Independent Scientific Review of the Randomised Badger Culling Trial and Associated Epidemiological Research

Report to Mr Ben Bradshaw MP

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Executive summary

Bovine tuberculosis (TB) is currently a major problem affecting cattle in large parts of the United Kingdom, and there is evidence that the number of herds infected and their geographical spread are increasing with time. In the financial year 2002/3, the British Government spent £73M on this problem which included £31M in farmer compensation, £29M on TB testing and veterinary service costs, and £13M for research into the disease. Bovine TB is a potential human health risk, though at present the dangers are considered to be small.

Control of bovine TB has proved difficult in countries where there is a wildlife reservoir for the disease. In the British Isles badgers are often infected by bovine TB and there is substantial evidence that they may be a cause of infection in cattle. Professor John Krebs chaired the last major review of bovine TB in cattle and badgers (Krebs *et al.*1997), which concluded that the total available evidence for a badger reservoir was "compelling" though stressed the lack of a formal experimental demonstration.

The Krebs Report recommended setting up a large controlled experiment to compare incidents of herd infection in areas where badgers had been proactively culled, reactively culled around infected farms, or left untouched as a control. The aims, as stated by the Krebs Report, were: "First, it would provide unambiguous evidence on the role of the badger in cattle TB. Secondly, it would provide quantitative data for a cost-benefit analysis of the different strategies, including 'no culling'". This project, the Randomised Badger Culling Trial (RBCT), was initiated in 1998 under the guidance of an Independent Scientific Group (ISG) chaired by Professor John Bourne. Defra also set up two further major projects recommended by the Krebs Report under the ISG's guidance, an epidemiological case-control study to determine factors affecting the risk of herd infection (the TB99 study), and a survey of the infection status of badgers killed by road traffic accidents (RTA) in the RBCT and surrounding areas.

A number of factors, including delays in training skilled staff and the foot and mouth epidemic of 2001 have delayed the RBCT, which is currently about two years behind schedule. In November 2003, the reactive treatment was suspended after it appeared to be leading to an increased risk of TB in cattle. There have also been substantial delays in the TB99 and RTA projects. The RBCT currently costs about £7M per year to operate and TB99, RTA and other associated research together about a further £1M. The present Panel was asked to review the progress of this research, to advise on the prospects for the projects achieving their objectives and the time scales involved, and to comment on how the results inform Defra policy-making.

There has been a lack of clarity and agreement over the key information that the proactive treatment of the badger culling trial can furnish. As originally envisioned, badger densities would have been reduced to near zero in proactive sites. A variety of factors have made this impossible. As implemented, the RBCT cannot prove that badgers are <u>not</u> involved in bovine TB transmission to cattle. It can, however, put a lower bound on the importance of badgers as reservoirs of infection. It can also supply potentially valuable epidemiological information such as the detailed spatio-temporal pattern of herd breakdowns, and its relationship with local TB prevalence in badgers. It will also provide information about the efficacy of a particular type of culling. It is important to realise, though, that an inconclusive result does not of itself mean that badgers are not a significant wildlife reservoir, nor that other types of culling will not work.

The reactive treatment was suspended because it was estimated to lead to a 27% increase in herd infections. The statistical confidence limits range from a 2% decrease to a 65% increase and it should be stressed that the estimated increase might just have arisen by chance. We advise that mention of estimates such as this should always be accompanied by measures of uncertainty. One suggestion to account for these results is that culling perturbs badger social structure in a way that leads to increased risk of transmission, perhaps by increasing local movements. We agree with the critics of this explanation who argue that at most sites there was insufficient time between the implementation of reactive culling and the increase in cattle disease to make this a likely explanation for the observed effect. This does not exclude the possibility of culling causing increased herd breakdowns through a perturbation effect in other circumstances.

It is not straightforward to predict the length of time needed for the proactive treatment part of the experiment to achieve its aims. One approach is to take the original accuracy goal (that if culling caused a 20% decrease in herd breakdowns it should be detected with 90% certainty) and ask when we can expect it to be achieved. The answer depends on assumptions about the expected variability in the data, and ranges from late 2004 to early 2008. Our opinion, supported by the data obtained so far, is that later dates are much more likely. Factors such as possible time lags between the initiation of culling and its effects on herd breakdowns, and past inefficiencies in culling, will tend to increase the time it will take for the experiment to meet its precision goals. However, if the reduction in the rate of herd breakdown exceeds 20%, either now or in the future, this will act to hasten the achievement of this target. In an Appendix, at present confidential because it involves explicit mention of unpublished interim results, we discuss further these calculations in the light of the data collected so far.

Continuation of the RBCT is likely to provide further important information about bovine TB epidemiology, in particular the detailed spatio-temporal pattern of herd breakdowns, and may indicate that the level of badger removal achieved in the trial results in fewer herd breakdowns. Against these benefits are the costs of the trial (both monetary and those related to animal welfare), its inability to prove a negative (that badgers are not significantly involved in transmitting the disease to cattle), and the difficulty of generalising the result from one culling method to others that might be implemented as a national policy option.

The interim results of the proactive treatment have been kept confidential to protect the integrity of the experiment. We understand the logic of this argument and agree that it has been the correct policy up to now. But we believe on balance that the delays in the implementation of the RBCT, the needs for Defra to make an informed judgement about the RBCT's future, and the urgency of formulating bovine TB policy, all argue in favour of the interim results being made available now to Ministers.

Both the TB99 and RTA projects have been delayed, partly through unavoidable problems associated with the foot and mouth disease epidemic, but partly through management problems for which MAFF were responsible. Lessons need to be learned for future projects of this type; in particular, we believe, there is a need for a single person to be responsible for each programme. Recent progress in both projects has been good. We expect initial analyses to be available in the next six months and that this will help decide their future. It has not proved possible for us to assess the likelihood of these projects achieving their objectives because interim data and analyses are not yet available. Providing the interim results are promising, we encourage investment in both future case-control studies and RTA surveys. However, it is essential if these studies continue that they are carried out to high scientific standards.

We believe that the formulation of bovine TB policy by Defra should not wait until the RBCT is completed. Defra has informed us that there is a current initiative to develop a ten-year TB strategy that will include recent scientific findings from the UK and Ireland which we very much welcome. Based on the conclusions of the Krebs Report and research since then, especially in the Republic of Ireland, we recommend that policy is based on the assumption that badgers are involved in disease transmission as a wildlife reservoir. More evidence on their precise role is strongly desirable, but we believe the weight of evidence currently justifies making this assumption.

Whether to introduce badger culling is a hard and politically sensitive decision for Ministers to make. Proposals for culling badgers based on economic, health and cattle-welfare arguments have faced strong criticism from individuals and non-governmental organisations on animal-welfare and conservation grounds. This disagreement underlines the need for more information on the effectiveness of culling. Although wider issues played a major part in the decision to stop the reactive cull, from a narrow scientific perspective we advise that this part of the trial was stopped too soon to provide information either in favour or against the effectiveness of reactive culling. Results of the Republic of Ireland Four Areas Study will be published soon, which should provide some information relevant to the UK, but we caution against too simplistic an application of these findings because both badger ecology and social attitudes to badgers as potential pests differ in the two countries.

The ISG and other groups have emphasised the importance of research on bovine TB diagnostics and pathogenesis, and the importance of vaccine development, though also stressing that neither are likely to provide short-term solutions. We agree with these conclusions. We also agree with the ISG and other groups about the value of research into husbandry practices aimed at restricting badger-to-cattle and cattle-to-cattle contact, and the great importance of encouraging their uptake by the farming community. We are concerned at the recent spread of bovine TB to new geographical areas and urge research into this, and the development of policies aimed at its minimisation.

The ISG have played an invaluable role in guiding these epidemiological studies and more generally in advising Defra on bovine TB policy. We believe, however, that the ISG have borne too heavy a responsibility for the running of these projects, and that links between policy formulation by Defra and the scientific input from the ISG have not been as seamless as would be desirable. In designing future projects of this size we would recommend that the essential independent scientific group has a less direct management role. We believe it important that a single relatively senior figure within Defra takes ownership of the whole research programme. He or she should have a strong science background, and should report to the Chief Scientific Advisor who we believe should have overall responsibility for ensuring the quality and policy-relevance of the science produced. We think that the independent scientific group should also normally report to the Chief Scientific Advisor, though should retain the right of access to the Minister.

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1 Background

1.1 Introduction

1.1.1 The presence of bovine TB in the national cattle herd has been a long-term and increasing problem for British agriculture (Figure 1). The pathogen responsible, *Mycobacterium bovis*, is also found in wild animals, particularly the badger, which has been suggested as a reservoir from which infection spreads to domestic animals. This has been highly contentious because conservation and welfare groups have objected to measures to reduce badger numbers. A brief history of bovine TB epidemiology in the UK, and Governments' responses to the problem are given in Section 1.2.

1.1.2 The last major review that dealt in detail with the link between bovine TB in cattle and badgers was by a panel chaired by Professor John Krebs in 1997. One of the major recommendations of the Krebs Report (Krebs *et al.* 1997) was that a large scale field experiment be set up to compare the incidence of

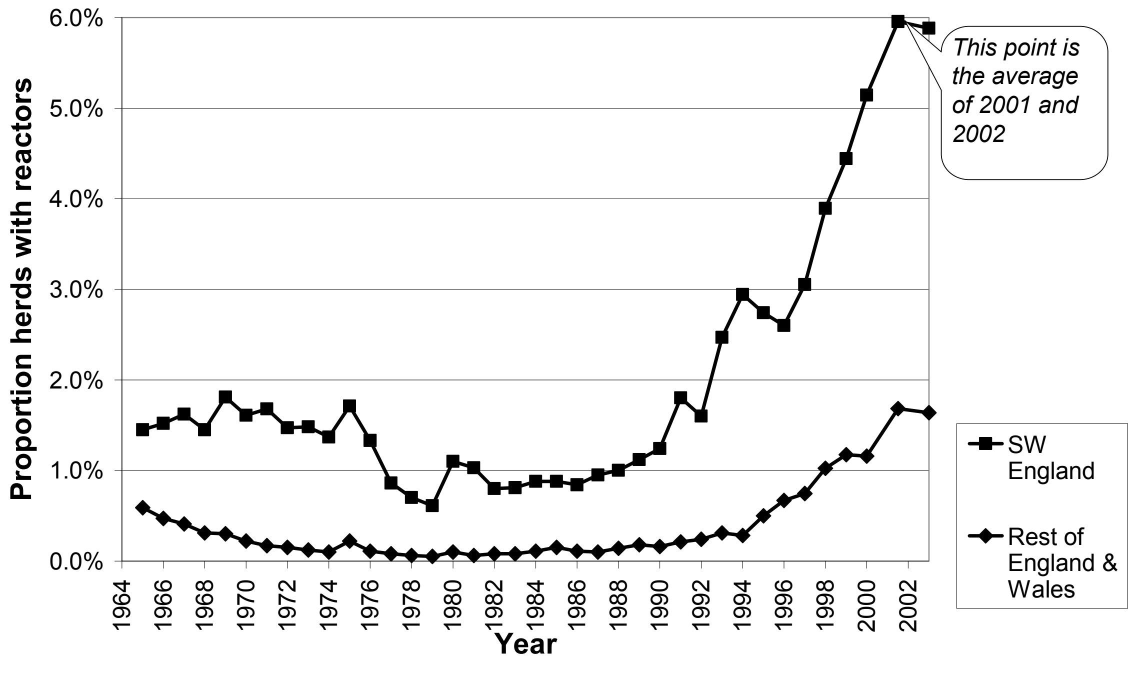

Figure 1. Changes in bovine TB incidence between 1964 & 2003. The figure shows the proportion of herds registered for testing in which reactors were found. The figures for 2001 and 2002 are potentially distorted because of the effects of the foot and mouth epidemic and are here plotted together (data from Defra).

the disease in cattle in areas in which badgers had been (i) proactively culled; (ii) reactively culled around farms where the disease was detected; and (iii) where badgers had been surveyed but otherwise not disturbed (controls). The experiment was called the Randomised Badger Culling Trial (RBCT).

1.1.3 The trial was initiated in 1998 under the guidance of an Independent Scientific Group (ISG) chaired by Professor John Bourne. In establishing the RBCT, MAFF encountered a series of problems beyond its control. These included the greater than anticipated trained manpower requirements, the polarisation of the debate between farmers and animal welfare groups and the consequent interference with the experimental treatments, and the foot and mouth disease epidemic of 2001. These problems have delayed the progress of the experiment by several years. The RBCT is currently costing about £7M per year to run and associated projects about a further £1M.

1.1.4 Defra announced the "Independent Scientific Review of the Randomised Badger Culling Trial and Associated Epidemiological Research" in April 2003. The terms of reference for the review are given in Box 1. During the course of its work, a decision was made by Defra to suspend the RBCT reactive cull treatment.

Box 1 Terms of Reference

To review the progress of the Randomised Badger Culling Trial and to advise Defra on the prospects for the experiment achieving its objectives, and the likely time scales involved. This may include:

a) To assess the degree to which foot and mouth disease and other factors that have affected the objectives, progress and running of the experiment since its inception may have reduced the likely policy-relevant scientific information the trials will generate.
b) To review progress on, and prospects for, associated field-epidemiological investigations into bovine TB such as the case-control questionnaire and badger road-traffic accident survey.
c) To assess the degree to which Defra research on the ecological epidemiology of bovine TB is and will provide the information required for science-based policy on the control of this disease

To comment on recent research that may influence the RBCT study on bovine epidemiology.

1.1.5 Our report is organised as follows. The remainder of Section 1 constitutes a brief history of bovine TB and its link with badgers. In Section 2 we discuss the RBCT, how the experiment has evolved over the years, the interpretation of the recently released results from the reactive treatment, and the future of the proactive treatment. Defra has carried out two other major observational epidemiological studies, a questionnaire-based case-control study (TB99) and a survey of the disease status of badgers killed in road traffic accidents (RTA) which are treated in Section 3. In Section 4 we attempt to place these three projects in the broader context of science input into bovine TB policy. Section 5 collects and summarises our recommendations. We have had access to confidential interim results from the RBCT proactive treatment areas that have informed our conclusions in Section 2. We explain how we have interpreted these results in an Appendix to the report which at present is to remain restricted.

1.1.6 In carrying out our remit we have had to request much information and analysis from Professor Bourne and the other members of the ISG, materially adding to their already considerable work load. We wish to record formally our thanks to Professor Bourne and the ISG for their cooperation and help. We are also very grateful to many staff from Defra for their unfailing help and assistance throughout our review.

1.2 Bovine TB and badgers

1.2.1 Bovine TB was a significant cause of human disease in the first half of the 20th century, though the human problem was largely brought under control by the introduction of milk pasteurisation. The role of badgers in the spread of bovine TB was first suggested by MAFF vets based on a study of the disease in Cornwall between 1970 and 1972. In 1971, a badger found dead on a farm in Gloucestershire, was confirmed to have died from generalised tuberculosis due to *M. bovis*; infection in the cattle on the farm had recently been confirmed. Further investigation led MAFF in 1973 to conclude that badgers posed a severe risk to cattle (MAFF 1976).

1.2.2 Initially, MAFF gave advice to landowners on killing badgers on their own land by trapping, shooting and snaring. But, largely on welfare grounds, the Ministry later concluded that gassing badgers in their setts was both more effective and more humane (MAFF 1976). Appropriate legislation was introduced and gassing operations began in August 1975, continuing until June 1982. The aim was to eliminate social groups of infected badgers from around those farms where the disease had been recorded.

1.2.3 In September 1979 Lord Zuckerman was asked to review the role of badgers in bovine TB epidemiology. He concluded (Zuckerman 1980) that badgers did form a significant wildlife reservoir for the disease and that gassing operations should be resumed (they had been suspended while he reported). He also recommended that gassing techniques be investigated, and the resulting study questioned its humaneness.

1.2.4 As a consequence, live-trapping followed by humane killing was introduced in July 1982 to replace gassing. In the same year the "clean ring" strategy was brought in. After an infection in cattle was diagnosed, sample badgers from local social groups were killed and investigated for infection. Groups containing badgers carrying TB were then completely eliminated, the process continuing until a clean ring of uninfected social groups around the infected farm had been established. Reestablishment was prevented by continuing trapping for six months (MAFF 1984).

1.2.5 Lord Zuckerman had recommended a further review after three years and this was conducted by Professor George Dunnet who reported in March 1986 (Dunnet *et al.* 1986). The report called for the development of a test that would enable the detection of infection in live badgers and thus obviate the need for widespread culling. In the meantime an "interim" control strategy was recommended in which badger culling was restricted to parts of the breakdown farm where transmission was thought to have occurred, and only if there was evidence implicating badgers.

1.2.6 Rising levels of herd breakdowns in the early 1990s led Ministers to instigate a new research plan for bovine TB epidemiology (MAFF 1994) and then in 1996 to set up the panel chaired by Professor Krebs. The main recommendations of the Krebs Report (Krebs *et al.* 1997) are summarised in Box 2 (page 13) and include the establishment of the RBCT (Box 2 Bi) and the development of a programme of statistical and epidemiological modelling and analysis which resulted in the TB99 and RTA studies (Box 2 Ai). The

Report also recommended setting up the ISG. We shall return to various aspects of the Report's recommendations in the following sections.

1.2.7 In April 1999, the House of Commons Agriculture Committee published a report entitled Badgers and Bovine Tuberculosis (House of Commons Agriculture Committee 1999). Its purpose was to examine whether the Krebs Report, as implemented by MAFF, provided a sound basis for the development of a solution to the problem of TB in cattle. The Agriculture Select Committee were "persuaded that the package drawn up by Professor Krebs and fleshed out by Professor Bourne offer the best hope of finding a scientific, effective and lasting solution." The committee also called for (i) work on other wildlife reservoirs in addition to badgers; (ii) further research on cattle to cattle transmission; (iii) more research on vaccines, especially for cattle; (iv) more funding for research on modelling spatial aspects of the epidemiology; (v) rapid implementation of the RTA survey; (vi) investigation of the role of trace elements in the incidence of TB in cattle and (vii) a fast-track review of the available scientific evidence for the most promising husbandry practices likely to assist in the control of bovine tuberculosis.

1.2.8 Dr Clive Phillips was asked to chair the fast track review of husbandry practices (point vii in last paragraph). His Panel concluded (Phillips *et al.* 2000) that "although the mechanisms of the disease are not precisely known, and should be the focus of future research, there are many precautionary husbandry measures that can be taken to limit the extent of this and other infectious diseases in cattle".

1.2.9 In April 2003, the House of Commons Environment, Food and Rural Affairs Committee (2003) published a further report on badgers and bovine TB. Their conclusions dealt with the then recently announced changes in livestock movement regulations; the dissemination of information about, and uptake of, best-practice husbandry methods to guard against TB; issues concerning the gamma interferon blood test; and the long-term prospect of vaccine development. It broadly supported the epidemiological field study programme of the ISG and noted that "the continuation of the culling trial is necessary to establish once and for all whether killing badgers has any impact on bovine tuberculosis in cattle." Amongst other recommendations it supported Defra's emphasis on clearing the post-FMD backlog of TB testing, and suggested that should the RTA provide a good indication of bovine TB levels in badgers its use should be extended beyond the present seven counties. It also called for a "Plan B" to be developed should the results of the RBCT prove inconclusive.

Box 2 Summary of recommendations of the Krebs Report (1997)

A. To understand the causes of herd breakdown, we recommend:

(i) Statistical analysis and epidemiological modelling to assess the correlates of local variation in risk, taking account of the presence of badgers, together with prevalence and severity of TB, and husbandry, climate and landscape variables. This will include:
  (a) collection of more detailed and transparent data on herd breakdowns;
  (b) a limited reintroduction of the road traffic accident survey in areas with high, low and increasing TB breakdown rates;
  (c) collection of additional data.

(ii) Application of molecular strain typing techniques in combination for longitudinal study of TB transmission between wildlife and cattle.

(iii) Development of improved tests for detection of *M. bovis* in badger carcases and in environmental samples using DNA amplification techniques.

(iv) Development of appropriate techniques for research to establish transmission routes.

(v) Analysis of the risk to cattle from other wildlife species in areas of high herd breakdown.

B. To evaluate the effectiveness of currently available strategies to reduce herd breakdowns, we recommend:

(i) A randomised experiment to be put in place immediately to determine the impact and effectiveness of 'no culling' and proactive and reactive culling policies in a minimum of 30 hot-spot areas identified including:
  (a) the formation of an independent Expert Group, including statisticians and mathematical epidemiologists, to determine the areas to be included in the experiment, to oversee the experimental design and to monitor progress and the TB situation in areas outside the experiment;
  (b) estimation of recolonisation times at sites subject to the culling strategies;
  (c) removal of lactating sows in the reactive and proactive culling treatments; and
  (d) further measures to enhance the efficiency of badger removal operations, including through increased involvement of farmers.

(ii) No culling should be undertaken outside the hot-spot areas subject to the experiment.

(iii) Husbandry may well play an important role as part of the long-term solution. MAFF should work with the farming industry to evaluate the effect of various proactive husbandry methods on the incidence of herd breakdown in areas outside the main experiment with:
    (a) the industry taking the lead and primary responsibility for implementation; and
    (b) MAFF facilitating, providing advice on the design and analysis of the experiment, and determining any incentives that might be provided.

C. To develop improved strategies to reduce herd breakdown, we recommend:

(i) Development of a vaccine to protect cattle against TB including:
    (a) better co-ordination with human TB vaccine programmes;
    (b) development of a diagnostic test to distinguish infected from vaccinated cattle;
    (c) research on the immune responses of cattle to *M. bovis* with the aim of identifying antigens which may be useful in vaccination or diagnosis;
    (d) effective liaison between those responsible for the initial laboratory phase and those responsible for the later stages to ensure the logistical requirements of implementation are fully taken into account in the early stages;
    (e) epidemiological modelling to predict the effectiveness required of a cattle vaccine; and
    (f) exploration of partnership with industry in vaccine development.

(ii) The option of a badger vaccine to protect against TB should be retained, including:
    (a) developing procedures for evaluation of vaccines in badgers;
    (b) development of a blood-based immunological test for badgers.

(iii) Further consideration should be given to the possibility of reducing TB infection in badgers through biological control, for example using bacteriophages.

D. Other recommendations are:

(i) Extending the use of integrative modelling, including:
    (a) harnessing external expertise in this area; and
    (b) better liaison between data collectors and modellers to ensure data gathered are best able to meet research needs.

(ii) A clear commitment by Government to ensuring data are made available for research at the earliest opportunity.

(iii) Research should be commissioned from those with best expertise from throughout the research community.

(iv) Development of a better co-ordinated approach to research through partnerships with industry, universities and other funding agencies.

(v) To review amount spent on research both in absolute terms and as a proportion of the total MAFF TB budget including consideration of the extent to which it would be reasonable for farmers to contribute to measures from which they benefit directly, bearing in mind the comparison with New Zealand.

(vi) The incidence of *M. bovis* TB in humans should be kept under review in the light of increasing incidence in cattle.

2 Randomised Badger Culling Trial

2.1 Design

2.1.1 The randomised badger culling trial (RBCT) was set up to provide quantitative evidence for the role of badgers in transmitting bovine TB to cattle, as well as information about the efficacy of different culling strategies. The experiment was designed to compare the number of herd breakdowns in (i) areas where badgers had been proactively culled (proactive treatment); (ii) areas in which culling took place reactively in a ring around a farm which had suffered a breakdown (reactive treatment) and (iii) in areas where no culling had taken place (control treatment). Badger populations were intensively surveyed in all areas, and control areas are also sometimes referred to as "survey only".

2.1.2 Thirty broadly circular 100km^2 'treatment areas' were grouped into ten 'triplets' (Bourne *et al.* 1998) within which the three treatments were allocated randomly. The 30 treatment areas were located in 'TB hotspot' regions where the risk of herd breakdowns is high, so that the effect of culling would be most easily detected. The Krebs Report estimated that if the true reduction in herd breakdowns in the reactive areas was 20% or more, then the experimental design should provide a 90% probability of detecting it within five years (assuming standard, 5%, statistical significance levels, and current levels of herd breakdowns). It was assumed that any reduction in the proactive areas would be detectable in a shorter time period, as the reduction would be greater. The ISG confirmed these targets, estimating that 385 breakdowns in the control areas during the trial would be required to yield this statistical power (Bourne *et al.* 1999).

2.1.3 The most critical data to be obtained from the RBCT are the number of herd breakdowns in the thirty treatment areas. Statistical analysis is required to test whether either culling regime has an effect. This needs to take into account variation in the number of herds in different treatment areas, differences in the time triplets were incorporated into the experiment and possibly other factors, such as differences in the historical incidences of bovine TB in different treatment areas, and potential time lags between the start of culling and any effect it has on the disease. The aim of the analysis is to estimate the relative effect of the culling regimes and to determine the confidence that can be placed on this estimate. In this report we follow the ISG in expressing the effect of culling as a percentage change in herd breakdowns compared with the control sites. Thus -25% implies there has been a reduction by one quarter in herd breakdowns while +25% indicates an increase by one quarter. There are various ways that statistical uncertainty in such estimates can be expressed; we again follow the ISG in using 95% confidence limits which implies that the chances that the limits do not bracket the true effect of a treatment are less than 1 in 20.

2.1.4 To give a concrete example (using the figures from the suspended reactive culling treatment and confidence limits that take account of observed variation, see Section 2.3), an estimated effect of +27% with confidence limits -2% to +65% implies that the best estimate of the consequences of culling is that it increases herd breakdowns by 27% but that with our estimated confidence limits it might lead to a worse outcome (a 65% increase) or to a very small improvement (a 2% decrease in breakdowns). Note that these confidence limits include 0%, the value at which the treatment has no effect on breakdowns. In Box 3 we discuss some further technical statistical issues.

2.1.5 In addition to the headline results of herd breakdowns in different areas, the RBCT was designed to provide important information on other aspects of bovine TB epidemiology. These include consequences of the experimental manipulation for badger social structure, TB prevalence and any knock-on ecological effects. It will also include information that can be gained from detailed spatial analysis of the pattern of herd breakdowns and its relation with badger distributions. This latter type of within-treatment-area information is observational hence difficult to interpret, but nevertheless it may make a significant contribution to understanding bovine TB epidemiology.

2.1.6 In an ideal experiment no one whose actions may influence the response other than through the manipulation is aware of which treatments are allocated to each experimental unit (the logic behind double-blind procedures for example). In the present context that would mean farmers, landowners, the veterinary service and the general public being kept in ignorance as to where culling was being carried out. This was impossible for ethical, political and

Box 3 Statistical issues

This box contains additional technical discussion of the statistical analysis of the main results to amplify our more general comments in the text.

The ISG used log-linear modelling techniques (Krzanowski 1998, McCullagh & Nelder 1989) to analyse the data. The response is treated as a count and a Poisson error variance is assumed. In addition to the treatment, the model must contain the number of herds at risk of breakdown, and a triplet factor to account for differences in the length of time each triplet has been part of the experiment (and possibly other factors common to all areas within a triplet). Other covariates can also be tested for their explanatory power: in the analysis of the results from the reactive culling treatment the rate of herd breakdowns in different areas prior to the start of the trial (estimated from data from the previous three years) was found to increase the fit of the model. A convenient way to express the magnitude of each treatment effect is as the odds ratio relative to the control group.

With these assumptions, when the model is fitted the residual deviance, which measures the remaining random component of the model, should be close to the residual degrees of freedom. Failure in this indicates either that unknown covariates are missing, or that the random component of the model has greater than Poisson variance. If the latter is true, the width of the confidence intervals placed around the estimates will be too narrow. An informal and conservative way of correcting this is to use an inflation factor (calculated as the square root of the residual deviance divided by the residual degrees of freedom) to increase the breadth of the confidence intervals (McCullagh & Nelder 1989). In the interim analysis of the results collected up to the end of August 2003 the inflation factor was 1.37 which leads to the confidence limits on the log odds scale being widened by 1.37.

The Poisson model assumes that individual herd breakdowns are statistically independent events. This assumption is incorrect if, for example, herd breakdowns are spatially correlated due to transmission of infection between neighbouring cattle herds. Multiple breakdowns in the same herd may also indicate non-independence of breakdowns. (Potential problems of non-independence have been discussed extensively by Dr Fiona Mathews of Oxford University in memoranda to the ISG and parliamentary select committees). The inflation factor does take some account of these possible dependencies and we agree with the statistical auditor (Mollison 2000) on the appropriateness of the ISG analyses. To us, all these factors counsel the use of the inflated confidence intervals and hence a conservative approach to inference from the data and the determination of the statistical power of the experiment.

It might be possible to address some of these deviations from the assumptions of the log-linear approach by explicitly modelling the spatial and temporal autocorrelation in the error distribution once the full data have been collected, though such analyses are notoriously demanding of data.

practical reasons. It is thus very important to try to establish whether any unintended effects of the treatments via people's behaviour may have influenced the results, and therefore have resulted in bias. We return to the issue of possible confounding effects in paragraphs 2.3.18 and 2.4.11.

2.1.7 A further type of bias may arise when the people responsible for an experiment become aware of its interim results before its completion. One straightforward way that this may affect the results is if it changes the amount of effort put into implementing a treatment. A more subtle issue is the consequences of testing the same statistical hypothesis on successive occasions as data accumulates (Armitage *et al.* 1969, Ellenberg *et al.* 2002). If a possible consequence of finding a strong result is the cessation of the trial then multiple testing may be misleading as one aberrant run of data may be unduly influential. The strategy adopted by the ISG in the light of these issues was that the first interim analysis should take place after a total of 100 herd breakdowns had been confirmed within the trial, or after 12 months from the completion of culling in the proactive areas of the first two triplets, whichever was the sooner. Further interim analyses would then be undertaken about every six months. Two such analyses took place prior to FMD; there was then a break since TB testing was largely suspended during the FMD epidemic, and two analyses in 2003. The results of the interim analysis were restricted to the two statisticians on the ISG. They would be seen neither by the full ISG nor by MAFF/Defra.

2.1.8 Similar problems with disclosure of interim results occur in many other experimental situations. In some, for example experiments with human drugs, the consequences of "not looking" at the data are so severe—possible human deaths—that statistically-designed "stopping rules" are put in place. However, these have a cost, typically the requirement of extra replication or a longer experiment to achieve the same statistical power. The ISG did not include a stopping rule in their experimental design, reasoning we suspect that it would be unnecessary in a fixed term study where the goal is to estimate treatment effects. We think this was a defensible position at the time, though because of the problems with the implementation of the experiment (Section 2.2), which could not reasonably have been anticipated, and the unexpected results from one of the culling treatments, the absence of a predetermined trigger for revealing data and potentially stopping one or both treatments has become a serious issue (see paragraph 2.3.24).

2.1.9 An important part of any large field experiment is to check that the manipulations are having the desired effect. Here, that means ascertaining that badger densities are very significantly reduced in proactive areas, and similarly but more locally reduced in reactive areas. Estimating badger densities is very difficult and requires detailed understanding of badger ecology. Some of the issues involved are described in Box 4. *We consider that understanding how the treatments implemented in the RBCT (and possibly other experiments) affect badger densities is very important both for interpreting and generalising the results of the trial. We recommend that Defra support further research into obtaining more detailed data on badger densities in the RBCT areas.*

Box 4 Estimating badger densities in trial areas

A critical part of any field experiment that aims to manipulate population densities is to estimate the success of the experimental intervention. This is particularly difficult here as badgers are nocturnal and fossorial with dynamic and flexible social organisation. The ISG has paid considerable attention to identifying efficient ways of estimating badger abundance.

A) Method based on social groups. Before a triplet is incorporated into the experiment all badger setts are surveyed and classified as "main" or "other". The territory of a social group is first assumed to contain a main sett and the other setts that occur within a Dirichlet tessellation based on adjacent main setts (Doncaster & Woodroffe 1993). The tessellation is refined by a range of survey and capture data, to give the best available picture of badger spatial organisation (ISG pers. comm.). Culling is then carried out and the locations of badgers recorded in relation to the predicted group territories. The percentage of territories from which any badgers are taken is used to estimate culling efficiency, and has tended to give figures of not more than 80% (data from six triplets, ISG pers. comm.). Social groups not culled tend to be on land where the landowner does not allow culling. There are several sources of potential error in this approach. First, there is evidence that not all main setts are correctly identified at initial survey, and any missed main setts lead to an overestimation of culling efficiency (an audit found 7.5% of main setts were not recorded, Cresswell Associates 2001). Second, it is likely that the percentage badger individuals removed is lower than the percentage social groups where successful trapping takes place, because not every member of the group will be trapped and culled (ISG pers. comm.). Assessing the size of this error is particularly difficult. Estimates of trapping efficiency can be compared with the numbers of badgers caught during follow-up culls. Where such data are available the number of badgers culled at follow-up has exceeded the number initially left behind based on estimated trapping efficiency. The extent to which this reflects overestimation of trapping efficiency or post-cull recruitment to the badger populations is unknown.

B) Method based on trapping rates. A second approach uses the reduction in the number of badgers trapped over time as a linear estimate of efficiency. This also gives figures of not more than 80% (ISG pers. comm.). However, this estimate takes no account of badgers inhabiting land where trapping is forbidden, though the WLU does undertake specific "remote trapping" along the boundaries of non-compliant land. A further problem is that it is known that badgers differ in their readiness to enter traps (e.g. Tuyttens *et al.* 1999a) and so capture rates may be initially high as relatively trap-prone individuals are caught, and low subsequently when the population consists of trap-shy badgers. This will tend to overestimate culling efficiency.

There are other possible ways in which badger densities might be measured:

C) Capture-mark-recapture (CMR) analysis is the classic technique for estimating animal abundance and has been used successfully on badgers (e.g. Rogers *et al.* 1997). The related capture-mark-resight approach where the mark can be detected without recapture is more cost-effective (Tuyttens *et al.* 1999b). However, both techniques are labour intensive and have not so far been applied in the RBCT. All CMR techniques suffer potential problems through violation of the assumption that all individuals are equally likely to be trapped, and in the way changes in population size due to births, deaths and migration are handled. Sophisticated statistical tools are available to deal with these issues, but they require extensive data to derive robust population estimates.

D) Wilson *et al.* (2003b) have recently demonstrated that individual badgers can be identified from microsatellite profiles constructed from DNA isolated from faeces. This is an important proof-of-principle study, though calibration of the technique through estimation of a badger population of known size suggests that at present prohibitively large sample sizes would be required to apply it to the RBCT.

E) Another possibility is the use of automated movement sensors, cameras and related techniques to record badger activities and numbers at setts. To date no such methods have been used in the field, and, at least for the moment, costs would probably preclude use in an experiment as large as the RBCT.

F) In the absence of practical direct means of accurately estimating badger densities, indices of abundance can be obtained by quantifying signs of badger activity, such as latrine use, number and usage of badger runs and activity around setts (e.g. Tuyttens *et al.* 2001). Le Fevre *et al.* (2003) reported on follow-up surveys of setts in 20% of the area of three triplets which showed trends across the proactive, reactive and survey only treatments in line with expectation. However, Wilson *et al.* (2003a) found that recording activity during a single visit to a sett offers a poor prediction of the number of resident badgers because of confounding environmental and behavioural variables. Longer term monitoring of sett activity may yield better indices of badger abundance, but this remains to be evaluated.

2.2 Implementation

2.2.1 It quickly became apparent that it was not going to be possible to set up all ten triplets simultaneously, largely because of the difficulty in obtaining sufficient trained manpower to define and survey all experimental and control areas.

2.2.2 The Krebs Report had envisaged that the densities of badgers in proactive culling areas would be reduced to near zero by the "total removal of badger social groups" which would allow a quantitative estimation of the effect of badgers on transmission of bovine TB to cattle, at least the short- to medium-term effects that might be revealed over the trial's time course. A series of factors have prevented this from being achieved and also influenced the effectiveness of the reactive cull. First, the culling of badgers in proactive areas can only be done with the landowners' permission and so a variable fraction of the total area of individual proactive sites have not been culled. Second, on animal welfare grounds a decision was made not to use snares, as assumed by Krebs, but to use cage trapping and shooting. Cage-traps are very much bulkier than snares, which reduces the efficiency of the trapping operation, and they are also more obvious and easier to tamper with. There is also evidence that a fraction of the badger population will not enter traps and so is unlikely to be caught by this method (Tuyttens *et al.* 1999a). Third, again on animal welfare grounds, no culling occurs from February to April inclusive when pre-weaning young cubs are in the sett. The ISG considered the effect of these factors (Bourne *et al.* 1998) and concluded that the treatment effects on badger densities would still be strong enough to meet the substantial aims of the RBCT. We return to the policy implications of these factors in Sections 4.2 and 4.3.

2.2.3 By the beginning of 2001 seven triplets had been included in the experiment. The experiment was then suspended from March until December because of restrictions on access to farmland due to the foot and mouth disease epidemic. This meant that for a period of nearly a year no new triplets were added to the experiment, no follow-up culling took place in treatment areas that had been subject to earlier proactive culling, and no reactive culling was implemented.

2.2.4 The second major consequence of the foot and mouth disease epidemic was the extra strain that it put on the State Veterinary Service (SVS), part of Defra, who were already over-stretched because of an outbreak of Classical Swine Fever (CSF). It is the SVS who are responsible for testing cattle for TB, which in the reactive areas triggers subsequent culling. The RBCT Standard Operating Procedures (SOP) state that reactive culls should take place as soon as possible after the provision of a "mapped notification" to the Defra Wildlife Unit (WLU) by the SVS (RBCT SOP 20. Reactive Strategy). However, in 2000 and 2001 the median time between breakdown and cull was 662 and 434 days (information from ISG & Defra). Thus at least during its early stages, the RBCT was severely compromised.

2.2.5 By the end of August 2003 a total of 26.5 triplet years had accumulated and analysis revealed the apparent increase in herd breakdowns in reactive areas that led to the suspension of this treatment. In Section 2.3 we discuss the interpretation of the reactive treatment results and then in Section 2.4 the future of the proactive treatment.

2.3 Interpretation of the reactive treatment

2.3.1 We present first a brief narrative of the events surrounding the ending of the reactive treatment. When the ISG's statisticians saw the interim results of the comparison of the reactive and control sites in October 2003 (which included data collected up to the end of August) they considered that the results needed to be shown to the rest of the ISG. Instead of the expected reduction in the number of herd breakdown in reactive areas, there had been a 27% increase, though the confidence limits were wide and on the margins of statistical significance (see paragraph 2.3.3). The ISG discussed the results and decided to inform the Minister (Ben Bradshaw) which was done on October 29th. They recommended that the reactive treatment be continued until the normal cessation of culling before the badger breeding season at the end of January, and that until then the interim results should not be published so that the experiment was not compromised. The Minister and the Secretary of State (Margaret Beckett) considered this recommendation but decided that the results should be made public as soon as possible and that the reactive treatment be suspended. The Chairman and statistician (Robert Curnow) on this Panel were asked by Defra's Chief Scientific Advisor (Howard Dalton) to review informally the statistics underlying the increased frequency of herd breakdowns in reactive sites and they reported their agreement that the analysis was appropriate but advocated using the wider type of confidence limit adjusted by an inflation factor (see Box 3). A press release announcing the results and the suspension of the reactive treatment was issued on November 4th. A scientific paper (Donnelly *et al*. 2003) formally describing the results and analyses was quickly submitted to the journal *Nature*, published online on November 23rd, and in print on December 18th.

2.3.2 There are three issues concerning the reactive treatment that we would like to comment on: (i) the statistical interpretation of the results, (ii) the biological interpretation of the results and (iii) the decision to suspend this part of the RBCT.

Statistical interpretation.

2.3.3 The ISG informed the Minister on October 29th that the number of herd breakdowns in reactive areas had increased by "27%, though it could be as small as 4.3% or as large as 53%". The confidence limits around the estimate of 27% are the standard "95% confidence limits" (based on the assumption of Poisson error variances, see Box 3) and imply that there is only a 1 in 20 chance that the true effect of culling is not included in this interval. Assigning confidence limits to estimates of this type is not straightforward and an argument can be made (Box 3) that they are wider, from -2% and 65%. This was the more conservative figure that HCJG & RNC recommended to be used when they were asked to review informally the ISG statistical analysis.

2.3.4 The statistical modelling approach adopted allows one to predict the number of herd breakdowns that would have occurred in the reactive areas if they had been treated in the same way as the controls (with badger surveying only). Donnelly *et al.* (2003) point out that in all triplets except one the observed number of breakdowns was greater than predicted. The exception was "triplet J" where, alone, no reactive culling had taken place by the cut-off date for data to be included in this analysis; it is thus not expected to show the same effect as the others. The probability of all nine areas showing the same response by chance is low, which is why Donnelly *et al.* (2003) described the results as "highly consistent".

2.3.5 We conclude from the statistical analysis of the data that there is strong evidence that the number of herd breakdowns in reactive areas is greater than in control areas. However, given that the confidence limits may encompass 0% and that there are other factors such as statistical non-independence that may influence the analysis (Box 3) we do not think it wise to exclude the possibility, at the customary statistical level of 1 chance in 20, that there is no real difference between reactive and control sites. In other words, the possibility that the 27% increase is a chance effect should be born in mind when considering these data.

2.3.6 *We recommend that in describing these results terms such as "nearly significant" or "strong trend" are used to describe the increase in breakdowns in reactive areas. We believe these are preferable to expressions that imply that the results are clearly significant at the customary 95% level.*

2.3.7 More positively, we can state that at the time the reactive treatment was abandoned the chance that herd breakdowns were substantially lower in reactive areas is vanishingly small. By substantially lower we imply here a reduction of 20% or more. We return below (paragraph 2.3.22) to the issue of whether the experiment was stopped too early for any beneficial effects of the reactive cull to be apparent.

2.3.8 One of the problems about communicating the results of experiments such as these is that the media and public, for understandable reasons, focus on the estimated effect and pay much less attention to the measure of uncertainty. *To try to counter this we believe it very important that all Defra press releases that present quantitative estimates such as these also include some generally understood statement about uncertainty, preferably statistically based confidence intervals.* The Defra press release of November 4th did not contain confidence limits. A Q & A brief on the press release published on the Defra website has in parentheses "[Detail: The increase is estimated to be 27%. The statistical approach used by the ISG gives 95% certainty to the finding that the increase lies between 4% and 53%.]" We would have preferred the uncertainty of the estimate to have been given greater prominence and for the more conservative confidence limits to have been adopted.

Biological interpretation

2.3.9 What is the cause of the near or just significant increase in herd breakdowns in reactive areas? Logically, there are three possibilities: (i) reactive culling increases the number of herd breakdowns, (ii) the increase is caused by some other accidental consequence of the treatment and (iii) the differences occurred by chance. The possibility of (iii) was discussed above and here we consider (i) and (ii).

2.3.10 How could reactive culling exacerbate transmission? Several studies had shown previously that badger culling could lead to disruption of badger social organisation and cause individuals to disperse and move outside their normal home range (Cheeseman *et al.* 1988, Roper & Lüps 1993, Rogers *et al.* 1998, Tuyttens *et al.* 2000a, 2000b), and the possibility that this may increase transmission – the perturbation effect – was appreciated. Donnelly *et al.* (2003) suggested such disruption might explain their data and that "studies are underway to investigate this issue". Note that a proven perturbation effect implicates the badger in TB transmission, though in a more complicated way than hitherto imagined.

2.3.11 Immediately after the cessation of the reactive trial Richard Clifton-Hadley (Statutory & Exotic Bacterial Disease Department, VLA), John Montague and Alick Simmons (both Veterinary Endemic Diseases and Zoonoses Division, Defra) expressed doubts about whether reactive culling could be responsible for the observed results. We have had the opportunity to discuss the issue directly with them, and also with Dr Chris Cheeseman (Central Science Laboratory, Defra) who made similar points at the same time.

2.3.12 The nub of their reservations is that insufficient time had elapsed since the initiation of the reactive culling for any effect it might have on herd breakdowns via badgers to be observed. Specifically, was there enough time (i) for the cumulative effect of reactive culling to have changed badger density or behaviour sufficiently to influence transmission; (ii) for transmission to have occurred; (iii) for the disease in these infected cattle to have progressed to a point at which it is detectable; (iv) for sufficient tests to have taken place to detect these extra cases as part of the annual round of TB monitoring implemented in these areas? Of the 1560 badgers slaughtered in the reactive

Box 5 The status of the reactive culling areas at the time of the analysis

The analysis of the reactive culling treatment took place using data collected up to the end of August 2003. The table shows when reactive culling started in each triplet (with the number of months the triplet had been active prior to sampling) and the number of badgers killed before the end of August. Information provided by Defra.

Triplet	Start of reactive culling (and months in operation)	Number of badgers culled before the end of August 2003
A	Jul. 2000 (38)	117
B	May 1999 (52)	301
C	May 2000 (40)	394
D	Aug 2003 (<1)	59
E	Jun 2002 (15)	169
F	Jul 2002 (14)	320
G	Aug 2002 (13)	172
H	Jan 2003 (8)	16
I	May 2003 (4)	12
J	-	0

Reactive culling in triplets A-C was severely affected by FMD; there were no badgers culled in triplet A in 2001 and 2002 while over this period 58 were culled in triplet B and 28 in triplet C. The figures for badgers culled in Table 1 of Donnelly *et al.* 2003 refer to a slightly later cut-off date.

areas, over 50% had been killed in the first eight months of 2003 (prior to the data cut-off date at the end of August), and no reactive culling had taken place in three of the nine triplets in the analysis before the start of 2003 (and in triplet D the first badgers were culled only six days before the end of the August 2003). Some more quantitative information on the extent and timing of the reactive culls is given in Box 5.

2.3.13 We discussed in detail these points with the scientists mentioned in 2.3.11. Our interpretation of their responses is that while they admit it is just conceivable that the effects of reactive culling might have had time to work their way through to herd breakdowns in some of the triplets (but obviously not in triplet D), their understanding of bovine TB epidemiology and the way the RBCT is conducted leads them to think it is highly unlikely.

2.3.14 *We find these arguments persuasive and pending more detailed analysis of the data recommend that the results from the reactive trials should neither be viewed as evidence for the perturbation hypothesis nor as evidence for or against the role of badgers in bovine TB transmission.* In planning the analysis of the reactive treatment results, it would have been better, on epidemiological grounds, to have included a pre-determined lag between the initiation of reactive culling and the inclusion of herd breakdowns in the analysis.

2.3.15 The more detailed analysis of the data should be accorded high priority. In particular, evidence for or against the perturbation hypothesis may be obtained by a detailed examination of the temporal and spatial pattern of herd breakdowns. One would expect the effect to be strongest in triplets that had been longest in the experiment (though this does not seem to be the case from the data in Donnelly *et al.* 2003). One would also expect the effect to strengthen with time. We understand that herd breakdowns are counted in all sites as soon as the triplets are recruited to the experiment rather than after the first reactive cull, and clearly the rate of breakdowns that occur in reactive areas before culling commences should be about the same as in controls. If reactive culling does increase transmission by a perturbation effect then one would expect an increased probability of herd breakdowns in the vicinity of the reactive cull, at least initially. Although we believe it important that these analyses are performed as soon as possible, it must be remembered that the number of herd breakdowns involved is relatively small, about 10 per site-year in the control areas, and that especially because of the FMD epidemic the experiment has been running for a relatively short period of time. Hence the power of the statistical analysis to distinguish amongst alternative hypotheses will not be high. Finally, we note the Defra-funded work led by Professor David Macdonald and Dr Chris Cheeseman that may help understand the importance or otherwise of the perturbation effect.

2.3.16 Are there alternative explanations, not involving badgers, that might account for the increased number of herd breakdowns in reactive areas? As mentioned in 2.1.6, for practical, ethical and political reasons, farmers, veterinarians and members of the public knew which treatments had been allocated to different areas. Could this knowledge have influenced the relative number of breakdowns recorded in different sites? Two possible mechanisms were suggested to us.

2.3.17 First, the frequency of TB checks in different areas might be influenced in some way by knowledge of the treatment being applied. More TB checks might reveal a greater number of herd breakdowns. Such a bias is relatively easy to check as records are kept of all herd surveys for TB. We have not seen the analysis but we understand from the ISG that there are no differences in test frequencies across treatments.

2.3.18 Second, farmers in control (survey-only) areas may be more motivated to pursue illegal means of badger control. It is known that some illegal badger killing is carried out, but assessing its extent is extraordinarily difficult, especially if badgers are killed by shooting rather than by snaring or other means that can be detected on the ground. If badger control by farmers was more prevalent in control areas then the observed results might not be due to increased transmission in reactive areas but decreased transmission in survey-only areas. This might occur if, in the absence of culling, farmers felt the need to kill badgers themselves, or because the perceived risks of detection are lower in control areas which are visited less often by RBCT personnel. Of course, such an explanation would require badger densities to be lower in control compared with reactive areas.

2.3.19 The limited amount of data currently available do not support this explanation. A preliminary analysis of the number of active setts across 20% of the area covered by three triplets (A, B and C) in 2002 suggested that, in line with the expectation of the experimental manipulation, the persistence of setts was lowest for the proactive areas, highest in the survey only areas and intermediate in the reactive areas (Le Fevre *et al.* 2003). Unpublished analyses of badger activity during 2000 and 2002 in three other triplets (E, G and H) suggest no strong differences between control and reactive treatments (Dr C. Cheeseman, pers. comm.). There are, however, potential difficulties with the use of activity indices as measures of badger densities (Box 4). In view of the debate over the interpretation of the reactive trial, more accurate information on at least the relative density in each treatment is critically important. Estimating the densities in reactive cull areas compared to control areas obviously has to be done very soon, ideally in the summer of 2004.

2.3.20 It is not a criticism of the design of the RBCT that there are potential confounding factors, such as those discussed here. These are inevitable given the size and circumstances of the experiment. Nevertheless, it is critical to try to assess the possible extent of these factors, both by monitoring variables such as the TB test frequency, and possibly also by using specialised survey and questionnaire techniques that have been developed to obtain quantitative estimates of sensitive information (Lohr 1999).

Cessation of the reactive trial

2.3.21 Ministers decided to halt the reactive treatment on November 4th 2003. Apart from the possibility that the treatment was actually increasing herd breakdowns, Defra (pers. comm.) believed that continuation of the reactive treatment might bring the whole RBCT into disrepute and imperil the proactive treatment through increased non-compliance. The ISG had recommended that culling be continued until the end of January, but it seems unlikely to us that ending the treatment in November rather than January would have had a major influence on the estimated effect of reactive culling, and we appreciate the political difficulty of Ministers continuing a treatment which appeared to be exacerbating the disease. Similarly, in the absence of pre-determined stopping rules, we believe the ISG statisticians had little option but to show the results to the full group, and for the ISG to inform Ministers.

2.3.22 Nevertheless, a strong argument can be made that the reactive treatment had not run long enough to test whether reactive culling might ever work as a policy option. Because reactive culling only results in the deaths of badgers around a farm where TB has been detected it is reasonable to suppose that the benefits of this policy will build up slowly over a number of years. At the time of cessation, only three triplets had been reactively culled for more than 15 months (Box 5), and here the implementation of the experiment had been severely affected by the foot and mouth disease epidemic and the subsequent delays in TB testing. Even if the perturbation hypothesis does explain the results so far, this does not exclude the possibility that culling might eventually reduce herd breakdowns: conceivably, transmission increases initially as badger social structure is disrupted, and then subsequently declines as the number of infected badgers is reduced.

2.3.23 Our purpose here is not to argue in favour of reactive culling, but *we advise that the results of the reactive culling treatment at the time it was halted should not be interpreted as evidence against (or of course for) a reactive culling policy*. And the experiment only provides evidence about one particular type of reactive culling and the manner in which it was implemented during the RBCT. It is possible that a more efficient reactive culling policy could be designed.

2.3.24 From a narrow scientific point of view that ignores the political and possibly legal implications of the experiment appearing to cause increased herd breakdowns, the reactive treatment was abandoned too soon, before the policy option of reactive culling could be properly evaluated. With the benefit of hindsight it would have been desirable in designing the RBCT to have anticipated the possibility of the reactive treatment initially appearing to increase herd breakdowns, for there to have been a pre-determined time lag before herd breakdowns were included in the analysis, and for an explicit stopping rule to have been agreed at the start amongst the experiment's stakeholders.

2.3.25 Is there a more general lesson to be learned about how scientific results such as this are communicated to Government? Ministers, once made aware of facts, are under enormous pressures to publish results and act quickly, not least because there is a risk that any delay is interpreted as politically motivated. Because the ISG reported directly to the Minister there was no time for Defra to obtain comments on the reactive culling results from its own expert staff, nor for the results to be more than informally reviewed externally. Were this to have happened, we believe the Minister would have been made aware of some of the issues discussed in this Section. *We recommend that in future a body such as the ISG reports initially to the Defra Chief Scientific Advisor, who should arrange for its advice to Ministers to be reviewed properly before* *its submission.* A body such as the ISG should retain the right to go directly to Ministers should it be dissatisfied with the way the Chief Scientific Advisor deals with its recommendations, but the presumption should be that their advice is normally channelled through the Chief Scientific Advisor's office.

2.4 Future of the proactive treatment

2.4.1 The continuation of the proactive culling treatment was not affected by the cessation of the reactive culling treatment. Defra's press release of November 4th 2003 stated "On the advice of the ISG, operations will continue in proactive areas because the data for these areas do not yet yield a statistically significant result".

2.4.2 We have had access to the analysis of the data collected up to the end of August 2003 from the proactive treatment. The level of analysis we have seen is equivalent to that in Donnelly *et al.* (2003) for the reactive treatment. In this section we attempt to address the points in our remit (Box 1) relating to the future of the proactive treatment, specifically "to advise Defra on the prospects for the experiment achieving its objectives, and the likely time scales involved".

2.4.3 At present the results from the proactive treatment have not been disseminated beyond this panel and the ISG, except for the statement quoted in paragraph 2.4.1 that the results are "not yet statistically significant". Confidentiality is being maintained to prevent biases entering the experiment (see paragraph 2.1.6). We are thus not in a position to explain in detail how we have arrived at our conclusions, as this would involve revealing the results. The way we have dealt with this issue is to add a confidential Appendix to this report where our more detailed reasoning is described. This Section will only be made public after the results of the proactive treatment are released. We begin by exploring how the accuracy of the estimate of the effect of proactive culling will improve as the experiment continues, and then turn to the issue of the dissemination of interim results.

The accuracy of estimation

2.4.4 We have tried to calculate roughly the length of time that the proactive treatment of the RBCT will need to run to achieve the targets first set down in the Krebs Report. To do this we have first made the assumption that the rates of herd breakdowns in control and treatment areas remain constant over time. We discuss the possible significance of violations of this assumption in paragraphs 2.4.7 to 2.4.12 below. In carrying out this calculation we have had to make a number of further assumptions and simplifications which to a certain extent are matters of judgement rather than clear scientific fact. So as to make the basis of our recommendations completely transparent, at least as far as we can without revealing data that are at present confidential, we describe these in some detail in the technical Box 6.

Box 6 Note on calculation of power and precision

This technical note explains the philosophy and calculations behind our attempts to suggest how long the RBCT will take to achieve a certain level of precision. We repeat some of the power calculations and estimates of precision that were made at the start of the trial, updating them with information that is now available from interim analyses. We stress, as have the ISG, that (i) power calculations, though generating precise figures, depend on assuming certain goals that are by their nature quite arbitrary, and (ii) that the precision that will actually be achieved by the trial is totally independent of the power calculation and determined by the data themselves (Bourne *et al.* 2000).

In planning the RBCT, the Krebs Committee and ISG had to determine the optimum number of triplets to include in the experiment, balancing the validation of the results that is obtained by comparison across sites with the amount of work involved. Given the decision to use ten triplets, then to a reasonable approximation the precision can be estimated purely by considering the number of breakdowns observed in the three different treatments. We follow this course here though recommend a more detailed study of inter-triplet variation.

Precision and power

Consider one of the two culling treatments and call the total number of herd breakdowns across all ten triplets for this treatment N_1; let the equivalent figure for survey-only (control) sites be N_2. The most straightforward assumption is that N_1, and N_2, have Poisson distributions with means μ_1 and μ_2 respectively. To analyse the data a log-linear model is fitted so that $\ln(\mu_1)$ and $\ln(\mu_2)$ are assumed to be linear in the effects of the two treatments and any relevant covariates. A useful way to express the results are as log odd ratios $\ln(N_1/N_2)$ (which can be anti-logged to give the more familiar odds ratio). Ignoring the effects of errors in adjusting for covariates, the variance of $\ln(N_1/N_2)$, is approximately $(1/\mu_1+1/\mu_2)$, which is itself estimated by $(1/N_1+1/N_2)$ giving an approximate standard error of $\sqrt{(1/N_1+1/N_2)}$.

A major issue with this type of analysis is the possibility of greater than Poisson variance, a potential problem appreciated by all involved (Mollison 2000, Bourne *et al.* 2000) and particularly stressed by Dr Fiona Mathews (unpublished memoranda).

As described in Box 3, to make some allowance for this, the estimated standard error, is sometimes multiplied by the inflation factor, *I*, the square root of the residual deviance divided by its degrees of freedom. An estimate of the standard error of $\ln(N_1/N_2)$ is thus

$$I\sqrt{1/N_1 + 1/N_2}\,. \qquad \text{Eqn 1.}$$

We can also ask questions about the "power" of the trial. Power, here, is a statistical concept that can be used to ask what effort is required to detect a true effect with a certain probability. The power calculation first carried out by the Krebs Committee specified that a 20% reduction (that is an odds ratio of 0.8) should be detected with a 90% probability. This is a high power but for a relatively small treatment effect.

With a 5% significance level, a power of 90% requires the probability that the observed log odds ratio is less than its hypothesised value by more than 1.64 standard errors is 0.9. This in turn requires that the difference between the expected value of the log odds ratio and its hypothesised value divided by its standard error be less than –1.64-1.28=-2.92. where 1.28 is the 90% point of the standard normal distribution. The number of breakdowns needed to achieve this power is therefore given by

$$\frac{-\mathrm{Ln}(0.8)}{I\sqrt{1/N_1 + 1/N_2}} = 2.92\,. \qquad \text{Eqn. 2.}$$

If we let *n* equal the expected number of breakdowns per year in control sites, *x* be the fractional reduction in culled sites (expected to be 0.8) then the number of years, *y*, required to achieve this power is calculated from

$$\frac{-\mathrm{Ln}(0.8)}{I\sqrt{1/yn + 1/ynx}} = 2.92\,. \qquad \text{Eqn. 3.}$$

The precision of the estimate of the odds ratio, expressed as a proportional standard error, associated with this power is

$$100I\sqrt{1/yn + 1/ynx}\,. \qquad \text{Eqn. 4.}$$

Calculations assuming Poisson variance

At the interim analysis in August 2003, 261 herd breakdowns had occurred in control sites that had accumulated 26.5 "triplet years" (ISG, pers. comm.). From this we can assume that the total number of breakdowns per year across all control sites is roughly 100. If we assume Poisson variation then we can use Eqn. 3 to calculate that the RBCT would require 3.8 years to achieve this power (or equivalently need 385 breakdowns in control areas). This figure is in the Krebs Report and Bourne *et al.* (1999). The precision associated with this length of experiment is 7.6%.

As 26.5 triplet years had accumulated by the end of August 2003 only another 12 triplet years are required to reach this target. This argument suggests that it will be reached in late 2004. This calculation does not take account of the results to date.

Calculations assuming observed variance

It is now possible to assess the degree to which the trial has greater than Poisson variance. Donnelly *et al.* (2003) give a value of $I = 1.37$, a figure derived from a model that included both the published reactive culling and unpublished proactive culling data. Using equation 3 and again assuming 100 herd breakdowns a year the length of time it is predicted to take to achieve the same statistical power (and the same precision) is 7.3 years. If this argument is correct the target would not now be reached until early 2008, about 3½ years later than when Poisson variance is assumed.

A test of the assumptions

As stated above these calculations make some simplifications, but we can test these against the reactive culling data. Substituting $N_1 = 331$ (the numbers of herd breakdown in reactive areas adjusted for covariates) and $N_2 = 261$ the estimated precision is 11% while the observed precision is worse, at 13%. This might suggest that the calculations above are slightly optimistic. However, the approximation is more accurate in predicting the precision of the unpublished proactive culling data (Appendix).

2.4.5 The Krebs Report defined a goal of the trial as being able to detect a 20% reduction in herd breakdowns with 90% certainty. This goal is to an extent arbitrary, and may or may not be useful in terms of informing policy (see Section 4.3.6), but nevertheless is a useful benchmark for determining the likely benefits of running the trial for different periods of time. With certain assumptions discussed in Box 6, the time required to achieve this goal depends on the number of breakdowns that occur, and the variability of the data. The simplest assumption about the variability, and the basis of initial calculations, is that it is determined by a Poisson process. However, it has been appreciated from the start that the variance may be higher than this. We are now in a better position than at the start of the trial to estimate how long it will need to run to achieve the target because from the data collected so far we can estimate both the herd breakdown rate and the realised variance.

2.4.6 *We advise that without knowledge of the proactive treatment results available so far, and assuming that the number of herd breakdowns remain at their current levels in control sites, then the RBCT should achieve the statistical target of distinguishing a 20% reduction in herd breakdowns from zero with 90% confidence sometime between late 2004 and early 2008. Whether sooner* *or later depends on arguments about the nature of the variability in the data. In our opinion a later date is much more likely.*

2.4.7 These calculations all assume that the number of herd breakdowns in control and culling treatments remains constant with time. But there are a number of reasons why this might not be so. We discuss these in the next four paragraphs and then in paragraph 2.4.12 explore what they mean to the likely time course of the experiment.

2.4.8 (i) There has been a national trend over the last decade for the number of herd breakdowns to increase (see figure on page 8). Though a major setback for the farmers involved, this has the beneficial by-product of increasing the power of the trial and reducing the size of the confidence intervals. However, unless TB increases even more rapidly over the next few years, we suspect this effect will be relatively minor.

2.4.9 (ii) The effects of proactive culling are likely to be cumulative and hence increase as the experiment progresses. Alternatively the effect of the treatment on disease transmission may be more complex: it is possible that proactive culling initially increases or has little effect on herd breakdowns (perhaps as has occurred in the reactive culling treatment), and the benefits only become apparent later. We think that for the majority of policy applications, the most important factor to be estimated is the medium-term effect of proactive culling after the initial transient effects have disappeared. The problem is that there is little evidence or theory to help decide how long the transient period might be, though statistical evidence that the number of breakdowns is influenced by <u>the length of time the triplet has been in the trial</u> would indicate the presence of such an effect. *We think it likely that the effects of proactive culling will become more marked with time, and statistical investigation of this should be made a priority.*

2.4.10 (iii) The efficiency with which the proactive culling is executed may change with time. It was clear from our discussions with Defra's WLU that they considered the treatment was currently being implemented more effectively that at any time in the past. Moreover, the disruption caused by the suspension of culling during the foot and mouth disease epidemic is now receding. If such processes are occurring then the estimated effect of proactive culling will increase with time. If this increase is large enough, a significant decline in herd breakdowns will be detected earlier than predicted above. It is possible that the presence of such factors could be detected statistically by seeing whether the number of breakdowns changes with absolute time (as well as the time the triplet has been in the trial). From a policy point of view, if the main aim is to establish the sustainable effect of proactive culling on herd breakdowns then it becomes more important to continue the experiment for long enough with efficient culling to detect this effect. *We think it likely that culling efficiency is better now than in the past. If this reduces the herd breakdown rates by more than 20% then the time required for the RBCT to meet its objectives will be reduced.*

2.4.11 (iv) Any other change in farming, the intensity of TB control services provided by veterinarians, or public behaviour that positively or negatively influences disease transmission may change over time. We do not know whether any such factors are in operation, though the high profile of the bovine TB problem and its link with badgers makes this very possible.

2.4.12 To summarise the last five paragraphs, we argued in paragraph 2.4.6 that if the number of future herd breakdowns in control and culling treatments was constant over time then the declared goals of the trial, to be able to detect a 20% reduction in herd breakdowns with 90% certainty, is likely to be met sometime between late 2004 and early 2008, depending on the variability of the data. Whether sooner or later depends on arguments about the nature of the variability in the data and, as we argued above, in our opinion a later date is much more likely. Factors such as time lags between the initiation of culling and its effects on herd breakdowns, and past inefficiencies in culling, will tend to increase the time it will take for the experiment to meet its precision goals. However, if the reduction in the rate of herd breakdown exceeds, either now or in the future, 20%, this will act to quicken the achievement of this target. In the Appendix, at present confidential because it involves explicit mention of the interim results, we discuss further these calculations in the light of the results so far.

2.4.13 We stress, however, that the declared goal is quite stringent, and also arbitrary. If the effects are larger than 20%, then they should be identifiable earlier and, at the other extreme, if the effects are smaller they may allow the ruling out of policy significant reductions in herd breakdowns at an earlier date.

Dissemination of the interim results

2.4.14 The optimal time for the RBCT to run is determined by a trade-off between the benefits of obtaining useful information to policy-makers and the costs of running a very large field experiment. When we refer to costs in this section and elsewhere, we not only are considering the financial costs but also the wider costs such as those involving animal welfare. The usefulness of the results is partly determined by the accuracy with which the effects of culling are estimated, partly by the magnitude of the effects themselves, and partly by the interaction of the two. To be more precise: first, the more accurate the estimates the more useful the information will be to policy makers. Second, in this particular experiment a clear result that proactive culling reduces herd breakdowns is more valuable than a result that cannot be distinguished from no effect. We stress that this is not because of an *a priori* bias in favour of the badger transmission hypothesis, but because the best the experiment can achieve is to put a lower bound on the role of badgers and an inconclusive result does not mean badgers are not involved in disease transmission (see also Section 4.3). Lastly, the required accuracy of the estimate of the effect of culling on herd breakdowns may depend on how big or small the effect is (see also paragraph 4.3.6).

2.4.15 The argument for continuing the proactive part of the experiment is that it is likely to provide further important information about bovine TB epidemiology such as the detailed spatio-temporal pattern of herd breakdowns, and its relationship with local TB prevalence in badgers. It may also indicate that the level of badger removal achieved in the trial results in fewer herd breakdowns. Against these benefits are its inability to prove a negative (that badgers are not significantly involved in transmitting the disease to cattle), and the difficulty of generalising the result from one culling method to others that might be implemented as a national policy option. In Section 4, where we describe exactly how we see science contributing to policy, we discuss in more detail the type of policy-relevant information that the RBCT might provide. But we acknowledge that the future of the RBCT cannot be based purely on the scientific case that it would provide new information. A wider assessment has to be made, by Defra, as to the costs and benefits of this information when placed alongside other products of the Department's research expenditure. For this to be possible we think two things must occur. First, for reasons we shall elaborate in Section 4, we believe Defra needs to formulate much more explicitly how the results of the RBCT will input into future bovine TB policy. Second, *we believe Defra now needs to see the interim results (and our commentary on them in the Appendix).*

2.4.16 There are both costs and benefits to the ISG revealing the interim results to Defra. There are two main benefits. (i) The interim results can immediately begin to feed into Defra bovine TB policy. Some aspects of the development of policy have been delayed while the results of the RBCT are awaited. Because of the delays in establishing the RBCT and the consequences of the foot and mouth disease epidemic, the results have been slower than expected to arrive. We think that were the RBCT to be continued its full results will not be available for up to five years or longer and that this argues for revealing what has been found so far to policy makers. (ii) The RBCT is a very expensive experiment and it is important for Ministers and their advisors to be clear that public money is being used to best effect to help formulate policy. As the policy relevance of the information about culling depends on the magnitude of any effects as well as their accuracy, we find it difficult to see how an informed decision can be made if Defra is ignorant of the interim results five years after the initiation of the work.

2.4.17 There are also several costs to revealing the data. (i) It may influence the behaviour of people involved with the experiment. The argument here is that perhaps farmers or landowners may react to interim results with poor statistical support and change their behaviour, perhaps by denying access to experimenters, or engaging in illegal badger killing (see paragraph 2.1.6). Alternatively, the results might spur animal-welfare protesters to engage in more interference with the study. It is difficult to gauge the potential importance of these factors. (ii) Decisions may be made prematurely based on data that are too provisional to be of real value. It is critically important that the interim nature of the results is fully appreciated by anyone basing decisions on them (we comment on this further in the Appendix).

2.4.18 *We think policy makers should see the interim results now as we believe the benefits of disclosing the results are greater than the costs.* We acknowledge that disclosure is a difficult and irreversible decision and we recognise that the Minister will also wish to take into account the views of the ISG before a final decision is made.

2.4.19 We also point out that our advice should not be construed as criticism of the ISG's original decision to maintain secrecy; it is because the RBCT has taken much longer than initially anticipated to establish, and because the number of herd breakdowns nationally is increasing, that we believe the interim analysis should be shown to Defra now.

2.4.20 If the interim results are revealed, and the RBCT is continued, we believe that the future flow of results should again be confidential for the same reasons the ISG gave in their initial experimental design. Clear rules should be formulated beforehand about when the results of the analysis should be again revealed; obviously at the end of the experiment, but considering other eventualities such as the (hopefully unlikely) possibility of another FMD epidemic or similar disaster. A clear rule is also needed to deal with the possibility, even if considered remote, of a significant increase in herd breakdowns caused by proactive culling. These recommendations are similar to those that the RBCT statistical auditor recommended be put in place after the first interim analysis (Mollison 2000).

3 Associated epidemiological research

3.0.1 This section deals with the two main field epidemiological research programmes carried out under the ISG's guidance in addition to the RBCT project; the TB99 questionnaire and the survey of badgers killed in road traffic accidents. We were asked to assess the likelihood of these projects achieving their objectives but because no analysis of interim data is yet available this has proved very difficult to do.

3.1 TB99 Questionnaire

3.1.1 It is clearly of the utmost importance to try to understand the risk factors associated with the probability of herd breakdowns on different farms. This was recognised by the Krebs Report, which recommended statistical analysis of the correlates of local variation in risk. The technique recommended by the ISG was that of a case-control study where information is obtained from a farm where a herd breakdown occurs and then from an additional number of uninfected farms, here three, from nearby localities. The difficulty with the analysis of non-experimental data such as these is that no true controls are possible, but the case-control method goes some way to compensate for this.

3.1.2 TB99 refers to the questionnaire designed in 1998 to investigate possible correlates of herd breakdown. It replaced an earlier and less statistically rigorous questionnaire (TB49, which was primarily a disease management tool) and consists of a series of questions divided into two sections. Part 1 deals with the management of the herd breakdown, and Part 2 explores the risk factors. The latter includes issues such as (i) the history of the herd, its size and management; (ii) the structure of the farm: its different land uses and buildings, and (iii) the local environment: the presence of woodlands, known badger setts etc. The questionnaire takes 2-3 hours to complete and has to be done by a trained interviewer talking to the farmer. Of the three control farms, the aim is for one to be contiguous with the farm on which the herd breakdown occurs, and the other two to be in the same region.

3.1.3 The case-control study was restricted to the RBCT areas but the form itself was used more widely to investigate the spread and management of bovine TB, though here without the collection of control data.

Table 1. The accumulation of data from the TB99 case-control study of risk factors for herd breakdown. Data from ISG (pers. comm.) as at January 2004.

Year	1999	2000	2001	2002	2003	Total
Cases completed	43*	147	42	398	319	949
With 1 control	7	12	3	87	36	145
With 2 controls	8	16	2	75	26	127
With 3 controls	11	21	1	20	8	61

* Includes 2 from 1998

3.1.4 TB99 was first used in 1999 with the aim of obtaining 100 case-control combinations by the end of 2000. The questionnaires were to be completed by vets from Defra-SVS through local Animal Health Offices (AHO). The data are collated by the VLA and are being analysed by statistical research assistants working with the ISG statisticians.

3.1.5 The returns from 1999 to 2003 are shown in Table 1 and clearly fall considerably below target. Data collection in 2000 was severely hampered by the outbreak of CSF which stretched Defra-SVS resources, and then the FMD outbreak in 2001 effectively caused a suspension of data collection with knock-on problems through 2002. In 2002, ADAS were asked to assist Defra-SVS in the collection of TB99 data with clear positive results. At the time of writing this report, the initial analyses of the 1999 and 2000 data (pre-FMD) are about to be announced.

3.1.6 An issue with the collection of the data has been the prioritisation of information (i) from Part 1 (disease management) versus Part 2 (risk factors); (ii) from case versus control farms; and (iii) from inside versus outside the RBCT area. Prior to 2002 Defra-SVS concentrated first on Part 1 data, and then on Part 2 data from case farms both inside and outside the RBCT areas, with control farms having the lowest priority. The ISG argued successfully in 2002 for greater priority to be placed on obtaining control data.

3.1.7 The TB99 programme was audited in 2003 by Dr Martine Wahl of Clinical Research & Communication (Basel) reporting in September (Wahl 2003). Her very thorough review of the complete process of data collection and handling led to a number of recommendations. (i) The TB99 questionnaire should be simplified and made easier to complete. (ii) Data collection should involve fewer people, and they should be trained in questionnaire techniques: she identified a problem with some data collectors leading the farmer in answering certain questions. (iii) Methodologies should be introduced to ensure greater consistency across AHOs in the way the survey is compiled and in the handling of data at the VLA, and mechanisms should be put in place for data quality assurance. (iv) The project should be run by a Project Manager with a small dedicated team.

3.1.8 The situation at the moment is that the initial results of the statistical analysis are awaited. Based on these results, the value of the case-control programme will be assessed and the TB99 form redesigned, almost certainly to make it simpler. Dr Wahl's review has been adjudged valuable by the ISG and her continuing involvement in the programme is believed to be worthwhile (ISG pers. comm.).

3.1.9 We agree with this plan of action. We think that the identification of risk factors is likely to continue to be a very high policy priority and expect that the continuation of a TB99-type study to be a cost-effective way of meeting this requirement. *We recommend continuation of a case-control study of risk factors, though subject to regular review to check the programme's performance and value-for-money.* We regret the delays in collecting and analysing the TB99 data, and while some of these have been unavoidable we think that within MAFF/Defra there has been insufficient appreciation of what a case-control study is, how the data must be collected, and the fact that controls are as important as cases. Part of this problem has arisen from the dual use of TB99 as both a management tool and an epidemiological study, and while efficiencies of scale may argue for this to continue it is very important that measures are taken to prevent the former compromising the latter. *We endorse strongly the auditor's suggestion that the case-control data collection is carried out by a small group of dedicated people who are aware of the need to avoid introducing bias. We also believe it very important that there is a single Project Manager responsible for the whole programme from data collection to analysis, and who can ensure the quality and consistency of the data*. He or she should have a background that includes experience in statistical epidemiology. Finally, we agree that Dr Wahl's continuing involvement is very worthwhile.

3.2 Road traffic accident (RTA) survey

3.2.1 Information about the prevalence of bovine TB in badgers is relevant to several aspects of policy development. A problem at the moment is that there is not a reliable test that can be used on live badgers. The Krebs Report recognised this and recommended the reintroduction of a survey of the infection status of badgers killed in RTAs. The ISG endorsed this, recommending the survey be carried out in the counties in which the RBCT was being conducted to allow their comparison and calibration. The original target was to perform post mortems on, and culture bacteria from, 1200 badgers per year. The work was to be carried out by Defra through the SVS.

3.2.2 Between the start of the RTA project in 2000 and June 2002 only 252 badgers had been processed. Again the problems were the CSF and especially the FMD epidemics, but it appears also that low priority was accorded to this project by Defra-SVS.

3.2.3 In June 2002, the responsibility for the collection of dead badgers was transferred to the Central Science Laboratory (CSL) at York. Between June 2002 and June 2003, 1082 badger carcasses were collected from the seven counties where the trial is taking place, 148 of which came from the trial areas themselves. No initial analyses have been available to us.

3.2.4 *We recommend that the programme be continued until at least two years' data from the RTA (with numbers at least approaching the target figure of 1200 badgers per year) and the RBCT (with proactive culling active at all sites) are available for comparison. This information should allow a decision to be made about whether RTA surveys are a useful epidemiological tool for monitoring TB prevalence in badgers.* It will also allow an informed decision to be made on the suggestion of the House of Commons Environment, Food and Rural Affairs Committee (2003) that should the RTA survey be found "over time to provide a good indication of the prevalence of bovine tuberculosis in badgers an extension to the survey should be considered".

3.2.5 It seems doubtful whether the data collected prior to June 2002 will be of much value. Both the experience here and in the TB99 study underline the importance of prioritising resources efficiently. A clear decision should be made either to carry out a project properly (collecting controls in the TB99 case or sufficient RTA badgers here) or not at all. Investing some but insufficient effort and resources is the least efficient use of research funds.

4 Science & policy

4.1 Introduction

4.1.1 Bovine TB is ultimately a problem because it is a cattle pathogen that affects animal health and welfare and may lead to premature death and reduced productivity. It is also a potential health hazard for humans though currently the risk in the UK is very small. Because of these effects, UK and European law requires regular testing of herds and the destruction of infected individuals, as well as specific methods of meat inspection in all slaughter cattle, and imposes various restrictions such as movement bans on farms where the disease is present. Farmers are compensated for destroyed animals and this and the costs of testing and other anti-disease measures lead to major expenditure by the Exchequer (the complete cost of bovine TB to Government in Great Britain was estimated to be £73M in financial year 2002/3; House of Commons Environment, Food and Rural Affairs Committee 2003). Though compensated for direct losses, farmers suffer indirect financial penalties, as well as significant stress and worry, due to the presence of bovine TB in their animals.

4.1.2 In this section we highlight the most important policy areas to which the RBCT and associated epidemiological research will contribute, and attempt to identify priorities and gaps where further research is required.

4.2 The presence and identity of a wildlife reservoir

4.2.1 The obvious best outcome of bovine TB policy is the elimination of the disease from the national herd. There is general agreement among epidemiologists that the practicality of this depends on whether there is a reservoir amongst wild animals for the pathogen, and if so whether removal of the reservoir is possible and acceptable. In the absence of a reservoir, testing of cattle and their prompt destruction if infected can lead to the eventual loss of the disease. The presence of a significant self-sustaining pathogen population in a wild host makes this impossible unless cross-infection can be excluded. The importance of reservoirs is highlighted by a comparison of TB incidence in other developed countries. TB is most important in the United Kingdom and the Republic of Ireland where badgers are thought to be a natural reservoir (see below); in New Zealand where the introduced possum is a major source of infection; and in parts of the United States, such as in Michigan, where deer form a reservoir. Elsewhere, disease control measures targeted at farm animals have eliminated or dramatically reduced the importance of the disease.

The presence of a wildlife reservoir in the UK

4.2.2 Is the relative lack of success of cattle-directed bovine TB control measures in parts of the United Kingdom due to the presence of a natural reservoir? There is abundant evidence that bovine TB is found in a range of wild species and that prevalence is particularly high in badgers. Badger-to-cattle transmission has also been experimentally demonstrated (though in a laboratory setting), and informal badger removal experiments (by which we mean experiments without replication and controls) have shown a reduction in herd breakdowns. The Krebs Report concluded (Executive Summary, p.6) "The sum of evidence strongly supports the view that, in Britain, badgers are a significant source of infection in cattle. Most of this evidence is indirect, consisting of correlations rather than demonstrations of cause and effect; but in total the available evidence, including the effects of completely removing badgers from certain areas, is compelling." The evidence implicating badgers discussed in the Krebs Report is summarised in Box 7. Since then there have been three significant developments affecting this argument.

4.2.3 First, a major badger removal experiment, the Four Areas Study, has been conducted in the Republic of Ireland. The results of this work have not yet

Box 7 Evidence for importance of badgers in bovine TB (from Krebs Report)

i) Herd breakdowns were reduced in four high-prevalence areas where badgers had been removed.
ii) Transmission of *M. bovis* from badgers to cattle can occur under certain laboratory conditions.
iii) There are associations between spatial and temporal patterns of *M. bovis* infection in badgers and in cattle, although biases in the data make it difficult to draw firm conclusions from these.
iv) Infected badgers in the wild can shed large numbers of bacteria
v) Badgers and cattle in the same area are often infected with the same strains of *M. bovis*.

been made public though press reports in summer 2003 indicated a significant effect of badgers. We have been briefed on the outcome of this experiment and believe it provides strong support for the presence of a bovine TB reservoir in badgers in Ireland that results in cattle infections.

4.2.4 Preliminary studies of clusters of herd breakdowns in disease hotspots have suggested that cattle-to-cattle transmission may be more important than previously thought (ISG pers. comm.), though further analysis is needed to confirm this. In addition, restocking of farms affected by the 2001 FMD epidemic has sometimes led to herd breakdowns caused by the introduction of individuals from areas of known high TB prevalence (ISG pers. comm.). Though the potential importance of cattle-to-cattle transmission has long been realised (reviewed by Goodchild & Clifton-Hadley 2001) these admittedly very preliminary findings have highlighted the need for more studies of bovine TB epidemiology within cattle.

4.2.5 The possibility that more cattle-to-cattle transmission is occurring than previously thought has been used to argue against the importance of badgers as a bovine TB reservoir. In our view, badger-to-cattle and cattle-to-cattle transmission are likely to operate simultaneously and the suggested demonstration of the latter does not contradict the evidence in the Krebs Report and elsewhere about the possible importance of the badger as a natural reservoir.

4.2.6 The third major development since Krebs reported has been the further politicisation and polarisation of the discussion about the role of badgers. This politicisation does not, of course, itself influence the weight of evidence implicating or otherwise the badger, but it highlights the importance of obtaining new evidence about the role or lack of role of the badger as a cause of infection of cattle. A second consequence of the polarisation has been the growing belief amongst farmers that the role of badgers is self-evident, which may have influenced their behaviour in control areas of the RBCT (Section 2.3).

The role of the RBCT in demonstrating a wildlife reservoir

4.2.7 Will the RBCT provide conclusive or at least additional evidence about the presence of a badger wildlife reservoir? As originally conceived in the Krebs

Report, the proactive treatment was to have involved the complete or near complete removal of badgers from experimental areas. This would have allowed a quantitative estimate of the effect of badgers in causing herd breakdowns. But as discussed in Section 2.2, the way badger culling has been implemented in the proactive areas has not resulted in the complete or near complete removal of badgers. Moreover, there is much anecdotal evidence that farmers may be killing badgers in control areas. *We conclude from this, as do the ISG, that while a beneficial effect of proactive culling on the number of herd breakdowns would indicate a role for badgers as a wildlife reservoir, the absence of such an effect would not rule out a contribution of badgers to the bovine TB problem.* Also, because it is very hard to assess the degree to which actual badger densities have been manipulated in the RBCT (see Box 4), it will be very difficult to translate the results of the experiment into a quantitative statement on the importance of badgers.

4.2.8 The reactive treatment of the RBCT was abandoned in November 2003 because the frequency of herd breakdowns appeared to be higher in these treatment areas compared to controls. One interpretation of this result is that reactive culling influences badger behaviour in a way that increases the rate of disease transmission. Such an explanation, if true, would implicate badgers as a wildlife reservoir. For reasons that we discussed in detail in Section 2.3 we do not find this argument compelling, and do not think the results of the reactive treatment provide evidence for or against the role of badgers.

4.2.9 The House of Commons Environment, Food and Rural Affairs Committee report on Badgers and Bovine TB (2003) stated (ninth conclusion and recommendation, p.26) "But we believe that the continuation of the culling trial is necessary to establish once and for all whether killing badgers has any impact on bovine tuberculosis in cattle". In a written note to our panel, Defra agreed with this conclusion and commented "This was always the central aim and should remain so." This is not the view of the ISG who agreed with a note we drafted summarising what we believed the RBCT could demonstrate: "To put a lower limit on the threat to cattle from bovine TB due to the presence of badgers. Because of the inevitable inefficiencies of any culling scheme, the trial can only give a lower limit, and cannot reliably estimate the average threat to cattle from badgers. A corollary of this is that a lower limit of zero does not necessarily exculpate the badger."

4.2.10 The Krebs Report anticipated the RBCT having two key results. We quote "First, it would provide unambiguous evidence on the role of the badger in cattle TB. Secondly, it would provide quantitative data for a cost-benefit analysis of the different strategies, including 'no culling' (Krebs *et al*. 1997, 7.8.20). Elsewhere (5.6.12) it states that the proactive treatment "will allow the estimation of the *maximum* possible impact of badger management on herd breakdown rate" (their italics). But the Report assumed badgers would be "cleared" from proactive areas (5.6.3) by the "total removal of complete badger social groups" (7.8.17). In our view, it was obvious from the start of the RBCT that, as implemented, it would not be possible to clear badgers totally from proactive areas and hence the first goal, as envisaged by the Krebs Report, could not be met. The RBCT could only put a minimum bound on the impact of badgers; it might provide unambiguous evidence that badgers were involved in cattle TB transmission, but, critically, it could not prove that they had no effect. The second goal listed in the Krebs Report remained unchanged, though the cost-benefit analysis obviously pertains to the particular strategies implemented in the RBCT. We view with surprise and concern the on-going confusion as to exactly what information the RBCT as implemented will provide. *We recommend that processes be put in place to ensure that in future there is better communication between Defra and groups such as the ISG responsible for managing policy-relevant science projects.*

Development of policy

4.2.11 Upon what assumptions about wildlife reservoirs should Defra base its future policy, and should such policy formulation wait until the results of the proactive treatment are made public? We believe that the Krebs Report was right in arguing that the evidence for the role of badgers was compelling. Since that report, new evidence has either supported these conclusions (the Irish study) or has not contradicted them. We do not believe the outcome of the proactive treatment will substantially change this picture – it will either further support the role of the badger or be inconclusive. It cannot exclude a badger reservoir or some role for badgers in bovine TB transmission. Though experimental proof of the role of badgers would be very valuable, in our view the risk of the RBCT returning an inconclusive result is sufficiently high that policy formulation and disease control should not be delayed until it has been completed. *We recommend that Defra bovine TB policy is developed on the assumption that badgers are a significant wildlife reservoir for the disease.*

4.2.12 Although we believe the arguments implicating badgers as a wildlife reservoir are compelling, we also believe that further research on alternative species of wild animals, particularly deer, is important.

Molecular epidemiology

4.2.13 We think it possible that application of modern molecular marking techniques may assist in establishing routes of infection between cattle and wildlife. To do this one requires a genetic marker that is neither so variable that all individuals are distinct, nor so constant that all isolates are the same. Such studies require a quantitative approach based on statistical population genetics, and work best when combined with traditional epidemiological techniques. Molecular epidemiology is not a substitute for conventional epidemiology, but rather an additional tool.

4.2.14 The most commonly used techniques in *M. bovis* epidemiology are spacer oligonucleotide typing (spoligotyping), several varieties of restriction fragment length polymorphisms (RFLP) analysis, and studies of loci with variable numbers of tandem repeats (VNTR) (Durr *et al.* 2000a). Their application has had a number of successes (Durr *et al.* 2000b). (i) The demonstration of geographical clustering of genotypes in the UK, and that cattle and badgers in the same area share the same bacterial type. This indicates transmission between the two species, but not its direction. (ii) The identification of separate genetic clusters indicating multiple sources of infection in New Zealand deer and cattle. (iii) Tracing an outbreak of bovine TB in fallow deer in Sweden to animals imported from the UK; and similarly (iv) showing that an outbreak in cattle in Holland derived from a bull imported from Austria.

4.2.15 The examples just given chiefly concern geographical or relatively large scale processes. To study epidemiological processes at the herd level, and the detailed interactions of domestic animals with wild species that may be potential TB reservoirs, it is likely that more variable loci will be required. The recent sequencing of several mycobacterial genomes, including the full genome of *M. bovis* (Garnier *et al.* 2003), has led to the discovery of new stretches of DNA that vary in size and copy number. *We recommend investigation of whether new molecular epidemiological techniques can help understand the transmission of* M. bovis *in the UK.*

4.3 Control of bovine TB in wildlife reservoirs

4.3.1 Given a significant wildlife reservoir the options for eliminating or reducing the disease are (i) controlling it in the reservoir; (ii) reducing badger-to-cattle transmission and (iii) removing cattle from areas where infection from the reservoir is likely. Here we consider the first of these options. Control in the reservoir implies either reducing prevalence of bovine TB in badgers, or reducing the numbers of badgers themselves.

4.3.2 The options for reducing the prevalence of bovine TB in a wild host such as the badger are very limited. No feasible method for curing badgers of TB is known, and there is currently no proven vaccine for badgers. It has not been within our remit to examine the medium and long-term prospects for a badger vaccine but we note (i) the recent scoping study by the ISG (Defra 2003) and (ii) the on-going experiments with a BCG vaccine in captive badgers in the Republic of Ireland (Southey *et al.* 2001). It may be possible to use results from the RBCT to explore different scenarios for vaccine application, were some to prove feasible. *We agree with the ISG that further research on badger vaccines is strongly justified, but that it would be wrong to make reducing the disease prevalence in badgers purely by vaccination a major component of a short- to medium-term national bovine TB policy.*

4.3.3 Culling is thus at present the only feasible way of reducing the importance of the wildlife reservoir, though one that is, of course, extremely contentious. Policy issues concerning culling include (i) the relationship between the fraction of badgers culled and the number of herd breakdowns; (ii) whether it is carried out proactively or reactively, and the temporal and spatial deployment of the culling strategy; (iii) indirect effects of culling on other rural environment issues; (iv) what methods are used to kill badgers with obvious implications for animal suffering and for cull efficiency; and (v) whether culling should be carried out by the Department, its contractors or through licensed killing of badgers by farmers.

4.3.4 The RBCT potentially offers useful information in the first three of these five areas (i) the benefits of reducing badger densities, (ii), the efficacy of particular reactive and proactive culling strategies and (iii) indirect effects. We discuss each in turn.

Benefits of reducing badger densities

4.3.5 In exactly the same way that the Krebs Report intended the proactive treatment of the RBCT to prove whether or not badgers were significant sources of TB infection to cattle, the experiment would also provide information on the maximum benefits that could be attained through removing badgers. Any herd breakdowns in an area from which badgers had been exterminated must arise from a different source. But as argued above (paragraph 4.2.7), badgers have not been removed completely from proactive sites, and it is not clear the degree to which control sites have been affected by farmer behaviour. The comparison of proactive and control sites can thus only set a lower limit on the importance of badgers for TB transmission. Were this treatment to have marginal or no effects on the frequency of herd breakdown, then the implications for policy would depend critically on how effectively culling had reduced badger density. Unfortunately, estimating the effectiveness of culling on badger population densities is very difficult (Box 4).

4.3.6 In examining "the prospects for the experiment achieving its objectives, and the likely time scales involved" (from our terms of reference, Box 1) we tried to establish what Defra would consider a "significant reduction" in herd breakdowns. To develop a hypothetical example, suppose that the data (i) suggested a 20% reduction in herd breakdowns with relative tight confidence limits or (ii) the same estimated reduction but with much broader confidence limits that included 40% and zero. If policy makers considered only a 40% reduction significant enough likely to justify certain options we might in the first case recommend discontinuing the experiment as having already achieved its goal of informing policy, while in the second case recommend its continuation. (This example is deliberately simplistic for illustrative purposes, and avoids, for example, issues concerning statistical stopping rules). Defra does not seem to have developed a set of policy options for bovine TB into which the output of the science it has sponsored can easily be input (though we recognise that the ten-year bovine TB strategy currently being developed may address this criticism). We acknowledge that this is not straightforward to do, requiring for example the relevant economic cost-benefit studies to be performed, and if these require information that is currently unavailable than the necessary research to be commissioned. *We recommend that in future, the potential bovine TB policy options are formulated in a manner in which the way in which the results from scientific studies will be used is made explicit and transparent.*

Efficacy of different reactive and proactive culling strategies

4.3.7 The RBCT can be considered a test of an actual culling strategy that might be implemented as part of a national bovine TB policy, and it may also provide information to help assess a broader range of culling policies. The value of the first type of information depends on the degree to which culling as implemented in the RBCT is a good approximation of what might be carried out across the country. The ISG deliberately designed the proactive and reactive culls to meet these criteria (Bourne *et al.* 1998, 1999), as best as they were able to judge. But, as they recognise, special circumstances associated with the RBCT might make culling within the trial either less or more effective than would be the case if it were implemented as part of a national strategy. More seriously, the results of the RBCT may have been influenced by the behaviour of farmers and animal welfare protestors in a way that is unlikely to be replicated in the implementation of a national policy.

4.3.8 We also note that Defra considers the contribution of the RBCT as a test of an implementable policy to be "very much less important" than the information on the risk of transmission from badger to cattle. In discussion with this Panel they gave two reasons for this: "Firstly, an experimental technique used in a controlled experiment is seldom useful as a field practice without much development and tuning. Thus if the trial yields a benefit from culling and therefore provides the unambiguous evidence of causation we could very rapidly work up more effective, easier, cheaper, and undoubtedly more controversial means of culling badgers. Secondly, social and political conditions are forever changing, experimental methods are usually fairly fixed. Thus our response in future once the evidence has been established may vary considerably from 'experimental methods'." These seem to us persuasive arguments, but only against a too simplistic translation of the results of the trial into the likely consequences of possible future culling policies.

Indirect effects

4.3.9 The final area in which the RBCT might influence culling policy is in the effect of culling on badger behaviour, social structure and ecology, information that will help in the design of any future control measure targeted at badgers; and the search for ecological and environmental consequences of badger culling that may influence its costs, efficacy, or acceptability. Defra has funded a series of such studies (Box 8). Much of this research is on-going and hence we have not been able to assess its value. In general, we believe this work that adds value to the RBCT to have been a very sensible extension to the programme, though to be subsidiary to the main aims of the trial.

4.4 Reducing transmission from a wildlife reservoir

4.4.1 The national cattle herd could be uninfected by TB yet coexist with a wildlife reservoir were it possible to prevent transmission. The problem of course is that wildlife and farm animals mingle extensively in the agricultural landscape, and the precise route through which cattle are infected is not known. There are three major policy issues in this area (i) the degree to which resources should be invested (and by whom) in reducing badger-to-cattle transmission; (ii) what is the best husbandry advice to give to the farming community; and (iii) how to ensure this advice is acted upon.

4.4.2 The main epidemiological investigation into the correlates of herd breakdown that can contribute to these policy issues has been a case-control study using the TB99 questionnaire. In this context, a case-control study assesses a series of potential risk factors on a farm that has suffered a breakdown and compares them with a series of matched, control farms that have not been infected. Case-control studies are often the only tool available for exploring certain epidemiological questions, though they suffer from a number of

Box 8 Current research projects supported by Defra directly relating to the trial and its interpretation.

Code	Title	Lead contractor
ZF0531	Ecological consequences of removing badgers from an ecosystem.	CSL
SE3107	Developing innovative methods to estimate badger population density.	CSL
SE3110	A molecular genetic analysis of badger social structure and bovine TB.	CSL
SE3108	An integrated study of perturbation, population estimation, modelling and risk (finished but not yet reported).	University of Oxford
SE3032	The long term intensive ecological and epidemiological investigation of a badger population naturally infected with *M. bovis*.	CSL
SE3009	The risk to cattle from *M. bovis* infection in wildlife species other than badgers.	University of Oxford
SE3010	The risk to cattle from wildlife species other than badgers in areas of high herd breakdown risk.	CSL
SE3002	Ecological correlates of tuberculosis incidence in cattle.	University of Warwick

methodological limitations associated with the non-random nature of the infected farm; biases in the responses of the farmers and the difficulty of choosing appropriate controls; that they can only investigate factors where significant variation already exists; and difficulties in determining causation. Despite these shortcomings they are still valuable for identifying or confirming major correlates of risk.

4.4.3 We commented in detail on the TB99 programme in Section 3.1 and the very unfortunate delays in its implementation which we believe have hindered the development of policy. Only now are the first results of the TB99 survey becoming available, and we believe that the rapid analysis of the results collected to date should be a priority. We concluded in Section 3.1 that case-control studies will continue to provide valuable science input into policy formulation, and that the suggestion of the TB99 auditor to establish a dedicated team led by a Project Manager is the best way to achieve this.

4.4.4 It has long been recognised that simple husbandry measures that separate cattle from badgers may have an important role in reducing the risk of herd breakdowns. The Krebs Report recommended that "the farming industry should take the lead in developing and implementing an experimental comparison of the most promising husbandry techniques". This has not happened, perhaps because it is not clear exactly which of many husbandry methods should be tested. We agree with the ISG's view that individual Defra-organised experiments on particular interventions are probably not an efficient use of resources because there are so many different possible measures that might be taken.

4.4.5 Defra have commissioned several studies and reports to assess the current consensus on best practice to reduce badger contact with cattle (summarised in Phillips *et al.* 2000). Interventions include making cattle sheds as badger-proof as possible, and raising the height of drinking and feeding troughs such that they cannot be visited by badgers. As is widely appreciated (e.g. House of Commons Environment, Food and Rural Affairs Committee 2003), maintaining the most up-to-date consensus; consulting widely with farmers, veterinarians and wildlife ecologists; and ensuring this information is easily available and accessible, are obvious and important tasks for the Department.

4.4.6 There is still the problem that none of these ideas about altering husbandry practices to mitigate the bovine TB problem are based on field experimental data. *We believe the arguments about the importance of limiting contact with badgers are sufficiently strong that this should not delay the implementation of best practice husbandry.* As testing all possible measures individually is unlikely to be cost-effective, one possible approach is to obtain evidence on whether a comprehensive set of badger separation measures reduces risk. This could be achieved if Defra paid for their full implementation on certain farms chosen at random from a pool of potential participants. The remaining farms would act as controls. If the full set of measures did reduce the herd breakdown rate then further work could tease apart which components were the most important. *We have not been able fully to scope this idea, and there* *are of course issues about the behaviour of farmers in control sites, but we recommend Defra consider whether there is any merit in this suggestion.*

4.4.7 The Krebs Report noted that MAFF husbandry guidelines were “apparently not widely heeded” and we believe that some farmers still are reluctant to implement husbandry practices for which there are excellent arguments that they will reduce the risk of herd breakdowns. It is beyond our remit to comment in detail on this, but as part of their developing 10-year bovine TB strategy we believe strongly that Defra bovine TB policy should include incentives to farmers to implement these measures.

4.4.8 The last few years have seen bovine TB appearing in new areas where previously it was rare or absent. Might there be a way to predict where the disease is likely to become a problem before it starts to cause herd breakdowns? If badgers are the major wildlife reservoir then one possibility is to monitor TB incidence in animals killed by traffic. The ISG have conducted a Road Traffic Accident (RTA) survey of badgers killed in the RBCT areas. Badger TB incidences are routinely assessed in the RBCT and though both they, and the RTA estimates of disease prevalence, are subject to different types of statistical error, their congruence would support RTA surveys as an epidemiological tool. The RTA research programme is discussed in detail in Section 3.2. In the absence of a more direct way of establishing the infection status of badgers we support research into the use of RTA data as an epidemiological tool.

4.5 Cattle-to-cattle transmission

4.5.1 Control of cattle-to-cattle transmission is important to minimise the problems associated with individual outbreaks, and, if cattle-to-badger infection occurs, to prevent the establishment of new reservoirs in previously uninfected wildlife. Policy issues include: (i) how much to invest in the development of better diagnostic tests and understanding the disease in cattle; (ii) can cattle husbandry and management practices be improved to limit contagious spread; (iii) how should cattle movement be managed to limit the geographical extent of the disease? We discuss here the role of the RBCT and associated research in helping develop policy in this area.

4.5.2 Where multiple reactors occur in a single herd it is at present very difficult to determine whether they arise from multiple infections from a source outside the herd or from cattle-to-cattle transmission (e.g. Griffin & Dolan 1995, Hancox 1999, Goodchild & Clifton-Hadley 2001). This is a problem where the use of modern forensic molecular genetic techniques may be helpful (see also paragraph 4.2.15). Further issues are the difficulty of conclusively establishing whether a cow is infected or not, and some gaps in our understanding of the course of the disease within an individual. Goodchild & Clifton-Hadley (2001) present a comprehensive review of cattle-to-cattle transmission and its consequences.

4.5.3 It is well known that the current tuberculin test for bovine TB provides less than perfect diagnosis of infection status (Krebs *et al*. 1997). The key measures of the accuracy of the tuberculin test are its sensitivity (the ability to identify truly infected cattle) and its specificity (the avoidance of false positive tests). Most estimates of the sensitivity of the test are in the range 70-95% depending on the method of its application (Monaghan *et al.* 1994, Goodchild & Clifton Hadley 2001). Estimated specificity, on the other hand, is very high, perhaps 99% (Wood & Rothel 1994). Though not without its own problems, the gamma interferon blood test, used instead or in addition to the tuberculin test, may provide better diagnosis (Wood *et al.* 1991). We are aware that there has been some disagreement between Defra and the ISG as to how a trial should be designed to assess the new blood test (House of Commons Environment, Food and Rural Affairs Committee 2003). We have not looked into this but just comment that while we realise the financial constraints within which Defra operates, it is very important to maximise the information that can be gained from such a trial, and the desirability of consulting as widely as possible on the design of such programmes.

4.5.4 The ISG has been very active in encouraging research into diagnostics and cattle pathogenesis which we broadly support though detailed consideration has been beyond our remit. Advances in this field will undoubtedly assist in the control of bovine TB. In deciding on the priority given to this research, a balance needs to be drawn between the degree to which advances will help prevent secondary infections and improve our understanding of the disease's epidemiology, and the fact that if the spread of the disease does involve regular re-infection from a wildlife reservoir then it addresses only part of the problem.

4.5.5 The TB99 survey includes a variety of questions concerning cattle husbandry and management practices, and analysis of its results should help guide drawing up best practice advice for farmers. It will be important to identify areas of current ignorance and uncertainty in designing future case-control surveys.

4.5.6 Some information on the local spread of bovine TB will be obtained from detailed spatial analysis of the pattern of herd breakdowns in different RBCT sites. Results concerning the spatial clustering of the risk of breakdown may be significant in the possible design of badger culling programmes, and in developing policy on herd testing and cattle slaughter. We believe mining the RBCT for relevant information here should be a priority.

4.5.7 The movement of infected cattle from areas of high TB prevalence to relatively disease-free localities where the infection may be transmitted to other animals is a tragedy for the farmers concerned but provides important epidemiological data. As mentioned in Section 4.2.3, such movements seem to have occurred quite frequently in the aftermath of the foot and mouth disease epidemic, and they are currently being investigated by researchers at Warwick University. Full analysis of these incidents should be a priority.

4.5.8 There are several potential policy options to reduce the risk of transferring the disease to new areas. These include the restriction of movement of cattle from areas of high disease incidence, and the mandatory testing of herds before movement is permitted. Nearly all such interventions require detailed information on individual cattle on particular farms, a situation that is now improved thanks to measures introduced after the BSE and foot and mouth disease epidemics. Most of these interventions are unpopular with farmers because to a certain extent they hinder trade. Their value can only thus be assessed within a broader cost-benefit analysis with multiple stakeholders (the individual farmer, the farming community and the country). Science input is important in helping quantify the trade-offs involved, but our reading of the data currently available points to great dangers in initiating new disease hotspots through cattle movement. *We recommend that scientific and economic research in this area be accorded high priority, and that awaiting these results Defra adopts a policy aimed at reducing as much as possible the risk of new outbreaks.* [Note added in final draft: we note a series of relevant proposals put out to consultation in Defra 2004]

4.6 Modelling

4.6.1 Like other wildlife and domestic animal diseases, the epidemiology of bovine TB involves complicated non-linear phenomena and is difficult to understand without a quantitative model. Models are clearly only as good as the quality of information used in their construction, but even when some processes are unclear the model may be helpful in identifying the most critical areas in which to invest research. In order to understand bovine TB epidemiology, the Krebs Report recommended the development of an integrative approach to modelling utilising multiple information sources and mathematical approaches.

4.6.2 The Krebs Report summarised earlier theoretical work on bovine TB epidemiology and there have been several important studies since then. Spread of the disease within badger populations has been extensively studied using different approaches, most recently by Shirley *et al.* (2003) who provide an entry to this literature. Few of these studies address badger-to-cattle or cattle-to-badger transmission (but see Smith *et al.* 2001a, 2001b) while the small number of investigations of within-herd transmission (e.g. Perez *et al.* 2002) have no link to badgers. Work on bovine TB in New Zealand where possums are the natural reservoir is less directly applicable but still relevant to the UK situation, for example as proof-of-principle that reservoir management can work (Barlow 1993, 2000, Roberts 1996).

4.6.3 There is general agreement among workers in this field that spatially explicit individual-based stochastic models have been useful tools for studying the potential impacts of specific interventions in detail (echoing recent experience with modelling the UK 2001 FMD epidemic). More generally, however, it is often useful to compare outputs using a variety of modelling approaches, and we concur with the Krebs Report in stressing the importance of an integrative approach.

4.6.4 In the context of the RBCT there are several areas where modelling may be helpful: as aids to interpreting field data, to help predict when the effects of culling will be reflected in changes in the rate of herd breakdown, to extrapolate the results beyond the specific regimes employed in the trial, and to help prioritise future research.

4.6.5 Perhaps the greatest challenge to developing useful models is our incomplete knowledge of bovine TB transmission processes. Not only do we not have estimates of transmission rates but we do not know the form of the functional relationship of transmission with badger densities, nor whether there are indirect effects of culling via, for example, stress-induced diseases or changes in contact behaviour.

4.6.6 Defra has funded work on modelling bovine TB in badgers (Project SE3007 Integrated modelling of *M. bovis* transmission in badgers and cattle) and this might well form the basis of a model that could be used to help assist the interpretation of the RBCT. For this to happen the existing model would need to be extended to include badger-to-cattle transmission, and re-parameterised for the RBCT areas with access to GIS and census data, as well as the RBCT results so far. *We recommend that the ISG and groups working on bovine TB modelling establish closer collaboration to explore the possible application of these models in the RBCT context.*

4.7 The RBCT and the interplay of science and policy

4.7.1 In this section we comment on some general issues of the interplay of science and policy concerning the RBCT and associated research.

4.7.2 The ISG was originally set up to oversee the design and analysis of the RBCT. It acts as an independent group of experts to guide the work of the RBCT and also helps ensure its credibility to groups innately suspicious of central government. In practice, the work of the group has expanded greatly beyond what we believe was originally envisaged. We have been very surprised at the level of detailed management with which the ISG has become involved. The reason why this has happened is that the ISG were committed to the successful execution of the trial and believed, rightly in our view, that this was only way to ensure this occurred. We wish to commend the ISG in general and

Professor Bourne in particular for their willingness to shoulder this very great workload.

4.7.3 Nevertheless *we believe it unfortunate that the ISG has had to take on this detailed management role, though in saying this we intend no criticism of the ISG.* It is unfortunate because it has meant the ISG, while remaining independent of Defra, has become very close to the experiment itself which may have hindered their ability, or stakeholders' perception of their ability, to give strategic advice to Defra on the progress of the RBCT.

4.7.4 We are also concerned about the workload this unanticipated management role has placed on the ISG, all of whom are either employed full-time by universities (or similar organisations) or are retired. This was particularly obvious to us in the statistical analysis. The project has benefited enormously from two of the UK's most distinguished statisticians being members of the ISG, but they are extraordinarily busy people and there is a limit to how much detailed analysis they can carry out. Defra recognised this and has funded two statistical research assistants, but we are still not convinced that the ISG has sufficient resources to carry out analyses fast enough to be optimally useful in contributing to policy. For example, it would have been useful to have had a detailed spatial analysis of herd breakdowns in the reactive areas at the time the decision was made to suspend this part of the RBCT. We stress, however, that these remarks should in no way be construed as criticism of the statisticians on the ISG.

4.7.5 In Sections 4.2.10, we described a lack of agreement between Defra and the ISG as to the precise aims and goals of the study. To Defra the objectives largely remain those set out by the Krebs Report, while to the ISG they have been substantially modified in the light of the experience of setting up the RBCT. Relations between Defra and the ISG have at times been strained, and we suspect this has hampered communication between the two, and has resulted in an unrealistic expectation in the Department of the information that the RBCT can provide.

4.7.6 Looking ahead we believe that as long as the RBCT continues it is very important that the ISG remains closely involved. They have unrivalled expertise and understanding of the experimental programme. Though we would advise a different management model for a new research programme, considering where we are *we recommend the ISG be fully supported in their continuing work on the RBCT*.

4.7.7 But we do not believe that the management structure of the RBCT and associated research that was inherited from MAFF by Defra is well suited to achieve the best science input into policy, and recommend that future projects of this size and profile are managed differently. For the reasons outlined in the Krebs Report we believe it critically important that an independent group of scientific experts is involved. As well as providing an autonomous voice, they enable Defra to utilise the very best expert advice available in the UK (and possibly elsewhere). *But within Defra we believe there needs to be a senior figure with a scientific background who can take ownership of a project of this size.* He or she needs the authority to be able to work with different sections within the Department, and to ensure that the requirements of science input into policy are both clearly identified and defined, and are met by the experimental programme.

4.7.8 We believe a science background is important in order that he or she can fully engage with the expertise available in an independent science advisory group. Some of the problems with the interpretation of the RBCT goals seem to us due to the lack of scientific expertise within parts of Defra. We think that the recent re-definition of the role of Defra Chief Scientific Advisor, and the establishment of an external science advisory committee will help rectify this. We have already discussed (paragraph 2.3.25), and would like to stress here, the importance we attach to Defra having access, both internally and through its advisory bodies, to the very best science input into all areas of project management and policy development.

4.8 General issues

4.8.1 We comment here briefly on two general issues concerning how best to ensure policy is securely science-based.

4.8.2 The RBCT has sometimes been criticised as a very expensive "academic" exercise, utilising an experimental approach that is inappropriate for a problem of this type. Science-related information upon which policy is based can be viewed as a series of alternatives, each associated with a provisional probability. The role of scientific input is to revise and update these probabilities based on observational and experimental data, and on theoretical investigation. In some areas, global warming for example, experiments are impossible and the probabilities of different alternatives (e.g. whether CO_2 created by humans is or is not the cause of increased global temperatures) change purely through observational and theoretical studies. In others, for example the effect of GM and non-GM crop management on biodiversity, very successful large experimental programmes have been conducted that are having a major impact on policy. Where they are possible, experiments are of particular value because by incorporating controls they allow much stronger inference about cause and effect, and hence say much more about the relative probabilities of different alternatives. *Experimentation is far from being the only approach to obtaining useful, policy-relevant science, but where logistically and financially practicable it is very likely to provide superior evidence compared to observational approaches.*

4.8.3 Finally, we return to a series of recommendations of the Krebs Report: that there should be clear commitment by Government to ensuring data are made quickly available to the research community; that research should be commissioned from those with the best expertise in the field; and that there should be a better co-ordinated approach to research through partnerships. It has not been within our remit to review the extent to which these recommendations have been implemented, but like the Krebs Report we believe these issues are very important for ensuring the very best science to help the development of policy.

5 Summary of main recommendations

5.1 Results from the reactive treatment

5.1.1 We recommend that in describing the results of the reactive treatment terms such as “nearly significant” or ”strong trend” are used to describe the increase in breakdowns. We believe these are preferable to expressions that imply that the results are clearly significant at the customary 95% level. (2.3.6)

5.1.2 Pending more detailed analysis of the data, we advise that the results from the reactive trials should neither be viewed as evidence for the perturbation hypothesis nor as evidence for or against the role of badgers in bovine TB transmission. Similarly, the results at the time the treatment was halted should not be interpreted as evidence against (or, of course, for) a reactive culling policy. (2.3.14, 2.3.23, 4.3)

5.2 Future of the proactive treatment

5.2.1 We advise that if the numbers of herd breakdowns remain at their current levels in control sites, then the RBCT will achieve the statistical target of distinguishing whether or not proactive culling can reduce the incidence of herd breakdowns by 20% with 90% confidence sometime between late 2004 and early 2008. Whether sooner or later depends on arguments about the nature of the variability in the data; in our opinion a later date is much more likely. (2.4.6)

5.2.2 Factors such as time lags between the initiation of culling and its effects on herd breakdowns, and past inefficiencies in culling, will tend to increase the time it will take for the experiment to meet its precision goals. However, if the reduction in the rate of herd breakdown exceeds 20%, either now or in the future, this will act to hasten the achievement of this target. In the Appendix, at present confidential because it involves explicit mention of the interim results, we discuss further these calculations in the light of the results so far. (2.4.12)

5.2.3 Continuation of the experiment is likely to provide further important information about bovine TB epidemiology such as the detailed spatio-temporal pattern of herd breakdowns, and its relationship with local TB prevalence in badgers. It may also indicate that the level of badger removal achieved in the trial results in fewer herd breakdowns. Against these benefits are the costs of the trial, its inability to prove a negative (that badgers are not significantly involved in transmitting the disease to cattle), and the difficulty of generalising the result from one culling method to others that might be implemented as a national policy option. To decide its overall value for money relative to other calls on the Department's research budget, we believe Defra needs to formulate much more explicitly how the results of the RBCT will input into future bovine TB policy. (2.4.15)

5.2.4 We do not think that Defra can make informed decisions on the future of the RBCT, and on short- to medium-term bovine TB policy, without having access to the interim results and recommend that this occurs. (2.4.15, 2.4.18)

5.2.5 We recommend that while the RBCT continues, the ISG is fully supported in their continuing important work with the trial (4.7.6)

5.2.6 We consider that understanding how the treatments implemented in the RBCT (and possibly other experiments) affect badger densities is very important both for interpreting and generalising the results of the trial. We recommend that Defra support further research into obtaining more detailed data on badger densities in the RBCT areas. (2.1.9)

5.3 Case-control (TB99) study

5.3.1 We recommend continuation of a case-control study of risk factors, though subject to regular review to check the programme's performance and value-for-money. We endorse strongly the recent auditor's suggestion that the case-control data collection is carried out by a small group of dedicated people who are aware of the need to avoid introducing bias. We also believe it very important that there is a single Project Manager responsible for the whole programme from data collection to analysis, and who can ensure the quality and consistency of the data. (3.1.9)

5.4 RTA survey

5.4.1 We recommend that the programme be continued until at least two years data from the RTA (with numbers at least approaching the target figure of 1200 badgers per year) and the RBCT (with proactive culling active at all sites) are available for comparison. The future of the programme should be based on the analysis of these results. (3.2.4)

5.5 Development of bovine TB policy by Defra

5.5.1 We recommend that Defra bovine TB policy is developed on the assumption that badgers are a significant wildlife reservoir for the disease. (4.2.11)

5.5.2 It is important to realise that the RBCT may not settle once and for all the question of badger involvement in bovine TB transmission. It can demonstrate a link, but it cannot demonstrate a link is absent. (4.2.7)

5.5.3 We recommend investigation of whether new molecular epidemiological techniques can help understand the transmission of *M. bovis* in the UK. (4.2.15)

5.5.4 We agree with the ISG that further research on badger vaccines is strongly justified, but that it would be wrong to make reducing disease prevalence in badgers purely by vaccination a major component of a short- to medium-term national bovine TB policy. (4.3.2)

5.5.5 We urge the implementation of current best practice husbandry methods to limit contacts between badgers and cattle, and support further research into how best to do this. (4.4.6)

5.5.6 We are very concerned (as are the ISG) about the recent geographic spread of bovine TB and recommend scientific and economic research into its basis and possible control measures, and that while awaiting these results Defra adopts a policy aimed at reducing as much as possible the risk of new outbreaks in currently unaffected geographical areas. (4.5.8)

5.5.7 We recommend that the ISG and groups working on bovine TB modelling establish closer collaboration to explore the possible application of these models in the RBCT context. (4.6.6)

5.6 Management of large science-based projects

5.6.1 We believe it unfortunate that the ISG has had to take on a detailed management and executive role in the RBCT, though in saying this we intend no criticism of the ISG for having done so. (4.7.3)

5.6.2 We recommend that in future a body such as the ISG reports initially to the Defra Chief Scientific Advisor who should arrange for its advice to Ministers to be reviewed properly before its submission. (2.3.25)

5.6.3 We recommend that processes be put in place to ensure that in future there is better communication between Defra policy units and groups responsible for managing policy-relevant science projects. (4.2.10)

5.6.4 Within Defra we believe there needs to be a senior figure with a scientific background who can take ownership of large science-based projects such as the RBCT. (4.7.8)

5.7 General points

5.7.1 We believe it important that all Defra press releases that present quantitative data include some generally understood statement about uncertainty, preferably statistically-based confidence intervals. (2.3.8)

5.7.2 We support the value of large-scale experiments in providing the sound science to underpin policy. (4.8.2)

5.7.3 We reiterate the recommendation of the Krebs Report that there should be clear commitment by Government to ensuring data are made quickly available to the research community; that research should be commissioned from those with the best expertise in the field; and that there should be a better co-ordinated approach to research through partnerships. (4.8.3)

Glossary and list of acronyms used

Gamma Interferon Blood Test	An alternative to the tuberculin test that involves culturing cattle blood cells with TB antigens and detecting a response through the levels of production of an immune cytokine
Herd breakdown	Loss of TB-free status in a cattle herd; typically determined by the tuberculin test
Inflation factor	A factor that allows confidence limits based on the Poisson distribution (q.v.) to be corrected when the variation is greater than expected
Mycobacterium	The causative agent of TB; several bacteria in this genus cause TB of which the most important are *M. bovis* (bovine TB) and *M. tuberculosis* (human TB)
Non-independence	In statistics the influence of the occurrence of one event upon the probability of the occurrence of another; many statistical methods assume events such as herd breakdowns are independent, and violation of this assumption may affect the validity of the analysis
Poisson distribution	The statistical distribution of the number of events occurring when they happen independently and at a constant rate over space or time; it is characterised by a single parameter, the mean
Reactor	An animal which gives a positive result (i.e. 'reacts') to the tuberculin skin test
Spoligotyping	A molecular typing technique that relies on differences in the number of certain DNA repeat sequences
Statistical power	The probability that a statistical test will be statistically significant at a specified level as a function of the difference between the true value of the parameter and its hypothesised value
Stopping rules	Rules that determine when an experiment should be terminated, typically set in advance using statistical methods to maximise the trade off between the information obtained and the effort expended
Triplet years	The cumulative sum of the number of years each triplet has been part of the RBCT
Tuberculin test	A test for TB in cattle that involves observation of the immune response to injection of the tuberculin protein derived from the causative bacterium

ADAS	ADAS (originally the Agricultural Development Advisory Service) is a research based consultancy to rural and land-based industries
AHO	Animal Health Offices of the State Veterinary Service.
BCG	Bacille Calmette-Guerin, an attenuated form of *M. bovis* that is the basis for most human and animal TB vaccines
CSF	Classical swine fever
CSL	Central Science Laboratory, York
Defra	Department for the Environment, Food and Rural Affairs
FMD	Foot and mouth disease
GIS	Geographical Information Systems
ISG	Independent Scientific Group (here referring to the panel chaired by Professor John Bourne that has supervised the RBCT)
MAFF	Ministry of Agriculture, Fisheries and Food (became part of Defra in May 2001)
RBCT	Randomised Badger Culling Trial
RTA	Road traffic accidents, here the programme to estimate bovine TB levels in badgers killed on the roads
SOP	Standard Operating Procedures, here the procedures developed by the ISG describing how the RBCT treatments should be implemented
SVS	State Veterinary Service (part of Defra)
TB	Tuberculosis, unless otherwise stated here referring to bovine TB caused by the bacterium *Mycobacterium bovis*
TB99	The farmer questionnaire designed in 1998 to assess factors correlated with the detection of the diseases on different farms
VLA	Veterinary Laboratories Agency
WLU	Defra’s Wildlife Unit charged with carrying out the RBCT

References

Armitage, P., McPherson, K. and Rowe, B.C. (1969) Repeated significance tests on accumulating data. *Journal of the Royal Statistical Society A* **132**, 235-244.

Barlow, N.D. (1993) A model for the spread of bovine TB in New Zealand possum populations. *Journal of Applied Ecology*, **30**, 156-164.

Barlow, N.D. (2000) Non-linear transmission and simple models for bovine tuberculosis. *Journal of Animal Ecology*, **69**, 703-713.

Bourne, J., Donnelly, C., Cox, D., Gettinby, G., McInerney, J., Morrison, I. and Woodroffe, R. (1998) Towards a sustainable policy to control TB in cattle (First Annual Report of the Independent Scientific Group on Cattle TB). MAFF Publications, London.

Bourne, J., Donnelly, C., Cox, D., Gettinby, G., McInerney, J., Morrison, I. and Woodroffe, R. (1999) An epidemiological investigation into Bovine Tuberculosis (Second Annual Report of the Independent Scientific Group on Cattle TB). MAFF Publications, London.

Bourne, J., Donnelly, C., Cox, D., Gettinby, G., McInerney, J., Morrison, I. and Woodroffe, R. (2000) Notes on statistical aspects of the badger culling trial (Memorandum to the Agriculture Committee – Annex A). http://www.defra.gov.uk/animalh/tb/publications/progress/isganna.htm

Cheeseman, C.L., Cresswell, W.J., Harris, S. and Mallinson, P.J. (1988) Comparison of dispersal and other movements in two badger (*Meles meles*) populations. *Mammal Review*, **18**, 51-59.

Cresswell Associates (2001) Independent Audit of Badger Trial: Audit of the Surveying and Social Group Delineation SOPs. http://www.defra.gov.uk/animalh/tb/publications/cresswell/index.htm

Defra (2003) Development of vaccines for Bovine Tuberculosis: Report of the ISG Vaccine Scoping Sub-Committee. http://www.defra.gov.uk/animalh/tb/pdf/vsssc.pdf

Defra (2004) Preparing for a new GB strategy on bovine tuberculosis. http://www.defra.gov.uk/corporate/consult/tbstrategy/consultation.pdf

Doncaster, C.P. and Woodroffe, R. (1993) Den site can determine shape and size of badger territories: implications for group-living. Oikos, 66, 88-93.

Donnelly, C., Woodroffe, R., Cox, D., Bourne, J., Gettinby, G., Le Fevre, A., McInerney, J. and Morrison, I. (2003) Impact of localized badger culling on tuberculosis incidence in British cattle. *Nature*, **426**, 834-837.

Dunnet, G.M., Jones, D.M. and McInerney, J.P. (1986) Badgers and bovine tuberculosis. Report to the Rt Hon Michael Jopling, MP and the Rt Hon Nicholas Edwards, MP. HMSO, London.

Durr P.A., Hewinson R.G. and Clifton-Hadley R.S. (2000a) Molecular epidemiology of bovine tuberculosis I. *Mycobacterium bovis* genotyping. *Revue Scientifique et Technique de l'Office International des Epizooties,* **19,** 675-688.

Durr P.A., Hewinson R.G. and Clifton-Hadley R.S. (2000b) Molecular epidemiology of bovine tuberculosis II. Applications of genotyping. *Revue Scientifique et Technique de l'Office International des Epizooties,* **19,** 689-701.

Ellenberg, S.S., Fleming T.R. and DeMets D.L. (2002) Data Monitoring Committees in Clinical Trials. Wiley, New York.

Garnier, T. *et al.* (2003) The complete genome sequence of *Mycobacterium bovis*. *Proceedings National Academies of Science USA*, **100**, 7877-7882.

Goodchild, A,V. and Clifton-Hadley, R.S. (2001) Cattle-to-cattle transmission of *Mycobacterium bovis*. *Tuberculosis,* **81**, 23-41.

Griffin, J.M. and Dolan, L.A. (1995) The role of cattle-to-cattle transmission of *Mycobacterium bovis* in the epidemiology of tuberculosis in cattle in the Republic of Ireland – a review. *Irish Veterinary Journal,* **48,** 228-234.

Hancox, M. (1999) Transmission of Bovine TB in cattle: a critical reappraisal. *Letters in Applied Microbiology*, **26**, 242-244.

House of Commons Agriculture Committee. (1999) Badgers and Bovine Tuberculosis. Fifth Report of 1998-99 Session. HMSO, London.

House of Commons Environment, Food and Rural Affairs Committee. (2003) Badgers and Bovine TB. Seventh Report of Session 2002-03.Report together with the Proceedings of the Committee, and the Minutes of Evidence and Appendices. HMSO, London.

Krebs, J., Anderson, R., Clutton-Brock, T., Morrison, I., Young, D. and Donnelly, C. (1997) Bovine Tuberculosis in Cattle and Badgers. Report to The Rt Hon Dr Jack Cunningham MP. Maff Publications, London.

Krzanowski, W.J. (1998) An Introduction to Statistical Modelling. Arnold, London.

LeFevre, A.M., Johnston, W.T., Bourne, J.S., Donnelly, C.A., Cox, D.R., Gettinby, G., McInerney, J.P., Morrison, I. and Woodroffe, R. (2003) Changes in badger setts over the first three years of the randomized badger culling field trial. Poster presentation at Society for Veterinary Epidemiology and Preventive Medicine Conference 2003 http://www.svepm.org.uk/Posters2003/poster_files/LeFevre.pdf

Lohr, S. (1999) Sampling Design and Analysis. Duxbury Press, London.

MAFF (1976) Report on Bovine Tuberculosis in Badgers. MAFF Publications, London.

MAFF (1984) Eighth report on Bovine Tuberculosis in Badgers. MAFF Publications, London.

MAFF (1994) Seventeenth report on Bovine Tuberculosis in Badgers. MAFF Publications, London.

McCullagh, P. and Nelder, J.A. (1989) Generalized Linear Modelling (Second Edition), Chapman & Hall, London.

Mollison, D. (2000) First report of the statistical auditor. Defra, London. http://www.defra.gov.uk/animalh/tb/publications/auditor/stats1.htm

Monaghan, M.L., Doherty, M.L., Collins, J.D., Kazda, J.F. and Quinn, P.J. (1994) The tuberculin test. V*eterinary Microbiology*, **40**, 111-124.

Perez, A.M., Ward, M.P., Charmandarian, A. and Ritacco, V. (2002) Simulation model of within-herd transmission of bovine tuberculosis in Argentine dairy herds. *Preventive Veterinary Medicine,* **54** (4), 361-372.

Phillips, C.J.C., Foster, C., Morris, P. and Teverson, R. (2000) The role of cattle husbandry in the development of sustainable policy to control *M. bovis* infection in cattle. Report to MAFF. MAFF Publications, London.

Roberts, M.G. (1996) The dynamics of bovine tuberculosis in possum populations, and its eradication or control by culling or vaccination. *Journal of Animal Ecology*, **65**, 451-464.

Rogers, L.M., Delahay, R., Cheeseman, C.L., Langton, S., Smith, G.C. and Clifton-Hadley, R.S. (1998) Movement of badgers (*Meles meles*) in a high density population: Individual, population and disease effects. *Proceedings of the Royal Society of London Series B – Biological Sciences*, **265** (1403), 1269-1276.

Roper, T.J. and Lüps, P. (1993) Disruption of territorial behaviour in badgers *Meles meles*. *Z.Saügetierkunde*, **58**, 252-255.

Shirley, M.D.F., Rushton, S.P., Smith G.C., South, A.B., and Lurz, P.W.W. (2003) Investigating the spatial dynamics of bovine tuberculosis in badger populations: evaluating an individual-based simulation model. *Ecological Modelling*, **167**, 139-157.

Smith, G.C., Cheeseman, C.L., Clifton-Hadley, R.S. and Wilkinson, D. (2001a) A model of bovine tuberculosis in the badger *Meles meles*: an evaluation of control strategies. *Journal of Applied Ecology*, **38**, 509-519.

Smith, G.C., Cheeseman, C.L., Wilkinson, D. and Clifton-Hadley, R.S. (2001b) A model of bovine tuberculosis in the badger *Meles meles*: the inclusion of cattle and the use of a live test. *Journal of Applied Ecology*, **38**, 520-53.

Southey, A., Sleeman, D.P.S., Lloyd, K., Dalley, D., Chambers, M.A., Hewison, R.G. and Gormley, E. (2001) Immunological responses of Eurasian badgers (*Meles meles*) vaccinated with *Mycobacterium bovis* BCG (bacillus calmette guerin). *Veterinary Immunology and Immunopathology*, **79** (3-4), 197-207.

Tuyttens, F.A.M., MacDonald, D.W., Delahay, R., Rogers, L.M., Mallinson, P.J., Donnelly, C.A. and Newman, C. (1999a) Differences in trappability of European badgers *Meles meles* in three populations in England. *Journal of Applied Ecology*, **36**, 1051-1062.

Tuyttens, F. A. M., Macdonald, D. W., Swait, E. and Cheeseman, C. L. (1999b). Estimating population size of Eurasian badgers (*Meles meles*) using mark-recapture and mark-resight. *Journal of Mammalogy,* **80,** 950-960.

Tuyttens, F.A.M., Delahay, R.J., MacDonald, D.W., Cheeseman, C.L., Long, B. and Donnelly, C.A. (2000a) Spatial perturbation caused by a badger (*Meles meles*) culling operation: implications for the function of territoriality and the control of bovine tuberculosis (*Mycobacterium bovis*). *Journal of Animal Ecology*, **69**, 815-828.

Tuyttens, F.A.M., MacDonald, D.W., Rogers, L.M., Cheeseman, C.L. and Roddam, A.W. (2000b) Comparative study on the consequences of culling badgers (*Meles meles*) on biometrics, population dynamics and movement. *Journal of Animal Ecology*, **60**, 567-580.

Tuyttens, F. A. M., Long, B., Fawcett, T., Skinner, A., Brown, J. A., Cheeseman, C. L., Roddam, A. W. and Macdonald, D. W. (2001) Estimating group size and population density of Eurasian badgers (*Meles meles*) by quantifying latrine use. *Journal of Applied Ecology*, **38**, 1114 – 1121.

Wahl, M. (2003) An audit of the TB 99 questionnaire. Unpublished report to Defra.

Ward, A.I., Delahay, R.J. and Cheeseman, C.L. (2003) Cattle husbandry and badger behaviour: Opportunities to manage badger to cattle transmission of *Mycobacterium bovis*? – An unpublished report to the Independent Scientific Review of the Randomised Badger Culling Trial and Associated Epidemiological Research.

Wilson, G.J., Delahay, R.J., de Leeuw, A.N.S., Spyvee, P.D. and Handoll D. (2003a) Quantification of badger (*Meles meles*) sett activity as a method of predicting badger numbers. *Journal of Zoology, London,* **259**, 49-56.

Wilson, G.J., Frantz, A.C., Pope, L.C., Roper, T.J., Burke, T.A., Cheeseman, C.L. and Delahay, R.J. (2003b) Estimation of badger abundance using faecal DNA typing. *Journal of Applied Ecology,* **40**, 658-666.

Wood, P.R., Corner, L.A., Rothel, J.S., Baldock, C., Jones, S.L., Cousins, D.B., McCormick, B.S., Francis, B.R., Creeper, J. and Tweedle, N.E. (1991) Field comparison of the interferon-gamma assay and the intradermal tuberculin tests for the diagnosis of bovine tuberculosis. *Australian Veterinary Journal* **68,** 286-290.

Wood, P.R. and Rothel, J.S. (1994) *In vitro* immunodiagnostic assays for bovine tuberculosis. *Veterinary Microbiology,* **40**, 125-135.

Zuckerman, Lord. (1980) Badgers, Cattle and Tuberculosis. Report to the Right Honourable Peter Walker, MP. HMSO, London.

A1 Appendix. Confidential discussion

The Appendix contains reference to material that is confidential at the time the Report is submitted, and is omitted from this version.