Badgers and Bovine TB: the Government response to the EFRA Select Committee's Tenth Report of Session 2007 – 08[1]

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[1] Badgers and cattle TB: the final report of the Independent Scientific Group on Cattle TB: Government Response to the Committee's Fourth Report of Session 2007 - 08

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the EFRA Select Committee's Tenth Report of 2007 - 08**

Introduction

1. The Government welcomes the opportunity to provide further information to the EFRA Select Committee in response to their inquiry into *Badgers and cattle TB: the final report of the Independent Scientific Group on Cattle TB.*

2. The Government has made clear in the Secretary of State's statement to the House on 7 July 2008 that it fully recognises the seriousness of bovine TB in England. From discussions with a number of farmers who have been affected by bovine TB the Secretary of State and Defra's Ministerial Team are in no doubt about how difficult life is for those living with the disease. The Committee suggested that the Government's contention that bovine TB is a regional disease was being used to play down its seriousness. The Government was stating a fact: high incidence areas are in the South West and the Midlands and for those most seriously affected, the economic and human consequences are devastating.

3. Outside high incidence areas the control framework based on surveillance, testing and slaughter is working effectively. There are, as the Committee's queries suggest, a range of options for expanding this programme by introducing new control measures or different ways of testing, but the degree of impact they would have on disease levels, and whether or not they would offer good value for money, are far from certain. The Government has to consider how best to use the available resources, and strike a balance between disease control and the costs such measures would impose on both the industry and the taxpayer. At present the best available measures are cattle measures. In the longer term vaccination of badgers and, ideally, cattle, will add to the range of tools available within the control programme.

4. The Government rejects the Committee's view that it "is opting out of leadership" and "sub-contracting important decisions" on bovine TB. This is not the case. Leadership in tackling bovine TB is not for government alone, nor is it achieved by government taking unilateral decisions about new cattle control measures. Imposing controls without consultation may be quicker in the short term but it is not the way to make progress on reducing the impact of this disease. The Bovine TB Partnership Group is intended to be exactly that: government and industry working together to take difficult decisions. It is up to industry to decide how quickly the job gets done, and the Government shares the Committee's concern that there might be a delay if the industry declines to participate.

5. This Government remains committed to working to find the best ways to tackle bovine TB, and the best way to do that is in partnership with the industry.

Cattle Measures

6. The Government did not attempt to introduce new cattle measures in July because these decisions need to be made with the industry. Such measures have not been ruled out but the farming industry should have the opportunity to be involved in decision making and that is why, in the Government's response to the Committee, it was stated that they would be discussed by the Bovine TB Partnership Group.

Cost Benefit Analysis

7. The Committee asked for details on the initial cost benefit analysis Defra undertook of costs of increased testing and increased use of the gamma interferon test (paragraph 12)[2]. These are provided at Annex A.

8. In summary, the initial analysis suggests increased testing or use of the gamma interferon test would come at a high cost with limited benefits – and would be difficult to justify in terms of government expenditure. For illustrative purposes: the cash costs to Government of skin testing a herd of 60 cattle would currently be in the region of £250, whereas applying the gamma interferon test to the same herd would cost around £1,280.

9. From the results of the analysis, 6-monthly tuberculin skin testing over 20 years would incur costs estimated at £294m exceeding the projected benefits in the region of £125m. Even with optimistic assumptions about both its costs and benefits routine use of gamma interferon testing would incur costs (estimated at £1,177m) far exceeding its benefits (in the region of £125m). This approach would not be permitted under present European legislation because gamma interferon testing may only be used in addition to the skin test. Therefore, the estimates understate the costs of routine use of gamma interferon.

Understanding of the gamma interferon test and its accuracy

10. The Committee asked for details of the work to be undertaken on increasing understanding of the gamma interferon blood test and its accuracy (paragraph 12). The selection of research projects at Annex B demonstrates that the Government has focused on having a good understanding of the gamma interferon test and this has been disseminated amongst the scientific community. However, the recent judicial review on gamma interferon showed there was much work to do on increasing understanding and confidence in the farming and veterinary communities.

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[2] Paragraph numbers in brackets refer to the EFRA Select Committee Report *Badgers and cattle TB: the final report of the Independent Scientific Group on Cattle TB: Government Response to the Committee's Fourth Report of Session 2007–08, Tenth Report of Session 2007–08* (published on 23 July 2008) which can be found at: http://www.publications.parliament.uk/pa/cm200708/cmselect/cmenvfru/1010/1010.pdf.

11. Increasing understanding and building confidence in the farming and veterinary communities are about communicating what the gamma interferon test can and cannot do effectively. The Government has already taken some steps through the advice in "Dealing with TB in your herd", an article in Farming Link and discussions held with veterinary bodies (RCVS, BCVA) and the TB Advisory Group. There is more work to do, the review of gamma interferon, which is scheduled to finish in the autumn, will include recommendations aimed at improving confidence in, and communication of, the gamma interferon policy.

Efficiency of the tuberculin skin test

12. The efficiency of the tuberculin skin test and the factors that affect it are reasonably well understood, and have been evaluated in a large body of evidence published in the international scientific veterinary literature over the years. In its current form the skin test is accepted by the World Organisation for Animal Health (OIE) and the European Commission as the international standard for ante-mortem diagnosis of TB in cattle herds and individual animals[3]. From existing evidence the animal-level sensitivity (the proportion of truly infected cattle identified as infected) of the test under UK conditions is estimated to be between 75.0% and 95.5%. Its animal-level specificity of the test (the proportion of non-infected cattle identified as negative) is considered to very high with a median value of 99.5% (78.8% to 100%)[4]. Systematic test and slaughter schemes relying on the skin test in its various guises have achieved eradication of bovine TB in those countries where cattle are the only maintenance host of *M. bovis* infection[5]. This has been demonstrated in Scotland, the North of England and many EU member states.

13. The actual performance of the skin test under field conditions is dependent not only on the attributes of the test itself, but also on the diligence of the tester in adhering to the correct procedure. This performance is continuously monitored in Great Britain by analysing a number of TB epidemiological parameters in the British cattle population. Additionally, Animal Health is responsible for managing the skin testing regime on the ground, which includes auditing the quality of tuberculin skin testing by veterinarians and approved lay testers.

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[3] Anon, 2008; de la Rua 2006a.. A list of references is on page 15.
[4] de la Rua *et al*, 2006b, 2006c.
[5] de Lisle *et al,* 2007.

14. The Committee was interested in details of any further work which Defra is undertaking to assess the efficiency of the skin test (paragraph 12). Defra is not sponsoring at present specific field or laboratory research into the efficiency of the skin test. However, it is clear that reliable estimates of test sensitivity and specificity would facilitate estimation of the number of infected cattle likely to escape detection and the modelling of new, more efficient combinations of testing strategies for bovine TB (within the constraints of EU legislation). In recognition of this, Defra is funding a systematic review and meta-analysis of the diagnostic characteristics of tests for bovine TB. The results of this meta-analysis should inform the development of an epidemiological model of TB surveillance strategies in cattle herds, including optimal combinations of diagnostic tests to achieve and maintain freedom from infection under different scenarios. A similar methodology has already been applied to the review of diagnostic tests for TB in farmed deer[6]. The project (SE3238: "Meta-analysis of diagnostic tests and modelling to identify appropriate testing strategies to reduce M. bovis infection in GB herds"), led by VLA epidemiologists with support from a working group of international experts, is due to start in September 2008 and should complete early in 2010. Further details of this project are given in Annex E.

The Bovine TB Partnership Group

15. The Government shares the Committee's concerns (paragraph 13) that discussions and decisions on cattle-based measures could be delayed if industry is not prepared to participate in the work of the Bovine TB Partnership Group. The Government could move ahead anyway, imposing new cattle controls on the industry and even new costs but this is not the way to establish measures that will be effective for the long battle against bovine TB which lies ahead. The Secretary of State has made it clear that control of the disease is not a matter just for the Government and that is why he decided to set up the Bovine TB Partnership Group. Government together with industry need to develop a joint plan for tackling bovine TB. The Government is ready to do this - what happens next and how quickly we move forward depends on the industry itself.

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[6] EFSA, 2008. Scientific report on 'Tuberculosis testing in deer'. Panel on Animal Health and 671 Animal Welfare, Question No. EFSA-Q-2006-179, Adopted on 30 January 2008. Annex to the 672 EFSA Journal 645, 1-34.

16.   The Government agrees with the Committee that those organisations (paragraph 23) which represent farmers affected by bovine TB should be considered as potential members of the Bovine TB Partnership Group. However, the form the Group will take, and the extent to which it needs to be resourced, will depend on Defra's discussions with the industry and the veterinary profession. Government has not developed a model for how this group should be constituted and operated in advance; it wants to develop the approach with industry as part of developing a genuine partnership.

17.   The Government is already working closely with the non-bovine sector to develop an agreed approach, for the control of TB in such species. It has set up a review of the current controls for TB in non-bovine species, including camelids (llamas and, alpacas), goats and cats; and to develop suitable policy options that are effective, affordable and proportionate to the animal and public health risks. A Working Group consisting of representatives from Defra, the Devolved Administrations, Animal Health and the Veterinary Laboratories Agency has been set-up to take the review forward. Members of the Working Group have met with key industry stakeholders, including the British Llama Society, the British Alpaca Society, the British Camelid Society, the Goat Veterinary Society, the British Goat Society and the Feline Advisory Bureau to gain an understanding of their issues and concerns; assess the risks and impact of bovine TB on their industry; and seek their views on how the risks might be addressed. The Government intends to continue to work with the non-bovine sector, as far as possible, on matters relating to the control of TB in these species.

Epidemiology

18.   The Government understands and shares the Committee's concern and frustration about the fact that a conclusive answer on the transmission of bovine TB cannot currently be produced. The epidemiology of bovine TB is complex and it is known that in cattle and badgers it is primarily a respiratory disease[7]. However if it is uncontrolled in either species, the disease may become disseminated and *M bovis* can be excreted, intermittently, in sputum, saliva, pus, urine, faeces and milk[8]. The work the ISG did on setting up the Randomised Badger Culling Trial (RBCT) showed it was not possible to implement the design of scientific experiment suggested by John (now Lord) Krebs to investigate the relative contribution of routes of transmission because it was not practical. TB transmission is not amenable to being investigated by experiments with controls because of the large number of variable factors, the impracticality of conducting controlled experiments on commercial livestock farms, and the need for data from a large number of representative breakdown herds[9].

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[7] Shitaye *et al.*, 2006; Clifton-Hadley *et al.,* 2006; Crawshaw *et al*, in press.
[8] Cassidy, 2005; Gallagher and Clifton-Hadley; 2000; Shitaye *et al.*, 2006.
[9] Ryan *et al*, 2006.

19. The inception and progress of the RBCT provided evidence to show that further research is unlikely to yield conclusive results on the question of the quantitative contribution of badgers to cattle TB and exactly how, where and when transmission occurs (Bourne *et al.*, 2007a). The level of proof required to determine absolute transmission rates in this instance far exceeds that of the association with risk factors required for many other diseases; and in the case of other diseases, it is accepted that such depth of information is not a prerequisite for implementing control measures. There are several reasons for this: the epidemiology; relatively low level transmission; the chronic nature and difficulty in detecting the organism; diagnosis of the disease, and the practicality of being able to reach a conclusive answer that is scientifically sound. The main difficulty is being able to know when and how animals were exposed to TB, because it is a chronic disease and only discloses through testing some time after the animal has been infected.

20. The evidence suggests that the contribution of the various means / routes of transmission and the associated transmission rates vary both geographically and over time, therefore there are no fixed values for any of the transmission parameters. It is important to note that reliable estimates of these transmission rate parameters are established for only relatively few other diseases and only under specific experimental circumstances. The extensive investigation over many years is itself indicative of the inherent complexity of the problem.

21. This level of uncertainty means the Government needs to focus on what is known. As the Government said in response to the Committee's Fourth Report of Session 2007-08, the relative importance of the routes of infection will remain an unknown and both direct and indirect transmission of TB between badgers and cattle may occur in farm buildings and at pasture[10]. The diagram below shows that the Government's TB control strategy is aimed at ensuring that, in relation to as many routes of transmission as possible, disease spread is minimised.

22. The Committee also asked for clarification of what the Government meant by "we will continue to consider new ideas" about the transmission of bovine TB (paragraph 14). This means that the Government is open to continue to fund new ideas for further research if they are forthcoming and have the potential to shed further light on the exact means of transmission between cattle and between cattle and badgers. The Government has a long and proven track record of funding a wide range of peer-reviewed research proposals in the area of bovine TB as illustrated by Annexes D and E.
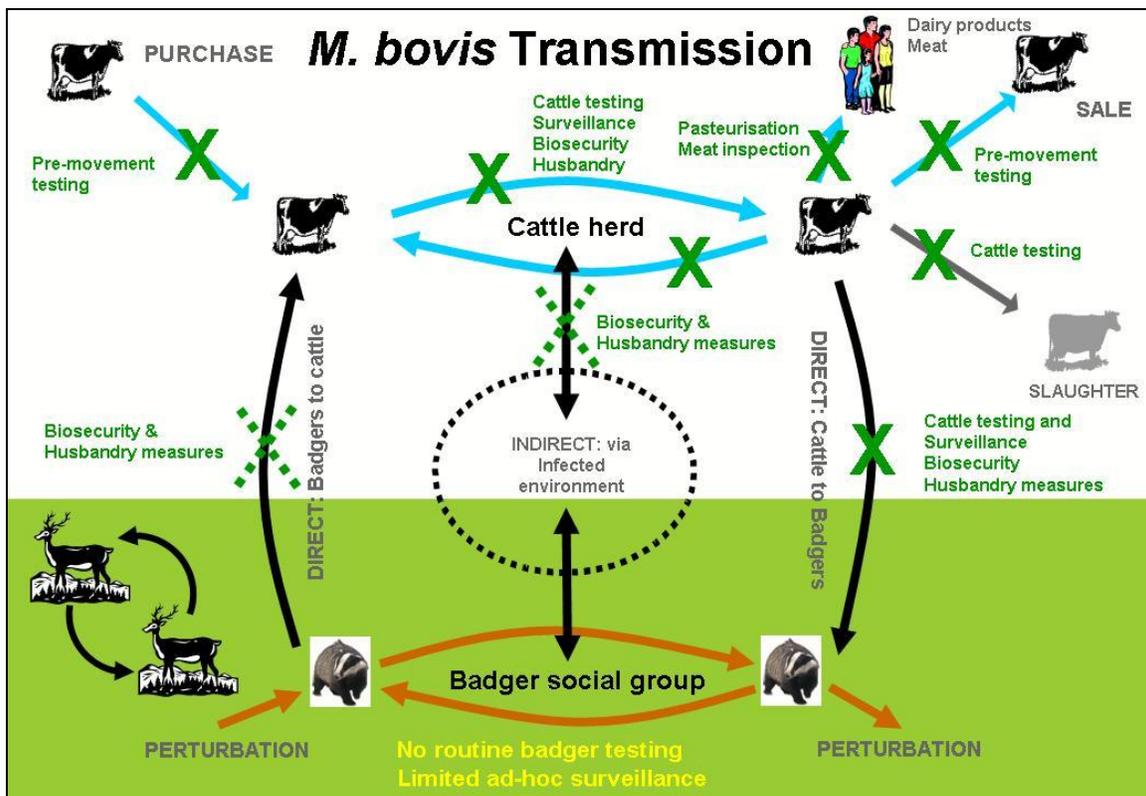
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[10] Johnson *et al*, 2005.

Diagram 1: Bovine TB transmission routes and available control measures. Note: the solid green crosses indicate those areas where current controls are likely to be highly effective in mitigating against that route of transmission of *M. bovis*. The dotted crosses indicate those routes of transmission where current measures are likely to be less effective.

Biosecurity

23. The Government agrees with the Committee's recommendation (paragraph 15) that it should make the results of the biosecurity research available as soon as possible and is keen to do so. CSL have presented their on-going research work to interested farming and wildlife groups, which has been well received. As the Government made clear in the response (July 2008) to the Committee's report, the Welsh Assembly Government was represented on the TB Husbandry Working Group and keeps us closely in touch with the Biosecurity Intensive Treatment Area project. The Government is awaiting their report on the project and will consider its potential for trialling a similar approach in England.

24. The Committee also questioned how the Bovine TB Husbandry Working Group will decide what biosecurity measures are effective (paragraph 15). The Husbandry Group has already done this, the first stage of its work was a comprehensive review of current research and other evidence. A list of the measures from existing advice and research, including The Philips Report: *TB and Cattle Husbandry, Report of the Independent Husbandry Panel* (May 2000) and the Central Science Laboratory (CSL) research on badger visits to farmyards (SE3029), was compiled. The Husbandry Group then worked to identify which of the evidence based measures farmers could

have some assurance worked, were practical and gave some value for any investment required. The overview of their work and assessment of the evidence base and explanation of why certain measures have or have not been included in the husbandry advice is available online at: http://www.defra.gov.uk/animalh/tb/pdf/husbandry_background.pdf).

25. The Group concluded that every farm is different in terms of what husbandry measures may be effective and a pragmatic approach is needed for many measures related to minimising TB risks. What was clear was that introducing a number of measures and implementing best practice advice which focused on the risks of transmission from both cattle and wildlife might result in a reduction of bovine TB incidence. This conclusion was supported by the findings of case-control studies TB99 and CCS2005 carried out as part of the RBCT which found sufficient evidence that by applying the broad principles of biosecurity it would be possible to reduce the risk of cattle becoming infected by other animals, including badgers, and thus reduce the risk of infection.

26. In paragraph 16 of their report the Committee suggest that the Government should provide more information on what "managing the impact of living in high risk areas means". This phrase refers to assisting those farmers with herds in high incidence areas which may experience re-infection from badgers to reduce the risk of infection, but also to continue to operate their businesses, recognising that they are likely to face recurring periods of movement restrictions. The statement on 7 July 2008 set out some options which might be considered, and for which incentives could possibly be offered, but remitted this issue for consideration by the Bovine TB Partnership Group.

Vaccines

Cattle vaccine

27. The Government shares the Committee's enthusiasm for making progress on the significant hurdles that need to be overcome before a cattle vaccine could be introduced (paragraph 18). In January 2008, as part of a discussion about bovine TB with the European Commission, the Government tried to establish clearly the circumstances in which a cattle vaccine might be acceptable. The indications were not promising because of the likely concerns from other Member States that TB infected cattle would then be undetectable using the tuberculin skin test. The Commission suggested that there might be room for discussion once a vaccine was closer to being available and it had been established that a DIVA test (Differentiating Infected from Vaccinated Animals) was feasible. While these initial discussions were not encouraging, the Government will continue discussions with the Commission and other Member States to keep them updated on progress. The Government will also continue to explore with them what can be done to ensure the required legislative changes can be made as rapidly as possible once the necessary scientific

information is available. However, it also recognises that most Member States have little interest in TB vaccination because they are disease free, and may be reluctant to see changes to a control system that has served them well.

Vaccines research

28. The Committee asked about the new vaccines research being commissioned and funding of each project (paragraph 20). This work will follow on from the existing research projects to take the badger and cattle vaccines and DIVA test through the next stage of the development and licensing process. Following extensive discussions with stakeholders, which identified a number of technical and practical issues, the new research will aim to address these issues and align the programme more clearly with stakeholder priorities. The terms of reference of the additional research are therefore:
    - To continue to pursue all avenues of research on vaccines for both cattle and badgers
    - To address the scientific uncertainties around oral badger vaccines in terms of both formulation and deployment to maximise the chances of success; and
    - To maximise the chances of cattle vaccines being used without trade restrictions by further developing the DIVA test, improving understanding of cattle sensitisation to the skin test by vaccines and increasing research on non-sensitising vaccines.

29. By developing a practical understanding of the logistics of vaccination, improving our scientific understanding and working in partnership with the farmers and the wider community at the local level, we hope to improve farmer confidence in vaccination and ensure an oral vaccine can be deployed rapidly once it becomes available. Therefore, the aims of the injectable badger vaccine deployment project are:
    - to support the long term goal of oral badger vaccination; and
    - to provide an assessment of the viability of injectable vaccination.

30. These aims can only be achieved working closely with industry in both the design and execution of the project. The total cost can only be determined once the design is finalised.

31. The timetable for licensed badger and cattle vaccines is at Annex C and details of on-going Defra-funded TB vaccine research projects (including costs) are at Annex D.

32. The Government will consider how progress with research into vaccines for bovine TB can best be included in Defra's Departmental Annual Report to Parliament.

Compensation

33. The Government has now lodged an appeal against the High Court judgement which is referred to in paragraph 22 of the Committee's report. The judgement accepted that, for most animals, the table valuation system is a significant improvement on the previous one which was based on individual valuations, and resulted in a significant and widespread over-compensation problem. However it did conclude that table valuations discriminated unfairly against owners of particularly valuable cattle. This does not mean, as the Committee's report states, that the court supported the view that table valuations were unfair to owners of pedigree cattle – Table valuations already treat pedigree animals separately to other animals and for most pedigree cattle, the determined table value (which is a true and contemporaneous open-market average price for same category cattle) will represent a reasonable approximation of true market value of a healthy animal. For example, in the latest table valuation for September 2008, male pedigree animals in the beef sector (aged over 12 months and up to 24 months) have a table valuation of £3,526 compared to less than £1,000 for non-pedigree animals in the same age groups; and for a number of other pedigree categories, it has been determined that individual valuations should be utilised for September 2008 - as allowed for in the legislation - in the absence of sufficient sales data existing to calculate an average market price. To quote the judgment at paragraph 77:

    "For the average animal, table valuations may provide an efficient, relatively inexpensive, easily administered and realistic means of determining fair compensation, and I accept the contention of the Secretary of State that in most cases the table valuations stipulated in the Order produce a valuation that is a reasonable approximation of true healthy market value. For most animals, I take it that the present scheme is a great improvement on the former provisions involving general individual valuations from the point of view of the public."

34. Once the Court of Appeal has had the opportunity to re-consider this case, and deliver its decision, the Government will make clear what the next steps will be.

Bovine TB and badger culling

The decision not to cull

35. In taking its decision on bovine TB and the potential role of badger culling in controlling the disease the Government considered whether action which met the criteria identified by the ISG and Sir David King (large area where there is a high and persistent incidence of TB cattle, sustained for a number of years and carried out effectively and humanely) could work in practice and what the risks were. In considering the practicality of large area culling the Government took into account the information that had been provided by the National Beef Association and the National Farmers' Union about their plans for a large area cull (VLA9) and the Secretary of State met with both organisations in February 2008 where they described their VLA9 plans. The plans, as the Committee have seen, did not provide detailed information on how this proposal would be implemented and what was provided did not indicate that further exploration would add to the broad range of evidence already available. VLA9 did inform policy considerations by providing a sense of the level of commitment to a cull in the area and of what the industry considered possible, as well as what concerns were, for example, over security. The Government took the view that the undoubted commitment was not enough to counterbalance the long-term risks of making the disease worse if culling became patchy, was not sustained, or was disorganised for any reason, therefore, even if more information on how VLA9 would have been implemented had been available, the Government does not consider it would have affected its judgment on the risks involved.

36. Other factors considered included the public acceptability of culling badgers; the likelihood that landowners would not consent to allow culling on their land; and the likelihood that public order problems could jeopardise the cull and contribute to making disease worse. The cost, and the need to sustain funding of a culling operation for a number of years, were important considerations. It would take time for herd owners to see an overall benefit in reducing cattle herd TB breakdowns. In the Randomised Badger Culling Trial this beneficial effect did not become significant over the culled and surrounding areas until the fourth annual proactive cull. Initially in the RBCT, at the same time a reduction in herd breakdowns was seen in culled areas an increase in herd breakdowns was seen in surrounding culling areas. In considering culling as one of the Government's TB control tools the likelihood that farmers would face increased cattle breakdowns in the short term was likely to endanger support for maintaining the cull. Having considered all these factors, the Government concluded that the risk of ineffective culling making disease worse was too high.

<u>Revisiting the policy</u>

37. The Committee requested a clearer indication of what evidence the Government would need or in what circumstances it may revise the policy on culling (paragraph 25). The Government has made clear that exceptional circumstances may mean we need to revisit the policy. In this case exceptional circumstances are unforeseeable and we cannot say what they may be. They would not be an application to carry out a large scale co-ordinated cull, even with a commitment to sustained delivery and funding from farmers. This is because the judgement underlying the policy is that culling, in the way the science suggests could be effective, would be difficult to sustain and could make matters worse by leading to an increase in bovine TB.

38. The scientific research underway that may produce new evidence comprises the projects recently commissioned to undertake further analysis of the huge amount of data available from the Randomised Badger Culling Trial and the ongoing post-culling analysis being led by Christl Donnelly. However new or additional scientific evidence may not sufficiently demonstrate that the level of disease risk from culling can be acceptable enough for the policy to be reviewed. Science cannot be expected to deal with all the aspects of carrying out an effective cull, including practicality.

Scientific Research

39. The Government is happy to provide the Committee with details of ongoing scientific research into bovine TB (paragraph 21). In addition to the summary of Defra-funded on-going research that we have provided at Annexes D and E, we propose that we notify the Committee as new research is commissioned and final results published in order that they are made aware of the work as soon as possible.

40. Details of all on-going and completed research projects are available on the Defra website at http://www.defra.gov.uk/science/default.htm and http://www.defra.gov.uk/animalh/tb/research/projects.htm respectively.

Scientific Advice

41. The Committee commented that they were disappointed with the Government's response to their recommendation that the dialogue continue between the Independent Scientific Group on Cattle TB (ISG) and the new Government Chief Scientific Adviser (Professor Beddington) (paragraph 26). The response was directed at the Committee's specific recommendation: the Government did not rule out further dialogue with the former members of the ISG. The Committee may find it reassuring to know that at least four former members (Christl Donnelly, George Gettinby, John McInerney and Ivan Morrison) of the ISG work closely with Defra on further research as contractors and as advisers and sit on the sub-groups of the Bovine TB Scientific Advisory Body.

Additional information

42. The additional information mentioned in this report is provided in the Annexes attached:

Annex A	Costs and benefits of increased testing and increased use of the gamma interferon blood test
Annex B	Research: gamma interferon blood test and its accuracy
Annex C	Timetable for cattle and badger vaccines (paragraph 20)
Annex D	Government funded vaccine research projects underway including breakdowns of the funding on each (paragraph 20)
Annex E	Update on Government funded scientific research into bovine TB underway (paragraph 20)

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COSTS AND BENEFITS OF INCREASED TESTING AND INCREASED USE OF THE GAMMA INTERFERON TEST

Background

The Government carried out a preliminary cost benefit analysis of increased routine cattle testing and increased use of the gamma interferon test. The analysis considered the cost of implementing each of these measures separately against the resulting savings from reduced testing and disease incidence during the 20 year period of the assessment. It attached no monetary value to the lower overall level of disease at the end of the control period that is assumed to result from the altered testing regimes. This was a simplified assessment to give an indication of the possible scale of costs and benefits of enhanced cattle testing. The Government's economic analysis is frequently refined and updated as needed to inform policy decisions.

Estimated benefits

The assessment of benefits was carried out without any specific epidemiological modelling of changes in testing regimes. An indication of the possible scale of the benefits was obtained from results of a simple model by the Veterinary Laboratory Agency (VLA) derived from that used by the Independent Scientific Group on Cattle TB (ISG). The VLA model was developed specifically to model the impact of several hypothetical vaccination scenarios against a baseline of the modelled future progress of bovine TB under present control strategies over a 20 year period. In the model, cattle vaccination directly affects both cattle to cattle and badger to cattle transmission. Testing and removal of more infected/infectious cattle could not achieve the same impact because it does not directly address badger to cattle transmission. Therefore it was assumed that the maximum benefit achievable from enhanced cattle testing (whether through more frequent testing or use of gamma interferon) would be the modelled percentage rate of reduction in cattle herd incidents achieved by cattle vaccination but only in those incidents arising from cattle to cattle transmission and not addressed by pre-movement testing. On this basis, the potential benefits of an enhanced cattle testing regime over 20 years would be in the region of £125 million.

The estimate of benefits is subject to great uncertainty because it depends on both the efficacy of the new intervention and on the disease situation. The version of the VLA model used for this assessment assumed that pre-movement testing is relatively highly effective in reducing cattle-to-cattle disease spread and that this would result in a declining disease picture. This assumption leads to a lower estimate of potential benefits than might be possible if the disease situation worsened over the 20 year period. This is because greater disease implies greater costs of disease control and therefore there are greater savings to be made reducing these costs with new measures.

Testing herds every six months
The analysis of costs assumed that 25% of herds in GB have one additional whole herd test per year - equivalent to all the clear herds now on annual testing moving to six monthly testing. It did not take account of any changes to 3 and 4 yearly testing areas e.g. to 2 yearly, which would be another possible scenario. On average, each extra herd tests would cost £900 including government and farmer costs. No account was taken of changes to the scale and duration of cattle bovine TB incidents that would arise through false positives (which would add to the cost of biannual testing) and through reduced spread within infected herds (which would add to the benefits). Herd testing intervals are currently based on historic incidence of test positive animals, as set out in EU Directive 64/432/EEC.

The conclusion the Government reached from the results of the analysis was that, over a 20 year period, 6-monthly testing would incur costs estimated at close to £300m, exceeding the projected benefits estimated in the region of £125m.

Routine gamma interferon testing
During 2007/08 29,655 gamma interferon tests were carried out – the associated direct costs (ie excluding the provision of compensation for reactor cattle) for the taxpayer were £952,000. The gamma interferon test is significantly more expensive than the tuberculin skin test although the cost might be lower if, for example, testing kits were purchased on a larger scale. The average cost of a herd test using gamma interferon was estimated in this analysis to be £1,600 more than using the skin test.

The analysis assumed that all testing in annual testing areas was carried out using the gamma interferon test in place of the present skin test. This approach would not be permitted under present European legislation because gamma interferon testing may only be used in addition to the skin test. Therefore, the estimates understate the costs of routine use of gamma interferon.

The gamma interferon test is more sensitive than the tuberculin skin test, capable of detecting more cattle infected with bovine TB at an earlier stage of infection and infected cattle that are missed by the skin test. However it risks producing an unacceptable number of false positive results, because of its lower specificity, in uninfected herds. It is therefore considered technically unsuitable as a routine screening test.

The conclusion the Government reached from the results of the analysis was that, even with optimistic assumptions about both its costs and benefits, routine use of gamma interferon testing over a period of 20 years would incur costs (estimated to be approaching £1,200m) far exceeding its benefits (estimated in the region of £125m).

RESEARCH: GAMMA INTERFERON BLOOD TEST AND ITS ACCURACY

Project SE3013: Pathogenesis and diagnosis of tuberculosis in cattle – complementary field studies

This study (which ran between 2000 – 2005) was designed to advance the understanding of cattle-to-cattle transmission of bTB in GB through detailed pathological and immunological investigation of cattle either naturally infected ("reactors") or exposed to *Mycobacterium bovis* ("in-contacts") and to assess certain diagnostic aspects of disease detection. Of the 200 reactor cattle selected, 55.5% had macroscopic visible lesions and, of the 200 in-contacts selected, 14% had macroscopic visible lesions. These in-contact animals were negative in the initial skin test. Some of these were at a very early disease stage and a portion of them would have been identified as reactors at a repeat skin test. However, the vast majority of these could have been identified more quickly and accurately in the field by using blood based tests and these results provide solid support to the use of the BOVIGAM gamma interferon assay. These animals would have been erroneously regarded as false positives by farmers and some vets in the past due to their skin test negative status, but holding the animals longer allowed them to develop visible lesions of tuberculosis.

The Final Report of this project is available on the Defra website at:
http://randd.defra.gov.uk/Document.aspx?Document=SE3013_5852_FRP.doc

Field trial in GB conditions

Between October 2002 and October 2005, Defra funded an Animal Health and Veterinary Laboratories Agency (VLA) conducted field trial of the gamma interferon test.

The slow farmer recruitment rate meant that the trial was unlikely to be completed before 2012. Given the significance of the bovine TB problem this was considered too long to wait and so the trial was terminated early and the decision was made to make increased use of the gamma interferon test. Useful data was collected and lessons were learnt from the trial and two reports were produced: an interim one on the first 150 herds was made available to the ISG and a final one which was a full analysis of the results from all 195 herds. The final report "Laboratory testing and epidemiology support for the national gamma interferon field trial" is available on the Defra website at:
http://www.defra.gov.uk/animalh/tb/pdf/gifn_trialfinalreport.pdf.

Specificity Trial (Great Britain)

A trial, established to evaluate the specificity of the gamma interferon test in British conditions, confirmed the findings of previous studies by concluding that the commercially available test had a specificity of between 95% and 97%.

Findings from the trial supported the view that it would be inappropriate to use the gamma interferon test for routine screening purposes because it risks producing too many false positive results in uninfected herds. However, there would be value in making greater use of it as an ancillary test in a variety of herd breakdown situations. Defra has also used these findings to develop the current policy for the increased use of the test.

A copy of the report, "Specificity Trial of the BOVIGAM IFN Gamma Test in GB Cattle" is available on the Defra website at:
http://www.defra.gov.uk/animalh/tb/pdf/gifn_specificityreport.pdf

Further information

Below is a list of other selected relevant scientific references concerning the diagnostic accuracy of the gamma interferon test. The ISG's final report also contains references to the skin and gamma-interferon tests.

- Anon. 2004. Chapter 2.3.3. – *Bovine Tuberculosis. Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* (5th Ed.). Office International des Epizootes.

- R de la Rua-Domenech, A V Goodchild, H M Vordermeier, R G Hewinson, Christiansen KH, Clifton-Hadley RS. 2006, "Ante mortem diagnosis of tuberculosis in cattle: a review of the tuberculin tests, γ-interferon assay and other ancillary diagnostic techniques". *Research in Veterinary Science* 81, 190-210.

- E Gormley, MB Doyle, T Fitzsimmons, K McGill, JD Collins. 2006. "Diagnosis of *Mycobacterium bovis* infection in cattle by use of the gamma-interferon (Bovigam) assay". *Veterinary Microbiology* 112, 171-179.

- M Vordermeier, A Whelan, K Ewer, T Goodchild, R Clifton-Hadley, J Williams, RG Hewinson. 2006. "The BOVIGAM assay as ancillary test to the tuberculin skin test". *Government Veterinary Journal* 16(1), 72-80.

- Martin Vordermeier, Adam Whelan, Glyn Hewinson, "The scientific case for the BOVIGAM assay". *Government Veterinary Journal* (in press)

TIMELINE FOR VACCINES

Defra has in place an extensive research programme which can broadly be divided into 5 work streams:

- BCG cattle vaccines (cannot be used with the current skin test due to sensitisation) – including work investigating prime boost strategies
- Differential diagnostic tests (to determine vaccinated from infected animals in place of the skin test, known as DIVA)
- Non-sensitising cattle vaccines – 10 year+ long term prospect
- Injectable badger vaccines
- Oral badger vaccines

Historic spending

Over the last 10 years up to March 2008 we have spent £17.8M on vaccines for bTB. The diagram and summary below sets out how this money was used and what it has delivered.

Work began in 1997 to generate live attenuated vaccines and DNA-vaccine constructs to develop vaccine candidates for both cattle and badgers. These were tested in small animal models.

The Krebs review reported in 1997. The report recommended development of cattle vaccines, which was considered more feasible and attractive than badger vaccination but with retention of the option of a badger vaccine. A research programme was set up, overseen by independent advisors (Vaccine Programme Advisory Group) and regularly peer reviewed. There was also a steering group chaired by the CVO from 2000-2006 to advise on licensing issues.

Spending on vaccines has increased as their potential importance, particularly of badger vaccines, has become apparent

Time period	Cattle vaccine spend	Badger vaccine spend
1997-1999	£0.55M	
1999 – 2005 (2 CSR periods)	£6.5M	£0.85M
2005-2008 (1 CSR)	£6.7M	£5.8M

Cattle vaccines and diagnostics

Just under £11M has been spent on cattle vaccines and associated diagnostics.

1999 – Number of approaches to vaccine development were investigated, including BCG (variable efficacy and sensitises cattle to tuberculin test), live attenuated vaccines, dead vaccines, subunit (proteins, peptides or DNA) vaccines and heterologous prime boost strategies. Initially it was expected that a non-BCG vaccine would be a candidate in parallel with human vaccine work. Work to develop a challenge model in cattle in which could be used to identify suitable DIVA antigens.

2001 - Work on antigen mining for specific antigens progressed after *M. bovis* genome sequenced in 2001 revealing specific antigens for *M. bovis* not in BCG. Basic immunology work on how BCG works and its effect on skin test (2001-04).

2002 – It was realised that non-BCG candidates were not forthcoming and work concentrated on identification of suitable antigens/adjuvants to improve the efficacy of BCG. Work on the differential diagnostics (Differentiating Infected from Vaccinated Animals, the so-called 'DIVA' test) required to allow BCG use commenced using specific antigens in interferon gamma test.

2005 - Neonatal BCG looked more promising than BCG in adult cattle and prime boost candidates BCG plus protein or subunit were also on the horizon (albeit with potential difficulties around GMO release). A decision was made to concentrate on optimising heterologous prime-boost approaches to improve BCG by:
- identifying vaccine subunit candidates that boost BCG-induced immunity in cattle;
- testing new adjuvant systems in combination with promising subunit vaccines in cattle;
- testing TB vaccines in cattle that are in phase I clinical trials in humans.

Work also continued on development of reagents for differential diagnosis that are suitable for use in vaccinated animals.

Work was started looking at new vaccine candidates and delivery protocols in a natural transmission study in cattle. It takes over one year to do each experiment and any experiment can only do relatively small numbers at a time due to health and safety issues around housing infected animals/risk to staff.

Started to engage in private/public partnership with a pharmaceutical company, Pfizer Animal Health, and commercial work to build links with BCG supplier SSI Copenhagen.

2007 - Policy work started to be addressed in earnest once the likely vaccine properties were known. Difficulties around EU negotiation (need to know candidate, data on DIVA-trade embargo risk etc).

Despite billions of dollars invested in human work worldwide, no alternative candidate vaccine to BCG yet available.

Badger vaccines and diagnostics

Just under £7M has been spent on badger vaccine development.

1999 - work commenced but less resourced than cattle in line with the Krebs recommendations.

Identification of vaccine formulations and delivery strategies suitable for non-oral and oral vaccination of badgers. We could not keep captive badgers at VLA at this time (VLA managers' decision on safety grounds) so used mouse and guinea pig challenge models. Collaboration with the Republic of Ireland to conduct a prototypical badger immunisation trial using BCG Pasteur to get preliminary efficacy data on injectable and oral formulations. This collaboration is still ongoing.

Initially there was no reliable way of telling if a live badger was infected, which makes any vaccination studies impossible. The first step was development of species-specific diagnostic tests and reagents e.g. made badger monoclonal antibodies for badger INF-g this work was ongoing until 2004.

2002 onwards- experimental BCG vaccination/challenge studies in badgers in UK and RoI to provide information on optimal vaccine dose, formulation, route of administration, immunogenicity and efficacy. Continuation of development of delivery systems and suitable formulation for oral vaccination of badgers - developed and assessed several different potential candidates including NZ lipid, formulation which is the current front runner. Difficulties with stability of formulation and BCG and its viability in environment and stomach acid needed initial basic research on physiology, biochemistry and microbiology.

Continued search for better vaccine candidates than BCG or adjuncts to improve BCG using small animal models.

2004 –VLA captive badgers used for initial BCG injectable safety study (no challenge involved). Validation of badger diagnostic tests in badgers culled in RBCT.

2005 - Preparatory work for Badger Vaccine Study (BVS) to test safety in the field. Experimental work ongoing on oral formulation of BCG Danish that is palatable and immunogenic to badgers, and suitable for delivery in the field – includes badger field work on bait uptake.

2006 – BVS started to get field safety and potentially some efficacy data for licensing injectable BCG. Efficacy studies in an experimental setting commenced.

Future work

The diagram below sets out the estimated timeline for future work required to deliver both cattle and badger vaccines.
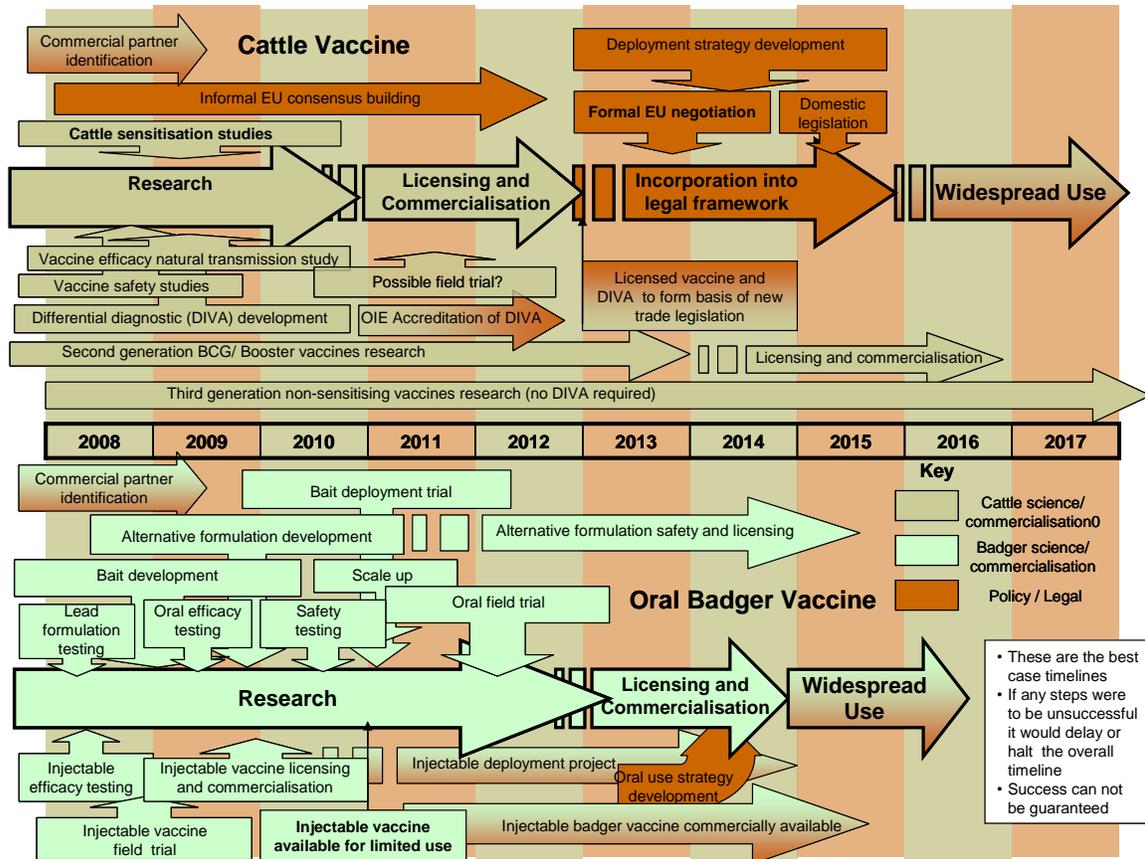
The estimated distribution of funding between cattle and badger vaccines (of all types including diagnostics) is shown in the table below. All long term costs are estimates and will depend on the precise nature of the research commissioned

Time period	Cattle vaccine spend	Badger vaccine spend
2008-2011	£12M	£8M
2011-2014	£10M	£7M

The larger budget for cattle research reflects the high costs of keeping infected cattle under stringent biosecurity (category 3) containment in the laboratory.

A summary of key dates is provided in the table below

Vaccine	Estimated earliest possible date	Likelihood of successful delivery on this timescale	Other
Cattle Vaccine	BCG+ DIVA (2012 – licensed not available for use) 2015 – available Incorporated in legislation	Medium	Non-sensitising vaccines 2018+
Injectable badger vaccine	2010	High	-
Oral badger vaccine	2014	Low	Alternative formulation -2015+

Cattle vaccines

Both efficacy and safety data are required for the licensing process. Studies into vaccine efficacy for BCG in a natural transmission setting is ongoing. Safety assessment in both neonatal (preferred vaccination age) and older cattle is underway. Licensing for use in all ages of cattle will enable a widespread initial use in all cattle followed by ongoing vaccination of younger animals. The experimental work for licensing is expected to be completed in 2011 with the licensing process completed in 2012.

Stakeholder discussions highlighted the need to ensure trade is not restricted if cattle vaccines are used. This has resulted in two additional projects. One looking at development and validation of the DIVA test to ensure it works in young animals and one looking at sensitisation of cattle to the skin test. These will be ongoing in parallel with the licensing process and feed data both into that and the policy development.

Non-sensitising vaccines were also identified as a possibility to address trade restrictions. Work is ongoing and will expand in 2010/11 once the majority of experimental work on licensing BCG is in place and more scientific expertise becomes available. These are a long term possibility and are very much at the research stage. It is not possible to say when or if they will be available.

Although the vaccine will be licensed as safe for use in cattle from 2012, EU legislation will prevent use of BCG. There are two key pieces of legislation which need to be considered:

- EU Directive 78/52/EEC and associated directives set out the criteria for national plans for the eradication of bTB. One of the criteria is a requirement to prohibit "anti-tuberculosis vaccination" under these plans. The adoption of a practice that was contrary to the requirements for such a plan, or a failure to prohibit vaccination would be very likely to be considered contrary to EC law.
- EU Directive 64/432/EEC aims to facilitate intra-community trade by ensuring that only animals with proven disease-free status can be exported to other Member States. Cattle must come from a herd with Officially Tuberculosis Free (OTF) status. As OTF status is determined through use of the tuberculin skin test and BCG interferes with this by providing false positives this legislation would need to be changed to allow the use of a DIVA test to replace the skin test in vaccinated animals

Formal negotiations for changes to the relevant directives can only commence once a licensed product is available. However, prior to this we will be aiming to ensure once a licence is in place, negotiations can commence as quickly as possible. It is not possible to tell how long negotiations will take, but based on previous experience we have allowed 3 years in the timeline for the changes to EU and subsequent domestic legislation.

Badger vaccines

The area where greatest certainty is possible as to the delivery timescale is injectable badger vaccines. The field safety trial is due to be reviewed in early 2009 to determine if it needs to run for a final year or if sufficient data has been collected. Laboratory safety studies are complete and efficacy studies for licensing will be completed by early 2009. The project is on track for a licensed injectable badger vaccine to be available in 2010.

The full badger injectable vaccine deployment trial is expected to be started once the licensed vaccine is available in 2010 but some preliminary logistics work may commence earlier in 2009. The aim of this work is to deploy the vaccine in such a way which supports the long-term goal of vaccination and provides an assessment of the viability of injectable vaccination.

The oral badger vaccine is still at the research stage and has not yet started the development and licensing processes. The timelines are therefore much less certain. The lead formulation, if successful, would be available for use in 2014. Experiments on efficacy and safety will commence in late 2008.

There is a significant risk that the current lead formulation will not meet all the necessary requirements for an oral vaccine. To mitigate this risk, part of the additional funding will be supporting the development of alternative formulations. These are less advanced and, therefore, if they are required, it will take longer to take them through to a licensed product. This will result in a delay of at least 12 months, possibly longer in an oral vaccine becoming available.

Another key concern is the uptake of vaccine by badgers. Deployment trials using the lead vaccine candidates will commence in late 2009.

GOVERNMENT FUNDED VACCINE RESEARCH PROJECTS UNDERWAY (INCLUDING BREAKDOWNS OF THE FUNDING)

This annex describes the aim, objectives, cost and duration of each of the Defra-funded on-going research projects concerning vaccine development. It also provides a brief description of each project. Titles of future research projects currently undergoing contract negotiation are provided at the end. Further details of these projects will not be available until we have received final project proposals for the research work and contracts for the work have been agreed and issued to the contractors. Details of all on-going and completed research projects are available on the Defra website at http://www.defra.gov.uk/science/default.htm and http://www.defra.gov.uk/animalh/tb/research/projects.htm, respectively.

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SE3222:	**Development of improved diagnostic tests for the detection of bovine TB**
Location:	**Veterinary Laboratories Agency**
Start date:	**01/07/2005**
End date:	**31/12/2008**
Total cost:	*£1 770 821*

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Aim
To identify and characterize novel diagnostic antigens to improve test specificity and to serve as reagents to differentiate infected from vaccinated cattle (differential diagnosis).

Objectives
- Complete antigen mining using comparative genome analysis.
- Perform antigen mining based on comparative transciptomes to measure early gene expression in *M. bovis* and BCG following infection of macrophages.
- Determine the kinetics of antigen recognition following experimental infection with *M. bovis*.
- Evaluate the use of antigens prioritised in objectives 1-3 to improve sensitivity and specificity of the gamma interferon assay and to allow differential diagnosis in vaccinated animals.
- Continue the collaboration with VSD, Stormont, Northern Ireland and AgResearch, Upper Hutt, New Zealand in order to optimise, standardise and evaluate antigen cocktails for use in diagnosis in GB, NI and NZ.

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Description

The incidence of bovine tuberculosis in GB has been increasing since 1988 despite the use of a control strategy based on tuberculin skin testing and slaughter of animals that react positively to the test. To improve the specificity and sensitivity of diagnostic tests is therefore a high research priority for Defra. The benefits of this approach are three-fold. First, improved sensitivity, particularly when novel diagnostic assays are used in parallel with the tuberculin skin test, would have a major benefit in reducing the economic burden of disease control. It has been estimated that an increase from 70% to 90% in test sensitivity would be equivalent to reducing the testing interval by a third with appreciable reduction in prevalence. Secondly, increased test specificity would have a further economic benefit by reducing the numbers of false-positive animals that may be slaughtered needlessly. Thirdly, in order to allow cattle vaccination to become a viable control policy option, diagnostic tests are required that can differentiate between infected and vaccinated cattle (differential diagnosis).

The gamma interferon test is permitted under EU law as an adjunct to the tuberculin skin test in cattle. It is a rapid and practical test and has potential to detect animals at an earlier stage of infection, but has slightly lower specificity than the tuberculin skin test used in the UK. The aim of this project is to develop specific diagnostic tests using comparative genomics to identify potential antigens that are then produced as peptide cocktails and evaluated using the gamma interferon assay. This approach is based on recent significant scientific advances achieved by VLA as part of Defra-funded projects to develop techniques for antigen mining. In this proposal we aim to complete our antigen screen to ensure that all possible candidates are identified. Specifically, we will apply a combination of comparative genomics (objective 1), and comparative transcriptomics (based on the differential gene expression of M. bovis and BCG inside bovine macrophages; objective 2) to identify species-specific proteins. Proteins identified in this way will be tested in cattle using peptide-based rapid screening techniques in combination with the gamma interferon assay. Antigens short-listed by these approaches will be tested for their suitability as reagents for differential diagnosis in the face of vaccination (objective 03) and for their ability to improve the specificity of the gamma interferon assay above that observed for tuberculin, particularly in animals at early stages of infection (objective 4).

The outcome of this project will be diagnostic reagents that allow the differentiation of vaccinated and infected cattle, that reach test sensitivities approaching that of tuberculin and which improve the specificity of the gamma interferon assay. In addition, antigens identified during this antigen mining operation will also be assessed for their suitability as potential subunit vaccine candidates.

SE3223: **Development of an oral BCG vaccine bait formulation for badgers**
Location: **Veterinary Laboratories Agency**
Sub-contractors: **Aston University/CSL/HPA/Immune Solutions Ltd**
Start date: **01/01/2006**
End date: **30/12/2008**
Total cost: **£1 460 714**

Aim

To: (i) develop a robust BCG formulation suitable for delivery to badgers in bait; (ii) assess its effectiveness using an animal model and its immunogenicity to badgers; and (iii) evaluate its safety to badgers and cattle in studies performed to GLP standards.

Objectives

- Lead vaccine formulations optimised and tested *in vitro.*
- Optimum bait formulation identified with which to deliver vaccine.
- Best vaccine formulation identified through protection studies in the guinea pig.
- Immunogenicity and safety of best vaccine formulation in bait evaluated badgers.
- Safety of best vaccine formulation determined in cattle.

Description

Bovine tuberculosis remains an economically important problem in Great Britain with potential zoonotic consequences. As such, Defra continues to have a statutory obligation to control tuberculosis in farm animals in Great Britain under the Animal Health Act of 1981, the Tuberculosis Orders, and various EC directives. The Krebs Report recommended that the option of a badger vaccine for tuberculosis should be retained alongside the development of a vaccine for cattle. The report by the Independent Scientific Group Vaccine Scoping Sub-Committee highlighted that oral delivery of BCG in bait would be the most appropriate means to vaccinate wild badgers on a wider scale, and that research efforts should be focussed on this approach. This project will build on recent advances in oral BCG formulation through the coordinated efforts of an international research consortium with expertise in vaccine production and formulation, as well as badger field work, vaccination and immunology. The outcome of this project will be an oral formulation of BCG Danish that is palatable and immunogenic to badgers, and suitable for delivery in the field. Formulations will be chosen that are suitable for large scale to GMP, thereby easing the progress to licensing and eventual evaluation and implementation in the field.

SE3224: **Continuation of the development for vaccines against bovine TB in cattle**

Location: **Veterinary Laboratories Agency**

Subcontractor: **Institute of Animal Health**

Start date: *01/04/2005*

End date: **31/03/2009**

Total cost: **£5 622 823**

Aim

To optimise the antigens and adjuvants used to formulate subunit vaccines for use in prime-boost strategies to boost BCG, to establish the duration of immunity to neonatal vaccination with BCG to provide the model for a prime boost analysis, and to improve the efficacy of BCG itself.

Objectives

VLA

- Evaluation of antigens identified in antigen mining project (SE3222) as subunit vaccine candidates.
- Selection of the most potent adjuvant for protein delivery.
- Determination of protective efficacy of subunit vaccine candidates in mice.
- Establish and validate immune correlates of protection and pathology.
- Compare vaccine efficacy of protein/adjuvant subunit vaccines developed in objectives 02 and 03 with proteins delivered by viral vectors in cattle.
- Assess the immunogenicity and protective efficacy in cattle of vaccines developed for the human TB vaccine effort now entering human clinical trials.
- Improving BCG through understanding of genome differences between BCG and *M. bovis*.
- Develop private/public partnership (PPP) with Pfizer Animal Health.

IAH

- Compare the immunity induced in neonatal calves to BCG Danish and BCG Pasteur.
- Establish the duration of immunity to neonatal vaccination with BCG to provide the model for prime boost analysis.
- Determine whether animals vaccinated with BCG as neonates can be effectively boosted at a later time point with either BCG or an alternative antigen in a prime boost strategy.
- Compare alternative antigens and immunological assays to distinguish between vaccinated animals that are totally immune from vaccinated animals that are infected or diseased.

Description

In 1996, Government tasked an independent scientific committee chaired by Professor John Krebs, to review the problem of bovine tuberculosis (TB) in GB. The recommendations of this committee were published in the Krebs' Report to the Minister of Agriculture Food and Fisheries in 1997. Government subsequently adopted many of the recommendations put forward by this report, including the recommendation that vaccination of cattle offered the best long-term solution for controlling the disease in the National Herd and that priority should be given to the development of a cattle vaccine against bovine TB together with an associated diagnostic test suitable for use in vaccinated animals. This view was re-affirmed in the House of Commons Environment, Food and Rural Affairs Committee's report on Bovine TB (2004) and by the findings of the Independent Scientific Group Vaccine Scoping Sub-committee. During previous Defra-funded projects, the VLA and their collaborators have made significant progress in developing TB vaccines for cattle such that we are on track with the time-scale for vaccine development outlined in the Krebs Report. Specifically they: (i) have shown that DNA or protein subunit vaccines used in combination with BCG gives superior protection against experimental challenge in cattle than BCG (heterologous prime-boost), and highlighted the need for better adjuvants for these sub-unit vaccines, (ii) have developed prototype reagents that allow discrimination between vaccinated and infected animals; (iii) have identified correlates of disease severity that can predict the success or failure of vaccination, and (iv) have developed an extensive network of collaborators involved in the Global effort to develop vaccines against human tuberculosis. This current proposal will build on these recent advances. It addresses Defra's TB research requirements identified in the AHWR research requirements document (September 2004) under heading R1. Specifically, it will concentrate on optimising heterologous prime-boost approaches to improve BCG by (i) identifying vaccine subunit candidates that boost BCG-induced immunity in cattle using antigen mining techniques developed in previous research contracts, and comparing the efficacy of these vaccines in mice and cattle (objectives 1,3,4); (ii) testing new adjuvant systems in combination with promising subunit vaccines in cattle (objective 2); (iii) testing TB vaccines in cattle that are in phase I clinical trials in humans (objective 6), and (iv) continuing to utilise the close and effective network of collaborations that we have developed with the human TB vaccine community (objective 5,6). VLA have also engaged in a private/public partnership with a pharmaceutical company (Pfizer Animal Health), and this relationship will be developed over the life of this proposal (objective 7). In addition, this proposal will support the continued development of reagents for differential diagnosis that are suitable for use in vaccinated animals.

SE3227:   **Evaluation of the protection efficacy of vaccines against bovine TB in a natural setting**

Location: **Veterinary Laboratories Agency**

Start date: *01/10/2005*

End date: **31/03/2011**

Total cost: **£6 781 127**

Aim

To determine the protective efficacy of novel TB vaccines for cattle in a natural transmission setting.

Objectives

- Develop a logistical framework for the project.
- Perform a proof of concept experiment to establish transmission rates.
- Determine the protective efficacies of cattle TB vaccines under conditions of natural transmission.
- Evaluate reagents for differential diagnosis.

Description

Bovine tuberculosis remains an economically important problem in Great Britain with potential zoonotic consequences. As such, Defra continues to have a statutory obligation to control tuberculosis in farm animals in Great Britain under the Animal Health Act of 1981, the Tuberculosis Orders, and various EC directives. Despite implementation of a test and slaughter strategy using the tuberculin skin test to detect infected animals, the incidence of bovine tuberculosis in cattle has been increasing exponentially since 1988. In 1996, an independent scientific commission chaired by Professor John Krebs to review the situation of bovine TB in GB concluded that the development of a cattle vaccine and associated diagnostic test had the best prospect of controlling the disease in the National Herd. This conclusion was re-affirmed in the House of Commons Environment, Food and Rural Affairs Committee's report on Bovine TB (2004) and by the findings of the Independent Scientific Group Vaccine Scoping Sub-committee, which highlighted that work on development and testing of vaccines should be maintained in order to produce a vaccine that is more effective than BCG in cattle. Significant scientific advances have been made towards this goal by VLA and our collaborators (especially AgResearch, NZ) as a result of Defra-funded projects. These advances have meant that Defra's TB vaccine programme is broadly on track with the timeline outlined by the Krebs' Report for the development of cattle TB vaccines.

However, as highlighted by Defra's Vaccine Programme Advisory Group (VPAG) at their inaugural meeting, a major barrier to progress in cattle vaccine research is the absence of experimental systems to measure vaccine efficacy in a natural transmission setting. Without this information, it is difficult to assess whether "laboratory" advances will have any significant impact in the field. The need to assess the ability of promising TB vaccine candidates to protect cattle against natural transmission of *M. bovis* was announced by the Animal Health Minister Ben Bradshaw to the House of Commons on 9 June 2005 and by Defra in an accompanying press release. In the press release it was stated that Defra would commission 'further work looking at new vaccine candidates and delivery protocols in a natural transmission study in cattle at the VLA. A naturally infected herd will be used to compare the effectiveness of several vaccines'.

The aim of this project is to establish a facility for generating natural transmission of *M. bovis* between cattle by assembling reactor cattle in a contained setting. This facility will then be used to determine the efficacy of promising vaccine candidates under conditions of natural transmission. This will be done by introducing sentinel vaccinated and control animals into the reactor herd and leaving them in-contact with reactor animals for 10-12 months. The protective efficacy of vaccine candidates will be determined by comparing disease rates between vaccinated and unvaccinated cattle. The first vaccine to be tested will be BCG given to neonates. Subsequent vaccines to be tested in this way will be prioritised on the basis that they have been shown to induce better protection against experimental challenge in cattle than BCG. This design was presented to and approved by VPAG, which includes a representative from the ISG, at its meeting on 12 May 2005.

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SE3233:   **Cattle TB vaccines: development of a DIVA test**
Location: **Veterinary Laboratories Agency**
Start date: **01/07/2008**
End date: **31/12/2011**
Total cost: **£1 692 978**

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Aim

To identify diagnostic reagents that allow the differentiation of vaccinated and infected cattle, that reach test sensitivities approaching that of tuberculin and which improve the specificity of the gamma interferon assay.

Objectives

- To define the antigenicity of the complete *M. bovis* complement of secreted antigens including all EAST-6 family members.
- To perform unbiased and comprehensive antigen mining based on a Gateway library approach.
- To define latency-specific antigens in cattle.
- Translational research.
- Continue collaboration with VSD, Stormont, Northern Ireland and AgResearch, NZ.
- DIVA test based on skin testing.

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Description

The incidence of bovine tuberculosis in GB has been increasing since 1988 despite the use of a control strategy based on tuberculin skin testing and slaughter of animals that react positively to the test. To develop vaccination strategies for cattle is an important part of Defra`s research into future control strategies. In order to allow cattle vaccination to become a viable control policy option, diagnostic tests are required that can differentiate between infected and vaccinated cattle (differential diagnosis) alongside current test and slaughter control strategies by developing so-called DIVA (Differention of Infected and Vaccinated Animals) reagents. This project is therefore aimed at the continued development and optimisation of such reagents, and the approach is based on and extends recent significant scientific advances achieved by VLA as part of previous Defra-funded projects. For example, a prototype DIVA reagent based on two defined antigens, ESAT-6 and CFP-10, has recently been validated and is now in routine use to enhance test specificity; another is being evaluated in a field trial. However, the sensitivities of these reagents are still lower compared to tuberculin and this sensitivity gap needs to be closed.

Principally, the VLA intend to complete their antigen screen to ensure that all possible candidates are identified. The assay system this project mainly targets is the gamma interferon test, which is already permitted under EU law as an adjunct to the tuberculin skin test in cattle. It is a rapid and practical test and has potential to detect animals at an earlier stage of infection; however, in its basic form, which employs tuberculin, it cannot be used as a DIVA reagent in combination with BCG. In addition, the VLA also intend to evaluate if the tuberculin skin test could be modified to allow DIVA by the application of defined and specific antigens in the skin test (objective 6).

This proposal describes a triple-track approach to improved diagnostics of product-development pursuing incremental improvement to current tests using targeted and library approaches (objectives 1-3), together with a basic research arm with a view to defining a new category of infected animals by looking at infectious-stage specific antigens (latency antigens) that may complement animals that are at disease stages when secreted antigens such as ESAT-6 or CFP-10 (objective 3). Lastly, this proposal also has a translational research objective to facilitate field application of reagents defined in this and earlier projects (objective 4). Further objectives ensure continued collaboration and synchronisation with similar research projects in New Zealand, Northern Ireland and the company producing the BOVIGAM IFN-gamma test, Prionics (objective 5), as well as evaluation of skin testing as DIVA reagent based on defined protein reagents (objective 6).

The benefits of this approach are three-fold. Firstly, DIVA reagents complementing novel vaccines will allow the implementation of vaccination as targeted control strategy alongside conventional strategies like test and slaughter and meat inspection. Secondly, improved sensitivity, particularly when novel diagnostic assays are used in parallel with the tuberculin skin test, would have a major benefit in reducing the economic burden of disease control even in the absence of vaccination. It has been estimated that an increase from 70% to 90% in test sensitivity would be equivalent to reducing the testing interval by a third with appreciable reduction in prevalence (see: Cox *et al.*, Proc Natl Acad Sci USA. 2005 102(49): 17588–17593). Lastly, increased test specificity would have a further economic benefit by reducing the numbers of false-positive animals that may be slaughtered needlessly.

The hoped for outcomes of this project will be diagnostic reagents that allow the differentiation of vaccinated and infected cattle, that reach test sensitivities approaching that of tuberculin and which improve the specificity of the gamma interferon assay. In addition, antigens identified during this antigen mining operation will also be assessed for their suitability as potential subunit vaccine candidates.

CB0115:	Field trial to assess the safety and efficacy of BCG vaccine administered parenterally
Location:	Veterinary Laboratories Agency
Start date:	01/01/2006
End date:	31/03/2010
Total cost:	£5 772 656

Aim

To collect data to determine the potential for investigating the likely benefits of widespread badger vaccination with BCG and that could be used to support a future application to the VMD for a marketing licence for the use of BCG vaccine in badgers.

Objectives

- To confirm safety in, and absence of shedding from badgers of a commercial Bacille Calmette Guerin (BCG) vaccine when given parenterally to wild badgers in the field.
- To investigate the immunogenicity and efficacy of BCG in wild badgers.

Description

The incidence of bovine tuberculosis (bTB) in cattle in the UK continues to increase and the disease is acknowledged to be a major threat to cattle production. Since the first isolation of *Mycobacterium bovis* from a wild badger found dead on a breakdown farm in 1971, badgers have become generally recognised as a wildlife reservoir and potential source of infection for other species. Although the contribution made by badgers to cattle infection remains unquantified, independent reviewers consistently support the view that badgers are involved in the transmission cycle. Furthermore, evidence from past badger culling strategies and from the Randomised Block Culling Trial (RBCT) of badgers indicates that culling alone is unlikely to be effective in controlling cattle TB. Similarly, it is widely considered that even diligent application of measures to control the disease in cattle will be insufficient to eradicate the disease while infected badgers remain as a reservoir of infection for cattle.

Vaccination remains a potential control option and this project aims to collect data on the safety and efficacy of Bacille Calmett Guerin (BCG), the vaccine licensed for human use in the UK, given by intramuscular injection to badgers in a field setting. BCG has been used experimentally in a wide range of species, none of which has shown any adverse effect due to vaccination and it is anticipated that this study will confirm those findings. The field study is relatively small in scale but it is hoped that it will demonstrate that BCG given in this way protects wild badgers against TB when naturally exposed in the field. If both safety and efficacy are confirmed, this study will provide essential data in support of any application to the Veterinary Medicines Directorate (the body responsible for licensing veterinary drugs in the UK) for approval to use BCG vaccine in badgers.

CB0116: **Efficacy testing of BCG vaccine in badgers**
Location: **Veterinary Laboratories Agency**
Start date: **01/04/2006**
End date: **31/03/2010**
Total cost: **£1 468 743**
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Aim

To obtain data on vaccine efficacy; both for the injected form of BCG vaccine, as well as for any oral vaccine formulation that arises from Defra project SE3223.

Objectives
- Obtain permissions, resources and protocols for the study.
- First experiment: Determine protective efficacy of BCG Danish vaccine injected intramuscularly (IM) at dose ($2\text{-}8\text{x}10^6$ CFU) to be used in the field study.
- Second experiment: Gather further data on the protective efficacy of BCG vaccine.
- Third experiment: Determine protective efficacy of BCG vaccine given orally.
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Description

Cattle tuberculosis remains an economically important problem in GB with the potential to spill over into humans. The frequency of occurrence of cattle tuberculosis continues to increase and badgers have been identified as a significant reservoir for the causative organism, *Mycobacterium bovis*. Furthermore, the recent Godfray report (2004) on the Randomised Badger Culling Trial recommended that the formation of cattle TB policy by Defra should be based on the assumption that badgers are involved in disease transmission as a wildlife reservoir. Previously, the Krebs Report (1997) recommended that the option of a badger vaccine for tuberculosis should be retained alongside the development of a vaccine for cattle. Consistently with these recommendations, Defra confirmed at a Vaccine Programme Advisory Group Meeting in Spring 2005 that they have a requirement for a licensed form of injectable human TB vaccine (BCG) for badgers. There are defined steps to achieving this licence: an experimental safety study performed to Good Laboratory Practice (GLP) accreditation. Completed successfully at VLA in 2004-5; a field safety study, which commenced in Summer 2006; and demonstration of vaccine efficacy. This typically comes from experimental challenge studies in the target species, and may be supplemented with data from field studies.

Given the small scale of the field safety study (which is unlikely to demonstrate vaccine efficacy in a statistically robust way) and the lack of any obvious parameter that can be measured and correlated with vaccine efficacy in badgers without actually infecting them with *M. bovis*, experimental vaccination-challenge studies would strengthen the claims for licensing the use of BCG in badgers significantly, and is the preferred option.

The VLA have already been involved in collaborative work led by scientists in the Republic of Ireland, where it has been demonstrated that BCG administered by injection to badgers conferred significant protection against experimental tuberculosis. These studies are encouraging and supportive in a claim for the use of BCG in badgers, however the data cannot be used directly for the licensing of a BCG vaccine in GB because an undefined vaccine (laboratory stock of BCG Pasteur) was used by the Irish scientists. However, the studies proposed in this project are modelled on the successful vaccination-challenge studies performed in Ireland.

Initial experiments will aim to determine the efficacy of injectable BCG used at the dose chosen for the field safety study and administered by a route (in the muscle) shown to be safe in the GLP study. It is likely that these studies will need to be repeated in order to provide convincing evidence of efficacy for submission to the Veterinary Medicines Directorate (the body responsible for the granting of animal medicines licences, including vaccines, in the UK).

The report by the Independent Scientific Group Vaccine Scoping Sub-Committee (2003) highlighted that in the longer term oral delivery of BCG in bait would be the most appropriate means to vaccinate wild badgers on a wider scale, and that research should continue on the development of an oral vaccine; to which end Defra are funding a three year research project (SE3223) at VLA. That project began in January 2006 and will result in candidate oral vaccine(s) for badgers by 2008-9. It is anticipated that one or more of these oral vaccine candidates will be tested for efficacy in the latter year(s) of this project.

Future research projects under contract negotiation

SE3224b: Continuation of vaccine development in cattle

SE3234: BCG GLP safety studies in cattle

SE3237: Matched contribution for EU vaccine proposal: Strategies for the eradication of bTB

SE3246: Development of an oral BCG vaccine for badgers - RESEARCH

SE3247: Development of an oral BCG vaccine for badgers - REGULATORY

SE3248: Specificity/sensitivity of ESAT6/CFP10 in the gamma interferon test

UPDATE ON GOVERNMENT FUNDED SCIENTIFIC RESEARCH INTO BOVINE TB UNDERWAY (EXCLUDING VACCINES)

This annex describes the aim, objectives, cost and duration of each of the Defra-funded on-going research projects into bovine TB (NB: details of all research projects concerning bovine TB vaccine development are provided in Annex C). It also provides a brief description of each project. A list of future research projects currently undergoing contract negotiation are provided at the end. Please note that these are subject to change until final contracts for the work have been agreed and issued to the contractors. Details of all on-going and completed research projects are available on the Defra website at
http://www.defra.gov.uk/science/default.htm and
http://www.defra.gov.uk/animalh/tb/research/projects.htm, respectively.
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SE3032:	**The long-term intensive ecological and epidemiological investigation of badger populations naturally infected with *Mycobacterium bovis***
Location:	**Central Science Laboratory**
Start date:	**01/04/2003**
End date:	**01/04/2011**
Total cost:	**£3 386 857**

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Aim

To continue to collect ecological and epidemiological data from the Woodchester Park badger population consistent with that obtained in previous years. Data has been collected from this site since the mid-1970s).

Objectives
- Obtaining data on the spatial configuration of badger social groups in the study area (by bait-marking)
- Collecting data on the size, structure and infection status of the population (by capture-mark-recapture and clinical sampling)
- The collation of collected data onto the existing Woodchester Park epidemiological and spatial databases.
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Description

The European badger (*Meles meles*) is implicated in the transmission of *Mycobacterium bovis* infection to cattle. The effective management of bovine tuberculosis in cattle is a fundamental responsibility of Defra. However, the development of a sustainable policy to control the spread of *M. bovis* from badgers to cattle can only be achieved through a deeper understanding of the ecology and dynamics of disease in the wildlife host, and interactions with domestic stock. This proposal describes the continuation of data collection from an intensively studied wild badger population at Woodchester Park in Gloucestershire. Since 1975 the Wildlife Disease Ecology Team of the Central Science Laboratory (CSL) has conducted research and provided advice on the ecology of badgers and the epidemiology of *M. bovis*, under contract to MAFF/Defra. The project has involved an intensive long-term programme of trapping and sampling badgers in a high density population in an area of high herd breakdown risk. This has provided data on spatial and temporal epidemiological patterns, ecological, demographic and behavioural processes that have enhanced our understanding of badger ecology, management and the epidemiology of *M. bovis* infection. The continued monitoring of the Woodchester Park badger population provides Defra with a strategic resource with which to explore a range of potential future policy options for the management of *M. bovis* transmission between badgers and cattle.

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SE3039:	**Identification of changes in individual and global farmer behaviour relating to the movement and management of cattle in the UK with particular reference to the introduction of bTB control measures**
Location:	**University of Liverpool**
Start date:	**01/05/2007**
End date:	**30/04/2009**
Total cost:	**£289 530**

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Aim

To monitor changes in farmer behaviour, particularly in terms of cattle movement, following the introduction of bTB control measures designed to assess the likely efficacy of legislation introduced to lessen the spread of bTB in the UK.

Objectives

- To identify the time-line of policy events relevant to changes in farmer behaviour.
- To conduct comprehensive time series and temporal analysis of cattle movement data.
- To identify farmer-perceived behavioural change since introduction of pre-movement testing and to understand these behaviours and factors that underlie them.

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Description

Bovine tuberculosis (bTB) control measures in Great Britain have recently been modified in an attempt to curtail the current epidemic. The mainstay of these measures is the pre-movement testing of cattle. These legislative interventions impose additional cost (both financially and in terms of time) on farmers and may, therefore, alter farm management, particularly with regard to cattle movement. There is therefore a need to monitor changes in farmer behaviour, particularly in terms of cattle movement, following the introduction of these measures to assess the likely efficacy of legislation introduced to lessen the spread of bTB in the UK.

The principal objectives of this work are to identify global and individual level behavioural changes that have occurred since the introduction of bTB control measures and to identify factors motivating these changes. The project consists of 3 interrelated studies. First, in order to make tangible correlations between behavioural change and modifications to bTB control, a review of all major policy changes to affect the livestock industry over the last five years will be conducted. A time-line of important dates in the announcement and implementation of Government legislation directly affecting the livestock industry will be produced. These include changes to the farm subsidies, handling of fallen stock, and lifting of the "over-thirty-months" scheme. Here the timing of reporting of the relevant legislation in the farming press will also be investigated.

Second, in order to identify changes in farmer behaviour with regard to cattle movements, a detailed network and time series analyses of RADAR cattle movement data will be conducted. Any such analysis needs to recognise the multiplicity of legislation and other pressures under which the cattle industry operates. The livestock industry has been required to adapt to changes in consumer demands, food safety, trade and movement controls over recent decades. Hence, recent bTB control measures are one part of a wide range of changes that have occurred during this time and variation observed in the movement data can only be attributed to recent modifications of bTB control measures by first identifying pre-existent underlying trends. This group have previously reported seasonal and long-term trends in cattle movement data for the period 2002-2005 (prior to recent changes to bTB control) and now propose to update existing time series analyses to include data from 2005 to early 2007 in order to identify changes that may be attributable to changes in bTB control.

Initial analyses will investigate the numbers of cattle moving as well as trends in the distances over which cattle are moved. However, analysis of individual farm-level data provides only limited information. Previous work using network analysis has demonstrated that substantial changes, important in the transmission dynamics of infectious agents, may be evident in the cattle movement network despite little or no apparent variation in individual farm measures. Therefore, the group will utilise their expertise in network analysis of large datasets to identify changes in the global behaviour of the cattle industry. They will formally identify change points in trends and correlate them with important dates in the announcement, implementation of bTB, control measures.

Thirdly the effect of recent changes to bTB control on farmer behaviour will be investigated through questionnaire and interview of farmers themselves. Concurrently with time-series analysis, a range of exploratory surveys will be conducted, together with personal interviews to assess factors and conditions which underpin motivation for change since the bTB pre-movement testing. The exploratory survey will identify perceived recent changes in the management of cattle on individual farms and within the industry more generally. Follow-up interviews will seek to verify these changes on-farm, [on-farm or on farms?] and to identify and explain factors responsible for the variation in changes among farmers in different regions. Subsequently, a questionnaire will be used to assess the most important factors impacting on relevant behavioural decisions. These surveys will be conducted in areas with varying degrees of sensitivity to the effects of TB in cattle. Such approaches are essential to capture the regional variation in disease prevalence. Where possible, perceived changes will be verified using RADAR cattle movement data.

This proposal has several strengths. First, it will utilise existing expertise in time series and network analysis to identifying trends in cattle movements, both in terms of farm-level factors (numbers of animals and distances moved, and types of premises moving cattle) and population-level factors (component size and density). Second, it will utilise expertise in measuring behaviour through analysis of movement records; and the proposal is strengthened by experience in communications with farmers. Third, the interdisciplinary skills of the project team will promote novel approaches to the evaluation of agricultural policy. This team have extensive experience in the investigation of the psychological aspects of decision-making and behaviour in a wide range of businesses. Application of these methods to the cattle industries will provide novel insight of the effect of bTB control on the behaviour of these sectors.

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SE3040:　　　　　　**A preliminary analysis of existing data to provide evidence of a genetic basis for resistance of cattle to infection with *M. bovis* and for reactivity to currently used immunological diagnostic tests.**
Location:　　　　　　**Roslin Institute**
Sub-contractors:　**Scottish Agricultural College/Veterinary Laboratories Agency**
Start date:　　　　　**01/07/2007**
End date:　　　　　　**30/06/2008**
Total cost:　　　　　**£144 211 (100% WAG funded, project managed by Defra)**

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Aim
To examine the extent of genetic variation for resistance of cattle to infection by *M. bovis.*

Objectives
- Identify herds and cattle present in the Defra VETnet TB database in CTS and dairy industry databases.
- Using the linkage established between VETnet, CTS and industry databases, develop an integrated database identifying both animals appearing in the VETnet TB database and their contemporaries present at the time of testing with pedigree and relevant aspects of performance.
- Define and calculate a set of epidemiological and genetic covariates to be used for modelling.
- Construct and refine models of TB-related data accounting for genetic, operational and environmental factors.
- Interpret outcomes and develop recommendations from final models.

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Description
There is both anecdotal evidence pointing to genetic variation for resistance of cattle to infection of *M. bovis*, and published experimental evidence in deer for significant genetic variation in resistance and reactivity to diagnostic tests. However this has not been properly quantified in the cattle population and it remains a possibility that such genetic variation exists and is a factor influencing the outbreak currently observed in the UK. The genetic variation may be expressed in resistance to infection, in the response to the diagnostic tests, or both. The opportunity exists to test these hypotheses using the data collected during the current outbreak on animals that react to the diagnostic test and/or exhibit disease and combining this data with industry databases, particularly dairy databases, that contain additional information on herd mates and pedigree.

The outcome of this analysis will firstly resolve the debate on the potential extent of genetic variation in the UK herd in resistance and reactivity to diagnostic tests and will inform subsequent epidemiological analysis. Secondly, given the

presence of genetic variation, the results will: (i) provide a preliminary quantification of the impact that current testing policies may have on the degree of resistance to infection present in the cattle population, and would provide recommendations on if and how the tests may be adapted to avoid such negative consequences; (ii) provide breeding companies with information that will allow them to target the marketing of bulls identified as genetically more resistant to areas in which *M. bovis* is more prevalent; and (iii) provide a firm foundation for the identification of genes with large effect on resistance, which in turn will lead to more effective breeding programmes.

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SE3119:   **Cost-effectiveness of farm husbandry manipulations**
Location: **Central Science Laboratory**
Start date: **01/11/2005**
End date: **31/10/2009**
Total cost: **£1 042 493**

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Aim

To investigate husbandry measures that might be effective at reducing badger to cattle TB transmission within the bounds of farm buildings.

Objectives
- Identify husbandry measures effective at reducing or preventing badger visits to farm buildings.
- See if different measures provide a detectable change in the risk of farms having a TB breakdown.
- Estimate the economic costs of different measures.
- Estimate the cost efficiency of different measures.

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Description
Recent research at the Central Science Laboratory (CSL) has identified visits to farm buildings by badgers (*Meles meles*) as potentially important in the transmission of *Mycobacterium bovis* (the causative agent of bovine tuberculosis) to cattle. Defra-funded project SE3029, undertaken at the CSL, indicated that this may be a common and widespread problem on cattle farms throughout the south-west of England and that certain farm husbandry characteristics may influence the frequency of visits. Experimental investigation of husbandry practices to reduce badger visits to farm buildings has been recommended by the Independent Husbandry Panel and the Godfray Review.

This project aims to identify and measure the benefits and costs associated with two broad husbandry practices by manipulating them on a series of farms within a factorial experiment. Each measure may achieve a different result. Therefore, an investment appraisal will be conducted to identify and estimate the potential benefits and costs of each husbandry practice. The benefits derived from each measure, both in isolation and in combination with others, will be assessed as the

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ability to affect a change in the frequency of badger visits to farmyard resources and quantify the effect this has on the risk of badger-cattle interactions (both direct and indirect) as a result of farmyard modifications. This will allow estimation of the benefits (valued in £GB) of disease exposure risk-reduction methods. Wider social benefits (e.g. potential benefits to farming communities) will be identified from an extensive literature review and discussions with the NFU and Defra. The cost–effectiveness of the manipulations will be analysed using profitability indicators such as net present value (NPV), benefit:cost ratio and internal rate of return. Risk and uncertainty will be assessed via sensitivity analysis.

The results will be directly relevant to Defra's policy on controlling TB in cattle by providing a quantified estimate of the benefits produced through improved farm husbandry methods. This will also be of direct benefit to the farming community who will be provided with information on which to make informed judgements on whether and how to invest in improved husbandry methods to reduce risks to herd health.

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SE3221:   **Volatile organic compound analysis for the rapid diagnosis of disease: TB in badgers and cattle as proof of principle**
Location: **Veterinary Laboratories Agency**
Sub-contractor: **Cranfield University**
Start date: **01/01/2006**
End date: **31/12/2008**
Total cost: **£457 390**

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Aim

Investigate new diagnostic methods, that might improve the means of testing live animals for TB, giving rapid, accurate results.

Objectives

- Build a device to allow collection of exhalations from cattle and determine if such samples of breath correlate to fresh samples.
- Obtain samples from cattle and badgers for analysis and determine the infection risk associated with such sales from TB infected cows.
- Determine the accuracy of e-nose and SIFT-MS for the detection of TB in cattle and badgers and identify the nature of at least two volatile organic compounds associated with TB.

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Description

Developments in genomics have highlighted the concept of "array technologies" and the potential power of understanding "disease signatures". Recently, significant progress has been made in developing tests for the rapid diagnosis of disease, based on the detection and analysis of volatiles present in clinical samples, using chemical sensor arrays coupled with multi-variate data analysis.

The generic nature of sensor technology is such that it has the potential to be applied across a wide range of core Defra activities. These include rapid pen-side detection and diagnosis of infectious diseases in animals, improving the speed of diagnosis of infectious disease by culture, improving the quality and flavour of food and environmental monitoring (of water, soil animal waste etc) for quality and contamination. It is thus a truly cross-cutting technology which has the potential to be applied to objectives under the six science themes laid out in Defra's Science and Innovation Strategy document.

The VLA have recently obtained proof of principle that it is possible to differentiate badgers and cattle with tuberculosis from healthy controls by analysing the volatiles present in serum using an electronic nose (eNose). The aim of this project is to evaluate more fully the analysis of volatile organic compounds (VOC) for tuberculosis detection using two different devices: the eNose and SIFT-MS (selective ion flow tube mass spectrometry).

Bovine tuberculosis remains an economically important problem in Great Britain with potential zoonotic consequences. As such, Defra continues to have a statutory obligation to control tuberculosis in farm animals in Great Britain under the Animal Health Act of 1981, the Tuberculosis Orders, and various EC directives. Despite the current test and slaughter control programme, the frequency of occurrence of bovine tuberculosis continues to increase and badgers have been identified as a significant reservoir for *Mycobacterium bovis*. The Krebs Report [1] highlighted the need to develop improved diagnostic assays for bovine and badger tuberculosis. These are expected to offer improvements in terms of diagnostic accuracy in both species and could have significant impact on the control of bovine tuberculosis.

If successful, the technology underpinning both approaches could be used to develop rapid diagnostic tests which could be performed on farms or in the field. Such a test for TB would complement current immuno-diagnostic assays such as tuberculin skin testing, blood-based IFN-gamma assays and serology. In the longer term such tests could be developed for use by farmers (or local vets) to monitor their own livestock for a range of infectious diseases. Tests/technology arising from this project have the potential for commercialisation, and as such this takes the work beyond the realm of the Evidence Base Unit (FFG, Defra).

SE3230: **The problem bTB herd – characterisation, prediction and resolution**
Location: **Veterinary Laboratories Agency**
Sub-contractor: **University of Cambridge, CIDC**
Start date: **01/04/2007**
End date: **30/04/2010**
Total cost: **£411 556**

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Aim
To define and characterise the problem herd, predict outcomes of possible control strategies and to recommend appropriate actions.

Objectives
- Defining and describing potential 'problem' herds with characterisation of principal risk factors.
- Defining and describing the avian reactor 'problem' herd.
- Developing decision trees for AH so that appropriate control actions can be based on data accumulated in (potential) problem herds <u>during a TB incident</u>, through analysis of cases, actions and outcomes.
- Developing decision tress for AH so that appropriate control actions can be based on data on potential problem herds and their surroundings, <u>before a TB incident has occurred</u>, through analysis of cases, actions and outcomes.
- Disseminating the above findings to Defra, AH and the broader scientific community.

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Description

Since the foot and mouth epidemic of 2001, both the distribution and intensity of bovine tuberculosis in the national herd of Great Britain have increased, such that until recently the national trend showed a yearly increase of 18% in confirmed incidents. The current control programme is designed to detect infection (by routine skin testing, slaughterhouse inspection and movement tracing), to remove infection as thoroughly as possible (by short interval testing) and to prevent spread to other herds (by pre-movement testing and movement restrictions).

By its nature, much of the programme is reactive. Parish testing intervals, for example, tend to be modified only after a changed risk of infection is detected, usually several months after the risk has actually increased. Pre-movement testing is a welcome recent step in preventing new cases occurring in areas of previous high or low risk, and the present proposal would yield needed methods for estimating its effectiveness. However, this programme, apart from modifying parish testing intervals and allowing discretion to treat some 'high risk' categories of herd more severely (such as dealer herds), treats all herds in a similar fashion. Yet some herds are known to be 'problem' herds, i.e. experience has shown that these herds are more likely to have new incidents (sometimes repeatedly), tend

to have more affected animals when they do break down, repeated short interval testing may take a long time to clear infection, or total or partial herd slaughter is deemed necessary to eliminate infection... and so on, depending on the definition of `problem herd` adopted.

This project first seeks to define and characterise the 'problem herd', then to predict outcomes of possible control strategies, and finally to select appropriate actions. For example, herds can be described according to their disease history before focusing on the characteristics of those herds that may predispose to the defined `problem`. VLA is now in an excellent position to define and characterise different types of 'problem' herd, using detailed and relevant datasets. They include VetNet, the British Cattle Movement System database, the TB99 and CCS05 herd questionnaires and VLA's molecular typing datasets. Both in size of database and in integrating them, VLA has more experience at using these datasets for investigating TB epidemiology than any other institute. 'Problem herds' will be focussed on in conjunction with the experience of specialists in TB in both Defra and Animal Health (AH) to help focus on the key characteristics for investigation.

Currently available datasets provide useful data on all types of 'problem' herd except for the thousands of herds that have positive avian tuberculin responses. These can delay identification of any bovine TB infection that has occurred. There are several aspects to be considered. For example, herds may not be detected as infected at a routine herd test, introducing a dangerous delay; individuals may not be detected during a confirmed breakdown, resulting in undue extension of the incident; or, again, herds may clear restrictions only to find further infection at the six month check test because infection was not detected at previous tests. This issue will be treated as a separate objective within the study.

It is anticipated that, by using the BCMS data in particular, it will be possible to quantify how dangerous these 'problem' herds are in terms of risk of spread to other herds. By using the full range of data it will be possible to attempt to quantify the risks they pose to themselves (in terms of further incidents and degree of within-herd spread). How costly these herds are in the context of the whole control programme could then be quantified, utilising cost data recently gathered in other Defra-funded projects. These outputs would inform the best approaches to controlling the bTB risk to, and presented by, these herds.

An important element of this study will be to develop tools for predicting which herds would fit into 'problem' categories, and tools for recommending cost-effective control actions (decision trees or in some cases Expert Systems). These could then help AH decide on what action to take to control the risk presented. The decision trees could use information accrued from suspected 'problem' herds, either: information accumulated before and during a TB incident, leading to recommendations for eliminating infection; or information that is available before infection has been detected, leading to recommendations for reducing the risk of the herd becoming infected or spreading infection. Information of significance might include: herd size, type, and other husbandry details (source: VetNet, CCS2005 and TB99 data); biosecurity details, e.g. efforts to exclude wildlife from buildings, to prevent cattle coming into contact with wildlife, or coming into contact with other herds (CCS2005 and TB99 data); movement history: numbers of animals moved into the herd, and the time they had spent in herds with various levels of bTB prevalence (source: CTS and VetNet data); distribution of the risk of infection with bovine TB in GB (geographical (GIS) analysis of VetNet data); and information gaps – and needs for additional investigations – as identified in this process. The project will develop decision trees that can enable AH to be more proactive in the elimination of infection in 'problem' herds, and to prevent the emergence of new problem herds.

SE3231: **Validation and epidemiological application of molecular methods for monitoring *M. bovis* survival and dissemination in the environment.**
Location: **Veterinary Laboratories Agency/University of Warwick**
Start date: **01/05/2007**
End date: **30/04/2010**
Total cost: **£1 309 583**

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Aim

To validate and optimise specific real time quantitative PCR methods for the detection and quantification of *M. bovis* in the environment.

Objectives

- To validate RD4 *M. bovis*-specific DNA-based surveillance methods and compare DNA extraction methods (Ring Trial).
- To prove that molecular detection correlates with detection of *M. bovis* cells in environmental samples.
- To determine viability of *M. bovis* cells and carry out typing studies of soil IMC extracts.
- To evaluate non-invasive molecular screening tool to detect hotspots of *M. bovis* contamination on farms with persistent bTB breakdowns.
- To evaluate an environmental screening tool to detect hotpots of *M. bovis* contamination on farms with persistent bTB breakdowns.
- To determine viability of *M. bovis* cells and typing studies of soil isolates.

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Description

Bovine tuberculosis (bTB) is a serious and growing disease of cattle in Britain. The study of *Mycobacterium bovis*, the bacteria that causes bTB, poses particular challenges with regard to its specific detection once deposited in soil due to its similarity to closely related species that are also found in the environment, and due to the intrinsic nature of the environmental bacillus once deposited via contaminated animal excreta. Information gained from sequencing the complete genome of *M. bovis* has revealed a number of unique DNA sequences (or regions of difference (RD)) compared to other closely related species, and these differences provide a basis for the development of highly specific DNA probes that detect and amplify only *M. bovis* DNA. A region of difference known as RD4 is deleted in *M. bovis* but not in other closely related species, and this fact was exploited to develop a DNA detection and enumeration technique (real time PCR) specifically for *M. bovis*.

This proposal will extend past research to optimise PCR assays that will allow discrimination between *M. bovis* and closely related species from environmental samples. A ring trial will be performed by participating research institutes (VLA and Warwick University) to test the sensitivity, specificity, reliability and reproducibility of the PCR on a range of positive and negative laboratory and field samples. Complementary studies will address questions about the viability, abundance and metabolic activity of *M. bovis* cells in different environmental substrates. Growth of the cells isolated from PCR positive environmental samples on culture media will be performed in an attempt to identify the strains found in the environment and compare these to strains found in the tissues of infected cattle and badgers. Towards field application of the PCR, environmental sampling protocols will be developed in the context of improving farm biosecurity, and as a non-invasive marker of badger infection.

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SE3232:	**The molecular basis and impact on host response of phenotypic variation across *M. bovis* molecular types**
Location:	**Veterinary Laboratories Agency/Institute of Animal Health**
Start date:	**01/09/2007**
End date:	**31/08/2010**
Total cost:	**£130 045 (BBSRC GPA)**

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Aim

To determine the impact of *M. bovis* molecular types on the bovine innate immune response and to identify the pathogen constituents that modulate this response.

Objectives
- Do distinct molecular types of *M. bovis* induce differential immune responses in the bovine host?
- What are the constituents of the pathogen that trigger these responses?
- Validation of immunomodulatory mechanisms.
- Data Management.

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Description
Bovine tuberculosis (bTB) is one of the most difficult animal health problems that the farming industry in Great Britain faces today. The number of cattle infected with bTB has been increasing year on year by 18%, which leads to serious losses for affected farms due to the slaughter of infected animals and the imposition of cattle movement restrictions. Government spending on disease surveillance and compensation to farmers has also been following this upward trend, with spending over 2004-2012 expected to top £1 billion. From these statistics it is clear that the current disease control strategy is not working, yet the reasons for this are not obvious. One possibility is that new forms of the

causative agent of bTB, *Mycobacterium bovis*, have evolved in GB that are able to circumvent the current control measures. Research by the VLA has found that evidence for this latter scenario is supported by the presence of a range of different types of *M. bovis* circulating in GB that seem to be successful in spreading around the country from their original place of isolation. This project sets out to determine whether these diverse types of *M. bovis* interact with the immune system of cattle in different ways, and so explain their success. To achieve this the groups will take advantage of the recent availability of the complete DNA sequences of both *M. bovis* and the bovine host. This will allow them to explore how the host and pathogen interact with each other at the level of individual molecules, and to build up a more detailed picture of how *M. bovis* causes disease in cattle. The information coming from this project will help government policy makers to develop new control strategies based on the exploitation of epidemiological information, and offers the chance to stop the upward spiral of bTB disease burden and linked expenditure in GB.

SE3235:	**To improve the sensitivity of spoligotyping for direct tissue application**
Location:	**University College, London**
Start date:	**01/09/2008**
End date:	**30/04/2009**
Total cost:	**£58 285**

Aim

To identify improvements which could be made to the current method of spoligotyping to increase sensitivity of the procedure.

Objectives

- To develop a modified LATE-PCR spoligotyping protocol.
- To validate this protocol and compare with the existing spoligotyping procedure in use at VLA Weybridge.

Description

Spoligotyping is a DNA fingerprinting technique which is widely used in identifying and tracking strains of MTB complex organisms involved in outbreaks of disease. The technique is particularly useful for typing strains of *M. bovis* and is used in the surveillance programme of outbreaks of bovine tuberculosis affecting cattle and other wildlife in the UK. This PCR-based method is perfectly adequate when applied to DNA of sufficient quantity and quality, such as that provided by culture, but yields a partial fingerprint in up to 50% of cases when applied directly to DNA isolated from clinical samples (compared to cultures of the same cases). This may be due to the sparsity of mycobacteria in some tissues.

This project will investigate improvements which could be made to the current method of spoligotyping to increase sensitivity of the procedure. It is hoped this will obviate the need for, or at least markedly reduce, the time of culture before typing is applied. The time to results could be reduced from a few weeks to a few days. This should find application in a range of situations, such as in routine typing of cattle tissues, slaughterhouse cases and environmental and fixed archival samples where culture may not be feasible.

SE3236	**Multiplex PCR to distinguish between *M. bovis* and BCG and *M. microtii***
Location:	**University College, London**
Start date:	**01/05/2009**
End date:	**31/08/2009**
Total cost:	**£31 540**

Aim

To develop a multiplex PCR which will simultaneously detect and quantify three members of the MTB complex *M. bovis,* the vaccine strain *M. bovis* BCG, and *M. microti.*

Objectives

- The development of specific PCR methods for *M. microti*, *M. bovis* BCG based on primers flanking specific deletions RD1^{mic} and RD1^{BCG} respectively. The combination of these methods with the *M. bovis* RD4 method (Taylor *et al*, 2007).
- "Checkerboard" optimization of PCR components & conversion of the optimal primer set combinations into Taqman methods using linear hybridisation probes labelled with appropriate fluorescent chemistries.
- Determination of minimum detection limits of the multiplex using environmental samples spiked with DNA standards and viable cells. Transfer to VLA RT platform & preparation of final report.

Description

Bovine tuberculosis is a chronic granulomatous disease mainly affecting lymph node and lung tissues of cattle. It is caused by *Mycobacterium bovis*, a member of the *Mycobacterium tuberculosis* (MTB) complex group of bacteria. At the genome level, *M. bovis* shares over 99% identity with *Mycobacterium tuberculosis,* the agent of human tuberculosis and other members of the MTB complex. Sequencing of key members of the MTB complex has shown differences due to deletions in the genomes which allow the development of methods for species identification. This proposal concerns the development of a multiplex PCR which will simultaneously detect and quantify three members of the MTB complex *M. bovis,* the vaccine strain *M. bovis* BCG, and *M. microti*, which mainly affects small mammals.

SE3239:	A county Parish Holding Herd (CPHH) level spatial and temporal analysis of the Randomised Badger Culling Trial (RBCT) dataset
Location:	University of Bristol
Start date:	01/10/2008
End date:	30/09/2010
Total cost:	£287 457

Aim

To perform finer scale analyses to look at the incidence of bTB in cattle by farm and in badgers in smaller space/time areas of the RBCT and to test the hypothesis that bTB cannot persist without the presence of both cattle and badgers and that removal of one or other leads to a decay in environmental persistence that may provide alternative policies for control of bTB.

Objectives

- Selection of the appropriate data from the VETNET and RBCT databases.
- Construction of definitions of closeness between farms and badger data and construction of time-dependent predictor variables to indicate numbers and percentages of close individuals (both badgers and other cattle).
- Construction of cattle movement predictors.
- Development of time to event (survival) models to examine risk factors.
- Assessment of the effect of the assumed perfect sensitivity/specificity of the TB test.
- Evaluation of plausibility of modelling competing risk models to model both risk of infection and probability of cure / re-infection based on data.
- Preparation of papers.

Description

In this project the researchers will look in detail at the relationship between TB cases in cattle and TB cases in badgers at a finer level than that looked at originally in the Randomised Badger control trial (RBCT). They will consider the areas of the RBCT selected for proactive culling and survey only and match data collected on culled badgers with the individual cattle herd breakdowns. They will then look at associations between individual cattle herd breakdowns (CHBs) that occur and the numbers of badgers both infected and non-infected with TB that are trapped and culled close to the herd along with other close CHBs that occur. They will also look at associations between CHBs and prior cattle movements both in terms of numbers of movements and the infection history of former herds. They will consider the hypothesis that removal of either badgers or cattle may successfully control bTB in cattle. Appropriate statistical analyses that account for the temporal nature of the data as well as the spatial structure that exists will be performed. They will evaluate whether such a finer grain analysis of the data results in different findings than the original trial area level analysis and how detailed and fine scale an analysis the data can support.

SE3240: **Spatial and temporal analysis of cattle herd breakdowns in the RBCT**
Location: **Central Science Laboratory**
Start date: **01/09/2008**
End date: **31/08/2009**
Total cost: **£61 286**

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Aim

To identify sources of unexplained variability in the response of cattle herd breakdowns to badger culling treatments in the Randomised Badger Control Trial (RBCT), by taking into account the finer spatial and temporal detail of treatments and responses.

Objectives

- To estimate the effects of uncertainty in cattle herd testing on the measured effect size for RBCT treatments, using Monte Carlo simulation.
- To characterise the spatial pattern of disease in the RBCT, in individual herds and badger social groups, using Mantel testing of similarity matrices.
- To characterise the spatial-temporal clustering of disease, among herds and badger social groups, using point pattern analysis based on K-function analyses.
- To analyse the influence of variation in treatments, including the timing, duration, location and extent of culling operations, on disease dynamics in badgers and cattle, using Generalised Linear Mixed Models and Generalised Geo-Additive Mixed Models.
- To undertake a survival analysis, analysing the influence herd, badger and environmental covariates on the hazard of cattle herd breakdowns, using Cox-proportional hazard models, allowing direct comparison with Irish badger culling analyses.
- To investigate the interactions among the components of the Cattle:Badger:Disease system, using Structural Equation Modelling.

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Description

The Randomised Badger Culling Trial (RBCT) examined the number of cattle herd breakdowns (CHBs) due to bovine tuberculosis in response to proactive and reactive badger culling, at the scale of replicated blocks of 100km^2. This design was entirely suitable for evaluation of policy options at a large scale. Unsurprisingly, there remained after statistical analysis considerable unexplained variability in the number of cattle herd breakdowns, much of which is likely to relate to the localised nature of environmental conditions, including the status of the badger population. This project will investigate the fine-scale nature of variation in the fate of individual herds during the RBCT, by conducting a range of spatially-explicit analyses that take into account small scale variation in time and location of treatments and responses. The project will address three elements of the identified research needs: 1. investigate the location and timing of CHBs in

relation to badger culling, and the infectious status of badgers; 2. identify the effect of variation in the extent of culling treatment areas within the 1-2km buffer zones; and 3. identify any differences in the outcomes seen on confirmed and unconfirmed CHBs.

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SE3241:   **Spatial-temporal analysis of the Randomised Badger Culling Trial**
Location: **Veterinary Laboratories Agency**
Start date: **01/09/2008**
End date: **28/02/2010**
Total cost: **£246 706**

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Aim

To construct a web-based interactive GIS mapping tool for the visualisation of the RBCT reactive data which can be used to assist in the epidemiological analysis of the reactive trial areas and provide a better understanding of how spatial and temporal factors affect the incidence of confirmed and unconfirmed breakdowns, and the effects of culling on a small scale.

Objectives

- To produce a web-based GIS mapping tool capable of visualising all relevant RBCT data, enhanced by information available from existing datasets (IACS, VETNET, CTS, VLA/Defra and ERGO archives), and by newly acquired or produced information about parcel-resolution land use.
- To conduct an epidemiological analysis of the data from the reactive areas, using the archive created in objective 1 and considering, in particular, the location, timing and severity of CHBs in relation to the location, timing and intensity of badger culling in the trial, and the infectious status of the badgers removed, incorporating *Mycobacterium bovis* genotyping of badger and cattle.
- To determine the likely proportion of unconfirmed breakdowns that represented true herd infections, their contribution to the epidemiology of bovine tuberculosis (bTB) within the RBCT trial areas and the extent to which these herds are spatially related to clusters of infected herds and infected badgers.
- Development of a method to estimate the contribution of badgers to bTB infection of herds using pattern analysis of numbers of reactors.
- To identify factors that can explain differences between farms within reactive areas that experienced a breakdown and farms that did not and which may protect from bTB, using the data archive compiled by objective 1 including new data relating to spatial features extracted from maps.

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Description

The ISG has performed and published a comprehensive and top-level analysis of the data collected by the Randomised Badger Culling Trial (RBCT) and associated studies. However, further insights would accrue from a descriptive

spatial-temporal representation of the data and sequence of events during the RBCT. In particular, further insights are needed into the mechanism by which culling may increase herd breakdowns and how this may be ameliorated.

The first aim of this work is to produce an archive of data pertaining to the reactive component of the trial that will include data collected as part of the trial and existing data sets maintained by the VLA, Defra and Animal Health. This will be supplemented with environmental data such as climate and landscape features, census data and Geographical Information System (GIS) databases including satellite imagery and aerial photography (objective 1). This archive will be used to construct a web-based interactive GIS mapping tool for the visualisation of the RBCT reactive data that will display and summarise the data collected in the reactive component of the RBCT in a collection of maps layering information that can be explored interactively.

This GIS tool will then be used to assist in the epidemiological analysis of the reactive trial areas. The location, timing and severity of infections in cattle herds will be evaluated in relation to the location, timing and intensity of badger culling during the trial. A descriptive epidemiological analysis will be performed to describe the sequence of events and the spatial and temporal relation between a confirmed Bovine Tuberculosis breakdown (CHB) on a farm, its associated culling operation and the distribution of subsequent breakdowns, incorporating badger activity, infection status and cattle and badger genotype information (objective 2). Part of this will be an extension of previous work carried out at the VLA to estimate the temporal relation between culling and subsequent breakdowns in the nearest herds and contiguous herds.

Within trial areas there were holdings that experienced a breakdown and holdings that did not. The visual representation of the reactive areas and data archive will be used to identify factors that may affect the risk of breakdowns, such as farm management factors and landscape and environmental factors that may affect exposure to badgers. Novel information about landscape factors such as length of boundaries, location of crops etc., will be extracted from the maps and utilised in a comparative epidemiological analysis to identify factors that may reduce the risk of a CHB (objective 5).

In addition, the wealth of data collected during the RBCT presents a unique opportunity to assess the importance of other factors that may greatly contribute to Bovine Tuberculosis control. In objective 3, factors will be identified that determine whether a unconfirmed breakdown will eventually be confirmed as truly infected with *Mycobacterium bovis* and assess the contribution of unconfirmed breakdowns to the epidemiology of bTB in all RBCT areas. In objective 4, the relationship between the monthly pattern of the number of reactors for breakdowns and the most likely source of infection will be estimated.

The research described will build on the knowledge base gained from SPIDA (a web based interactive mapping tool developed at the VLA) and could also be viewed as a pilot for how environmental, landscape and disease data might be combined to inform control strategies. It will enhance the RBCT data archive providing an extensive array of new environmental variables in the reactive area for current and future research. The epidemiological analyses proposed will provide a better understanding of how spatial and temporal factors affect the incidence of confirmed and unconfirmed breakdowns, and the effects of culling on a small scale.

Future research projects under contract negotiation

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SE3238:	**Meta-analysis of diagnostic tests for bTB in cattle**
Location:	**Veterinary Laboratories Agency**
Start date:	**01/09/2008**
End date:	**29/01/2010**
Total cost:	**£175 289**

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Aim

To establish the best estimates of the classical test characteristics of sensitivity and specificity for diagnostic tests for bovine tuberculosis in cattle in GB and how we can maximize accurate diagnosis using single tests or a combination of tests and use this information in a control strategy to reduce the incidence of bTB in GB.

Objectives

- To provide a qualitative description of diagnostic tests currently used to assess infection with *Mycobacterium bovis* in cattle including test practicality.
- Through bibliographic searches of scientific databases identify studies that have measured test sensitivity and/or specificity of diagnostic tests for *M. bovis* in cattle.
- Using standard meta-analysis techniques estimate the sensitivity and specificity of diagnostic tests that are practical to use to assess infection with *M. bovis* in cattle in GB.
- To show how combinations of tests may be used to control bTB in GB and potentially achieve freedom from infection.

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Description

Bovine tuberculosis (bTB) caused by *Mycobacterium bovis* is a significant endemic disease in cattle in Great Britain (GB). There were confirmed new incidents of bTB in 2.5% of British herds in 2006 and the incidence has been rising steadily since the early 1990s. The single intradermal comparative tuberculin test (SICTT) is the bedrock to current control of bTB in GB, but other tests exist including the interferon gamma blood test which already supplements the SICTT in specified circumstances. Reviews have been conducted of diagnosis of bTB in cattle, but there has been no attempt to conduct a statistical analysis to summarize available data about the accuracy of the tests. There is no consensus about the best values to use for GB. The study will identify published data measuring the performance of a range of diagnostic tests for bTB including the SICTT, interferon gamma, culture of *M. bovis*, histology, post-mortem inspection and other blood based tests. A Working Group comprising over 15 experts in veterinary disease, bTB and diagnostic tests will review these studies

and extract information about the accuracy of the diagnostic tests. These data will be combined using standard statistical methods to obtain best estimates of the accuracy of the tests. This information will then be used in statistical models to predict the best combination of tests that could be used in strategies to control and reduce the incidence of bTB in GB. A range of models designed to represent the different disease scenarios across GB will be developed and the effect of a range of testing strategies including frequency of testing and different combinations of diagnostic tests will be examined. The project will draw heavily on the experiences of the Working Group that recently conducted the review of diagnostic tests for bTB in deer and developed models for designing control strategies for achieving freedom from infection with *M. bovis* in deer.

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SE3242:   **Further analyses of spatial and temporal trends in the cattle data associated with the Randomised Badger Culling Trial**
Location: **Imperial College, London**
Start date: **15/10/2008**
End date: **30/04/2010**
Total cost: **£379 625**

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Aim

To investigate any seasonality in the risks of TB infection, estimate the impact of proactive and reactive culling on infection incidence, analyse the effects of proactive culling using individual herd data including measures of local TB risk and investigate ongoing trends in TB incidence among cattle herds in proactive and survey-only trials areas.

Objectives
- Analysis of seasonality in TB infection incidence.
- Investigating biological plausibility – estimation of the impact of proactive and reactive culling on infection incidence by quarter year.
- Analysis of the effects of proactive culling using individual herd data including measures of local TB risk.
- Ongoing monitoring of TB incidence in cattle herds in RBCT areas.

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Description
An important challenge in understanding how, when and where tuberculosis (TB) transmits to and between cattle is that infections are not immediately apparent. In most cases, infections are detected when cattle are tested using a skin test which measures each animal`s immunological response to the bacterium that causes TB in cattle (*Mycobacterium bovis*). The skin test indicates the presence or absence of infection, which can be later confirmed after a post-mortem examination of the animal, but it does not provide information on when the infection occurred. Thus, those investigating the disease learn that an infection occurred, but subject to caveats about test performance, the insights are limited

to the knowledge that the infection happened between the date of the current skin test indicating infection and the date of the most recent past skin test (if any) showing no evidence of infection.

This limitation means that careful statistical analysis is required in order to investigate any seasonality in the risks of infection. This project will investigate this issue directly to determine whether cattle appear to be at higher risk of becoming infected with *M. bovis* in some months than others. If there were big differences in risks by month, then advice to farmers regarding biosecurity measures (designed to limit opportunities for disease spread) could be improved by highlighting when extra vigilance would be most beneficial.

Not being able to determine precisely when cattle became infected also complicated interpretation of the results of the Randomised Badger Culling Trial (RBCT), which tested two potential badger culling strategies to determine whether they reduced the amount of TB in cattle. This project will also investigate, using statistical models, what the information collected from skin tests performed on cattle in the RBCT means in terms of how badger culling affected the risks of cattle TB infections over time, in RBCT trial areas and on nearby land. Further analysis of RBCT data will also investigate if/how badger and cattle herd densities immediately surrounding herds affected their TB risks and the impacts of badger culling on these TB risks.

Finally, the project will investigate ongoing trends in TB incidence among cattle herds in proactive and survey-only trials areas following the completion of a Defra-funded contract which ends on 31 March 2009. The results will be reported to Defra in August 2009 and February 2010. The results of these investigations will be submitted to scientific journals where they will be subject to review by independent scientists prior to publication. Furthermore, members of the project team will give presentations of the results both to other scientists and to stakeholder groups.

SE3243:   **Analysing the Randomised Badger Culling Trial from a National Cattle Perspective**
Location: **University of Glasgow**
Start date: **01/10/2008**
End date: **30/09/2010**
Total cost: **£127 926**

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Aim

To ask what the national British perspective can tell us about the RBCT analysis and to extrapolate from the RBCT and determine how best to control the spread of the areas where cattle are deemed at high risk of becoming infected (HRAs).

Objectives

- Determine the best fit and likely credible ranges for herd BTB prevalence, consistent with recorded breakdown rates.
- Determine the overlap in at the population (herd-to-herd) level between core regions for *M. bovis* genotypes.
- Develop simple cellular automata models of genotype mixing at the herd level.
- Determine whether inclusion of badger density and genotype distribution data in GB result in a statistically significant improvements in fit for models of BTB spread due to cattle movements.
- Identify the extent to which breakdowns in the RBCT may be influenced by events at the national geographical scale.
- Identify better ways of predicting rate of High Risk Area (HRA) spread.
- Identify appropriate control strategies for new HRA's, including new boundaries to established regions and isolated HRA's.

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Description

The epidemic of bovine tuberculosis (bTB) in British cattle is a growing problem with substantial economic costs to farmers and the government. It is both a problem of animal health and a zoonosis with occasional serious health consequences. While there has been considerable time, effort and expense devoted to understanding the causes of its spread and its control, thus far a coherent, integrative study that uses the considerable datasets characterising the genetic population structure of *Mycobacterium bovis* (the aetiological agent of bTB) and the demographics of British cattle to describe the epidemic on a national scale and evaluate control policies in this context has not yet been undertaken.

The Randomised Badger Culling Trial (RBCT) confirmed the role of badgers in the maintenance of bTB in GB, and provided evidence that cattle-to-badger transmission is potentially an important part of the epidemiological picture. Further, it was recommended that the benefits of badger culling were largely offset by an increase in incidence outside removal areas, unless those removal areas were impracticably large. However, the Chief Scientist's report on the RBCT re-opened the case for badger culling, making the assessment of alternative control strategies of vital importance. Interpretation of the RBCT on a national scale will require more inference about how bTB transmission might vary with badger densities and cattle demographics across GB, a problem exacerbated by the substantial increase in the last decade of the geographical areas where cattle herds are tested annually for bTB, and therefore deemed to be at high risk (HRAs). In contrast to the RBCT, the Offaly study in the Republic of Ireland has shown that under the conditions in Ireland, widespread culling of badgers was an effective strategy. While interpretation of these results in the GB epidemiological, social and legal context should be undertaken with caution, they emphasise that identifying the most viable British control strategy requires a more precise understanding of whether or not currently defined HRAs are likely to become more widespread, where these areas are likely to be, and whether a single approach to control is appropriate across all GB.

This project will use RBCT data on the relationship between badger and cattle bTB both in the presence and absence of culling in combination with the populations genetics data derived from all bTB breakdowns throughout GB, and the detailed recording of individual cattle movements in the cattle tracing system. *M. bovis* genotypes derived from cattle show a remarkable level of spatial clustering; with patterns that appears to have been stable for at least the past decade. Using a combination of simple mathematical models of within-herd and spatial-spreading epidemics and tools from social network analysis, how these patterns are maintained will be analysed. This project will therefore provide insights into how HRAs themselves spread, thereby better informing control of bTB with the aim of preventing this spread, and providing additional insight into the extent to which the recommendations from the RBCT are dependent on the locations chosen for the RBCT triplets.

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