential withdrawal period between administration of the vaccine and meat being allowed to go into the food chain. The potential periods of withdrawal implemented within the model will be determined by the experimental work and will give an indication to VMD the reduction of human risk if such a withdrawal period is introduced. As described above, the fate of any Cattle BCG within or on the surface of a beef product during preparation and cooking will be included within the risk assessment.

During the development of the risk assessment, consideration will also be given on if/how meat inspection at the abattoir will provide any barrier to the potential dissemination of CattleBCG within the food chain. If it is thought to have an impact on the risk, the meat inspection stage will be included within the risk assessment.

**Table 2:** Combinations to be included in the Meat Products Risk Assessment

| Product | No withdrawal | Withdrawal |
|---|---|---|
| Mince | ✓ | ✓ |
| Offal – Kidney, Liver | ✓ | ✓ |

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