



## Report on Bovine Tuberculosis Workshop

**A workshop hosted by the Boyd Orr Centre for Population and Ecosystem Health at the University of Glasgow, UK**

May 9<sup>th</sup>/10<sup>th</sup>, 2013, Gartmore House, Gartmore, Stirling, UK

<http://www.gla.ac.uk/research/az/boydorri/>

The aim of the workshop was to bring together individuals across science and policy themes together, considering both the serious problem in Britain and Ireland, but also the wider perspective, particularly that in the European Union. There were a total of 34 participants coming from different parts of the world including New Zealand and South Africa.

The workshop was run over four sessions on two days, with each session starting with a framing talk, followed by breakout group discussions and a report back to the group as a whole. Thanks very much to Ricardo de la Rua-Domenech (AHVLA, UK), Frazer Menzies (DARD, UK), Darrell Abernethy (University of Pretoria, South Africa), William Wint (Environmental Research Group Oxford, UK) and Susanna Lewerin (Swedish University of Agricultural Sciences, Sweden) who acted as moderators.

The themes that were covered (comments in italics are additional notes and do not reflect directly comments made at the meeting):

1. Risk-based surveillance for bovine Tuberculosis (bTB), with a framing talk by Paul Bessell (Roslin Institute, University of Edinburgh, UK).
2. When is a reservoir host a reservoir host, with framing talks from Clare Benton (AHVLA, Woodchester Park, UK) and Aurelie Courcoul (ANSES in the Maison-Alfort Laboratory for Animal Health, France)
3. On the second day, there was a presentation of results from the workshop survey followed by a discussion of the implications of a 'perfect' diagnostic test, then on social factors and, in particular, on the role of farmer behaviour.

4. Michael Deason (University of Glasgow, UK) presented some of his preliminary results on an extended study looking at whole genome sequencing of *Mycobacterium bovis* (the causative agent of bovine TB) in Northern Ireland.

## Summary of sessions

### I. Risk-based surveillance for bovine TB

The framing talk by Paul Bessell discussed the work he led which established a risk-based scheme for Scotland. The scheme centred on the identification of (i) particular risk factors for bovine TB breakdowns in Scotland and (ii) subgroups of herds where either bovine TB is only rarely identified and/or where it is identified by means other than regular herd testing. The emphasis was on the reduction in test frequency, where such tests are unlikely to produce an added benefit to the surveillance programme. In the case of Scotland, there were two key elements to the design of the programme – first, the importance of imports of cattle from high-risk areas of England and Wales and from both Northern and Republic of Ireland as a risk factor for herd breakdowns. Second, the large number of herds where cattle are not kept for a prolonged period, send many cattle to slaughter, and therefore are both less likely to have an on-farm outbreak, and are more likely to be picked up at slaughter. Further, onward risk from these is relatively low, due to the rarity of these farms selling on cattle to other farms. The use of Bayesian statistical approaches allowed for the formal consideration of the duration of freedom from disease in the statistical risk model.

The breakout session that followed discussed the utility of risk-based surveillance in other situations considering both Britain and countries abroad.

The following key points were identified:

#### 1. Endemic and non-endemic areas would require different approaches.

- a. Non-endemic must be conservatively defined and it would be useful to identify transitional areas, which are more likely to shift from being non-endemic to endemic, and these would have to be monitored carefully. At best, misidentification reduces efficiency, but also has the potential to exacerbate the problem and help create new endemic areas.
- b. These defined areas may be quite broad, heterogeneities within areas should be identified to determine if there is potential for localized areas to become problem areas, and/or identify better targeting of surveillance.
  - i. For example, different abattoirs are likely to have different identification rates, and this may result in more missed cases than expected. The consequences for missing cases for long periods are potentially high (e.g. Probst *et al.*, 2011).
  - ii. Improvement in surveillance occurs through exploiting heterogeneities in risk to individual premises, for example differences in trading practices or in the housing used may be important.
- c. While some factors will be unique to each area, some factors such as the role of cattle movements might be common across them. Whether they can or should be exploited does however depend on the advantage that can be gained or lost.

- d. While substantial benefit could be derived from efficient surveillance in non-endemic areas, it is in the endemic areas that most of the benefit can be found, albeit through tackling a more difficult problem, typically one of better identifying herds that are likely to spread bTB to other herds.
  - i. Especially in endemic areas, should also consider the potential of other tests (e.g. blood tests) as a way of early and/or better and/or cheaper identification of cases.
- e. Nonlinear effects must be considered; for example passing above or below the threshold criteria of officially TB freedom has a usually high impact.

## 2. Statistical models must be developed to inform risk.

- a. While the principles may be well understood without the statistical models, these are required to form the evidence base on which changes in policy are determined – they are also useful for determining when risk-based surveillance is going wrong.
- b. Statistical models are often based on proxies for real risk factors, and are therefore susceptible to being the wrong proxies – this is especially an issue where changes in legislation, for example, changes the relationship between the proxy and the real risk factor. For example, herd size and number of cattle bought in are often correlated and both can be risk factors for bovine TB. Targeting surveillance on the basis of one of these but not accounting for the other, may result in unintended consequences.
- c. Models do not take into account compliance issues. Statistical models only consider the current situation and are not designed to account for changes in the underlying behaviour of the farmer population in response to changes in surveillance. *This can have a positive effect (see for example, Gates et al., 2012) but may also have a negative one.*
- d. The models are only as good as the data going into them
  - i. Some risk factors will remain hidden
  - ii. The models will be based on historical risk factors
  - iii. The data may be precise but not robust

## 3. The role of social and economic factors.

A benefit of targeting surveillance is the opportunity to influence behaviour, for example, to encourage farmers away from risky behaviour and towards safe behaviour. However, this itself is fraught with difficulty, as any inclusion of social factors (either explicit or implicit) makes outcomes less predictable.

- a. Costs will be spread over government, the farming community and society at large. Whose cost is being accounted for?
- b. There will be legislative limits on what is possible.
- c. Farmer buy-in will be critical, as will that of vets in the field - the more targeted the surveillance is, the more important this will be, especially since more precise targeting allows for more latitude in interpretation and 'bending' of rules.
- d. Public opinion matters (are risks affecting public confidence in food security or have animal welfare implications). This will likely influence outcomes even if they are not formally part of a cost-benefit analysis.
- e. The extent to which activities are culturally dependent, even if they are not economically driven may be important; these factors themselves may change over time.

## II. Wildlife Reservoirs

This session started with two framing talks, one by Clare Benton from AHVLA at Woodchester Park, UK and the other by Aurelie Courcoul from ANSES, Laboratory for Animal Health, France.

Clare Benton's talk concentrated on the question of what makes badgers a more likely reservoir host than other possible wildlife species. The argument centred around a combination of disease prevalence in the population, disease pathology in the individual, epidemiological contact (both within and between species and at the population and individual scales) and the ecology of the disease in the population. Compared to other potential reservoirs, badgers 'tick most of the boxes', with only feral pigs (or wild boar in other countries) have the potential for a similar fit. Aurelie Courcoul concentrated on the existence of specific disease clusters in France. There were two key factors that have led to a strong suspicion of the role of wildlife (mainly wild boar and badgers) in maintaining disease in a subpopulation of cattle herds. First, geographical clustering of cases in an area with dense wildlife: there was a poor correlation between herd outbreaks and cattle movements and some elements suggesting local transmission. Second, for the particular clusters of infection were found, with closely associated spoligotypes in both wildlife and cattle. Whether or not this is an increasing problem remains to be seen.

The breakout sessions concentrated on the question of whether or not Britain and Ireland had unique problems, or may simply represent examples of what might happen in other countries, should a combination of events to occur.

1. Factors affected the role of wildlife that could change circumstances from having a reservoir population to a non-reservoir one.
  - a. If *M. bovis* becomes adapted to the wildlife species (*there is speculation this may for example, have been the case for badgers*)
  - b. Nutritional stress may increase the susceptibility of the population
  - c. Population pressure may increase exposure/contact with cattle
  - d. Increased density of wildlife may increase transmission and therefore prevalence
  - e. Concurrent infections in the wildlife population may affect immune response, for example, and therefore, increase susceptibility
  - f. Habitat management will have an impact
  
2. How do you find when a species with evidence of presence of infection suspected of contributing to disease in cattle?
  - a. Genotyping – molecular data will indicate clustering of cases but can't identify whether one species is the maintenance host for the other, or if both are necessary. *Also could examine the bacterial population diversity, but this would require sufficient sampling of the bacterial population in the wildlife host and may be expensive to do and/or difficult to interpret*
  - b. Look for geographical clustering of cases. *This assumes that geographical clustering implies increased prevalence, rather than simply increased density of the underlying population. As for (a) above, indicative rather than conclusive*
  - c. Identify changed problem in the cattle population (*indicative rather than conclusive*)
    - i. Relationship to cattle contact patterns (spatial, movement etc.)
    - ii. Relationship to population demographic studies (densities etc.) for both populations (cattle and potential reservoir) and statistical

correlates between changes in the bTB incidence and changes in the demographics.

- d. Assess via intervention studies (e.g. Randomised Badger Culling Trial) in both species. *This is probably the clearest evidence of proof of a relationship, but is potentially very expensive and even in the case of the RBCT does not definitively say whether or not the reservoir species is necessary for maintenance in cattle, though it clearly indicates that badgers have an impact.*
- II. Other issues
- a. A comprehensive survey of all possible reservoir species is likely to be difficult, but it may be that the observed species are simply spillover species rather than maintenance hosts, and the real culprit is another wildlife species.
  - b. Sampling of environment for *M. bovis* – are there lots of bacteria circulating? This may indicate a problem, *especially if the diversity is greater than the one found in cattle (cf. whole genome sequencing)*
  - c. Is abattoir surveillance sufficient to control the disease, if there is a zoonotic risk, and is it sufficiently sensitive to indicate when a potential problem is occurring – this may depend, for example, on how good traceability is back to the farm of disease origin
  - d. Why are foxes different in England/France (is there bacterial evolution?)
  - e. More than just a need to understand the traditional ‘ecology’ of wildlife, should also consider how to combine approaches and take the ecological perspective

III. The Questionnaire. All participants were asked to fill in a questionnaire, the results of which are summarised in the appendix. Two key points that were picked up from this were an interest in improved diagnostic testing, and also the role of social factors. Each of these was discussed in breakout sessions.

#### III.a. **Would a perfect diagnostic test be a ‘magic bullet’?**

Much has been made about the poor sensitivity of the current standard test, particularly in GB where the comparative test is used, in order to increase specificity in the presence of environmental mycobacteria. While this is mitigated somewhat by using a combined ‘standard’ and ‘severe’ interpretation of the SICCT test (the latter used when there has been a reactor under the standard interpretation, and therefore increased suspicion of disease), nonetheless it is likely that a significantly better test would be a useful tool in the control armoury. Therefore, we asked the question of what would the impact of a perfect diagnostic test be?

1. Much of the question if its utility depends on whether or not there is a meaningful wildlife reservoir present, and the extent to which infection at the herd level is driven by the reservoir. If mainly reservoir driven, then the impact is likely to be small.
2. The precise meaning of a ‘perfect’ test was discussed – perfect in what way? Important points to consider
  - a. The duration of the test sensitive period, and how early an exposed animal becomes test sensitive
  - b. Does test sensitivity correlates well with infectiousness (ideally, would only want to pick up those that are infectious or would become infectious and/or present a risk to human health)
  - c. What is the practical frequency of usage of the test? E.g. if a tested animal cannot be effectively retested for several months, this may



people engaged in a proper dialogue with the local population, rather than simply 'studying' them.

The polarised debate such as the one that centres around bovine TB in Great Britain, a proper understanding of the drivers of behaviour and why people make the decisions they do is a vital step forward, though one that all too often we fail to make. Outside of GB, the problems associated with this debate are difficult to understand (*though the behaviour is typical of many polarised debates, and probably the nature of the conflict is fundamental to aspects of human nature*) but is viewed seriously by at least a segment of the British public and as such must be taken seriously by those responsible for control of the disease. It was also suggested by the moderator (RRK) that the nature of the argument put to farmers to 'sign up' to control may itself be viewed as irrational – compliance is expected of farmers for policies which do not represent 'good value' for farmer interests in that the disease does not appear to be a major health or economic concern except as this is related to legislative needs, as opposed to issues of animal health and welfare. It was noted, however, that cessation of control (and the concomitant increase in cattle bTB that would result) would result in an increase in human bTB cases, most likely in the farming community and amongst veterinarians.

#### Specific comments

1. Any approach to control will need to be 'farmer owned' (*or at least positively engaged with by farmers*) – this requires that farmers be incentivized to participate in control.
  - a. There was some call for the deregulation of TB control, effectively placing it in the hands of the farmers. This would represent a radical departure from current approaches, but one that already finds favour in some sectors
  - b. It may be possible to take a middle road, where government continues to mandate activity, but the approach is "farmer owned" (government says what but not how to do it)
  - c. Deregulation could result in an increase in the overall infection pressure, with increased exposure of the human population and therefore we could observe increased zoonosis
2. The veterinary profession, while critical to the process of controlling disease, may have a conflict of interest as bTB testing (in GB at least) forms a steady source of income
3. If transmission is (at least partly) behaviour driven, any change in policy and its impact on behaviour, may have unintended consequences
4. Perception is as important as reality, and education on biosecurity risks and other factors will be an important component of engaging with the farming community
5. Any changes must consider not just direct monetary costs but other costs
6. What do we need to know about farmers?
  - a. Variation in behaviour
  - b. Need to know what is actually being done, not just what researchers and policy makers want to hear
  - c. What are attitudes to not just the disease and its implications but also to bTB control?
  - d. Need to know more about the ends of the behavioural spectrum: why are the compliant compliant, and the risk takers risk takers?
  - e. How important are risk takers, *and can either extreme types 'nudge' others to behave similarly?*

- f. Does science matter, or is the scientific evidence irrelevant to the ways farmers and vets (and policy makers) behave? What is the trust in the scientific agenda?
- b) Need to understand fundamental aspects of current controls – what does a +ve test really mean
- c) Is there a social stigma attached with a herd breakdown? Distinguishing between having a breakdown and being a risk to others is important and may require different approaches to management
- d) Not just farmers but all stakeholders need to be understood and engaged
- e) How do we go about identifying farmer behaviour?
  - i. Look at 'focus' groups
  - ii. Everyone has an agenda
  - iii. What do we need to know?
  - iv. Perception of risk
  - v. Effect of intervention
  - vi. Need to avoid fuzzy questions
  - vii. Extrapolation from surveys is difficult
  - viii. Take a participatory approach between and amongst groups
  - ix. Do we need better interrogation techniques
  - x. Learn from other fields
  - xi. Consider both risky and protective behaviour – what are the existing drivers, and how can we get fewer/more farmers to practice them?

III. Whole Genome Sequencing (WGS) – what could it do? The final session on whole genome sequencing started with a framing talk by Michael Deason from University of Glasgow, UK, who discussed the results of some preliminary studies in Northern Ireland. These studies showed that – individual-to-individual transmission could not be tracked very often due to the very few observed mutations, but often differences between outbreaks in individual herds could be distinguished. Further, there was a close relationship between types in cattle and local badgers. Spatial patches of similar genotypes were observed, leading to a hypothesis that bTB persistence occurs through the establishment of local patches of infection, which then are spread through longer distance jumps – thus, there are at least two processes driving transmission and persistence. The framing talk was followed by a brief overview by RRK, who put forward the argument that use of this technology is becoming very inexpensive, and main form the basis for a paradigm shift in how we control bTB. The breakout sessions concentrated on ways in which WGS could make a difference.

- 1) A direct estimate of mutation rates could be used to estimate temporal patterns of spread (when did bTB arrive in a region? When was the most recent common ancestor of two lineages of bacteria/when did the lineages diverge?)
- 2) Sampling issues that require considering:
  - (a) Is 40% confirmed reactors (i.e. reactors from which we can currently derive bacteria) dense enough or do we need more?
  - (b) The number of samples per herd tends to be low in general
  - (c) Wildlife under sampling is an issue
  - (d) How expensive would it be to get sufficient samples for epidemiological purposes – *this is dependent on the nature and scale of the question being asked and is especially the case for reservoir hosts (such as the badger) where sample collection may be a particularly difficult problem*



- 3) Possible uses other than contact tracing
  - (a) Identification of much more refined groupings of related infections may have implications for vaccine development, as it may be possible to identify:
    - (i) The existence of superspreaders.
    - (ii) Better targeting of diagnostics, for example using proteomics-based approaches?
    - (iii) Identify important genes.
    - (iv) Look for evidence of BCG attenuation?
  - (b) Anomalous transmission patterns/local scale variation.
  - (c) Genetic population structure at WGS level of hosts and pathogen?
  - (d) Transcriptomics.
- 4) There are also 'obvious' epidemiological uses, that may be proved to be feasible when more data are available – these will inevitably be constrained by considerations of available data (including biases in selected samples) as well as the resolution of phylogenetics and variability in observed mutation rates. Thus this 'wish list' may be modified as more data become available.
  - (a) What does the transmission structure look like in an area with a before a suspected local transmission problem and after it – are there differences in the genetic 'signature' of transmission? *This might for example, take the form of identifying changes in the underlying bacterial population diversity.*
  - (b) There could be a signature associated with a single individual experiencing multiple infection events (within-host diversity) and comparing this to possible epidemiological roles?
  - (c) Mutation rate could be correlated to duration of infection. *Current results would suggest a considerable variability in mutation rate estimates, which may make this difficult.*
  - (d) Variability in mutation rate may be the evidence for environmental survival, if it could be determined that there was a difference in mutation rates for bacteria in host (whatever the stage of the infection) as compared to environmentally persisting bacteria.
  - (e) Clusters of infection could be used to identify "problem herds", that may be responsible for other infections in other herds (either deliberately or inadvertently).
  - (f) Gaps in the phylogenetic signature could identify where there has been transmission but no reactors.
  - (g) The ability of wildlife reservoir hosts to maintain infection on their own could be assessed by comparing relative bacterial population diversities.
  - (h) Better identify adaption and strain selection.
- 5) Some additional points
  - (a) What is a reliable prediction?
  - (b) Ensuring robustness over precision
  - (c) While the bovid genome is likely to be cost effectively sequenced on a regular basis, SNP chips for cows and other hosts could be developed to identify particularly susceptible or infectious groups of animals, for example.
  - (d) Are larger/more complicated models always better?

## Conclusions:

The purpose of this workshop was to bring together a combination of scientists and government representatives with differing points of view by virtue of their training and experience, and across multiple countries and with a variety of bTB-related problems, to establish points of common interest and open up new avenues of thought. The workshop was structured over four sessions. The first two reviewed two important epidemiological considerations across all countries (i) the use of risk-based surveillance to reduce cost/improve detection as this is particularly important for a disease such as bTB, which has a long incubation period and poor diagnostic test (ii) the risks associated with a wildlife reservoir, as exemplified by the situation in Britain and Ireland. Sessions three and four concentrated on (iii) topics identified as important in a questionnaire presented to all participants and (iv) the role that whole genome sequencing of *M. bovis* could play in the control and eradication of bovine TB. The intention of these last two sessions was to open up discussion in a more free-ranging manner.

It is hoped that this workshop will result in further, continued interactions – thus the contents of this document and all presentations will be put up on the University of Glasgow website (<http://www.gla.ac.uk/research/az/boydorr/meetingsevents/2013-bovinetuberculosisworkshop/>), along with contact details of participant members.

## References

- Probst, C., C. Freuling, I. Moser, L. Geue, H. Köhler, F. J. Conraths, H. Hotzel, E. M. Liebler-Tenorio, and M. Kramer. "Bovine tuberculosis: making a case for effective surveillance." *Epidemiology and infection* 139, no. 01 (2011): 105-112.
- Gates, M. C., V. V. Volkova, and M. E. J. Woolhouse. "Impact of changes in cattle movement regulations on the risks of bovine tuberculosis for Scottish farms." *Preventive veterinary medicine* 108, no. 2 (2013): 125-136.

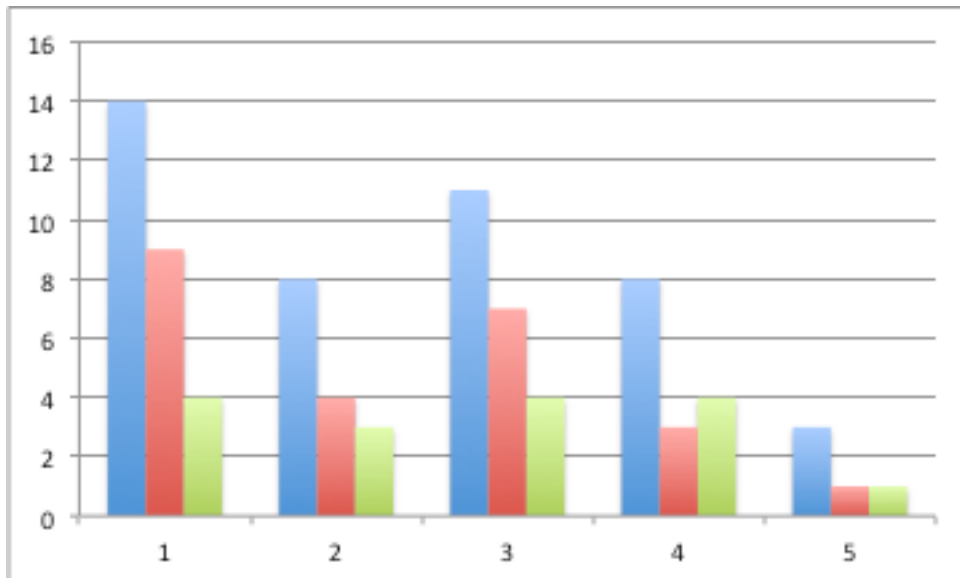
## Appendix – Results of the questionnaire

i) Where would you rank bovine Tuberculosis (bTB) in terms of the most important livestock diseases facing your country<sup>1</sup> today? If it is not first, what would you rank first. By 'most important' we mean in terms of impact on your livestock industry.

UK (1<sup>st</sup>), Non-UK average rank (2.7, under assumption 'low' means '5')

ii) What is your primary concern (if any) regarding current bTB levels in your country or its possible emergence/re-emergence?

1. Wildlife (please specify country and wildlife species)
2. Poor cattle biosecurity
3. Cattle movements (within-country)
4. Cattle movements (international)
5. Other livestock (please specify)

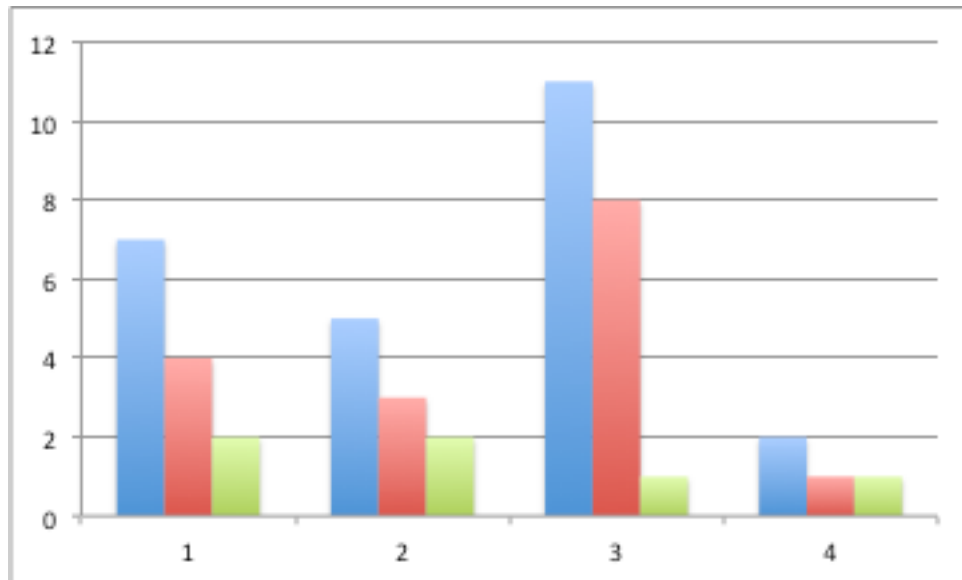


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<sup>1</sup> Here and below we mean your area/country/region of interest with regards to bovine TB – please specify if different from above

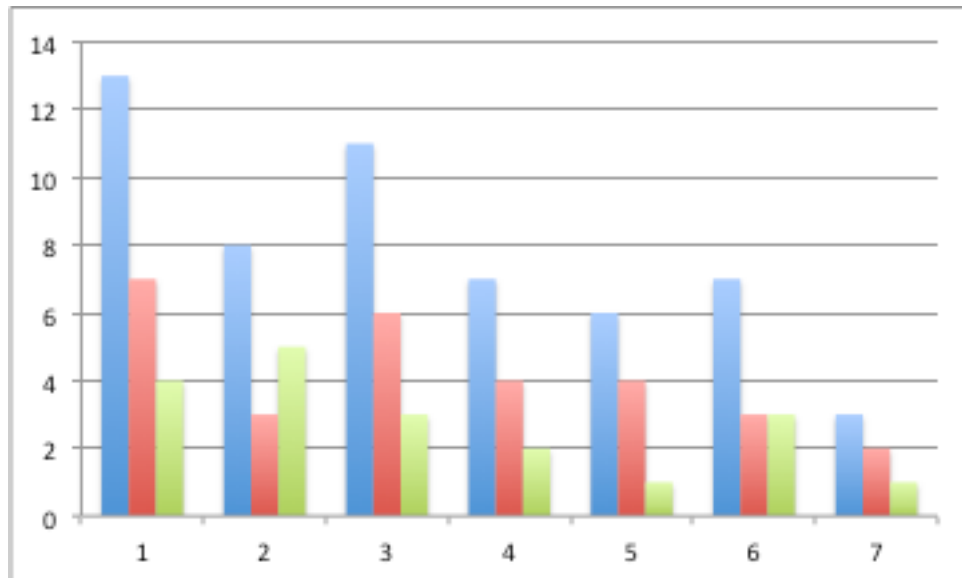
iii) In your view, what is your primary concern (if any) regarding bTB in your country for the future (if different from current concerns, state why)?

1. Wildlife (please specify country and wildlife species)
2. Changes in the cattle industry
3. Prohibitive costs associated with effective disease control strategies
4. Other (please specify)?



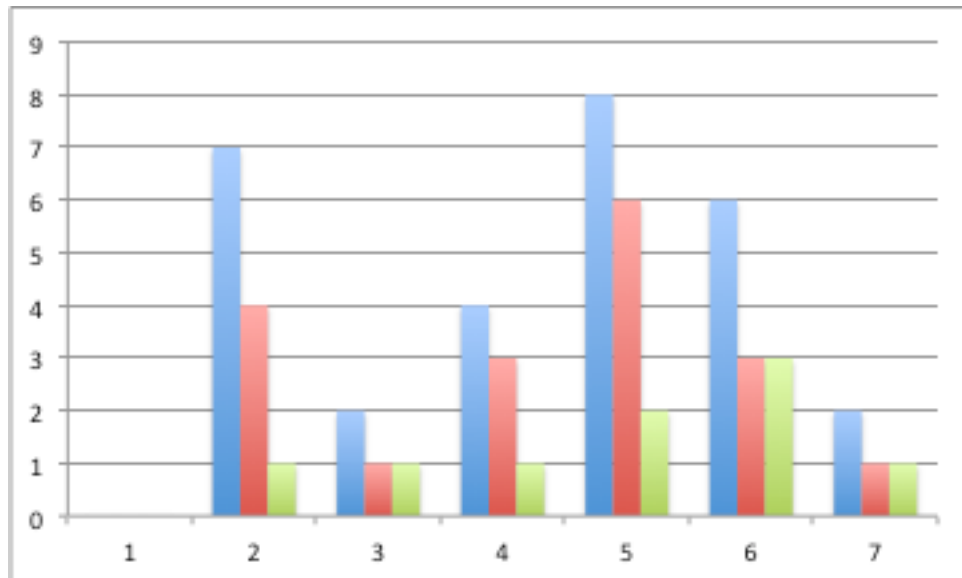
iv) What analytical approaches do you currently use (tick as many as is appropriate)?

1. Frequentist statistics
2. Bayesian statistics
3. Qualitative risk assessment
4. Quantitative risk assessment
5. Mathematical models (analytical)
6. Simulation models
7. Other (please specify)



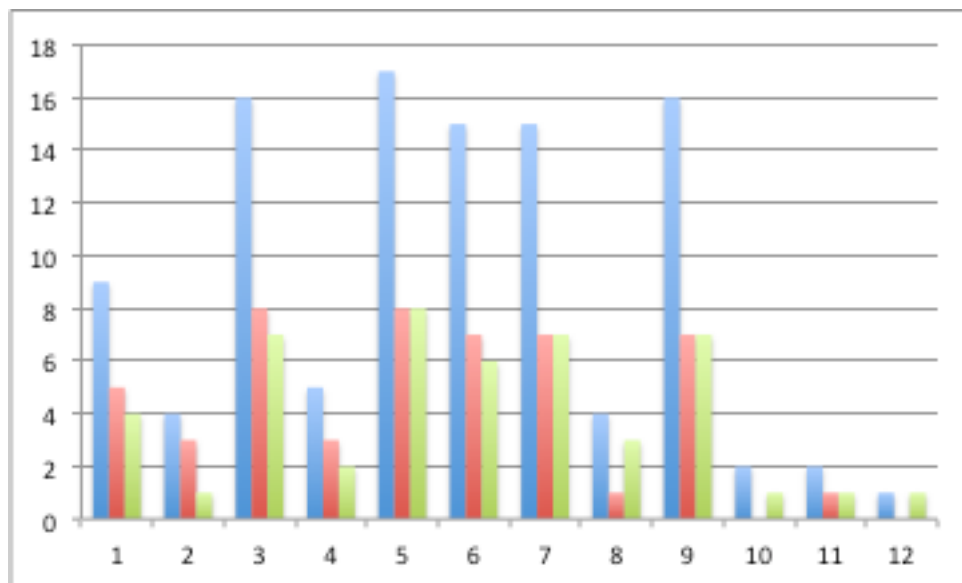
v) What additional tools would be most useful to you now?

1. Frequentist statistics
2. Bayesian statistics
3. Qualitative risk assessment
4. Quantitative risk assessment
5. Mathematical models (analytical)
6. Simulation models
7. Other (please specify)



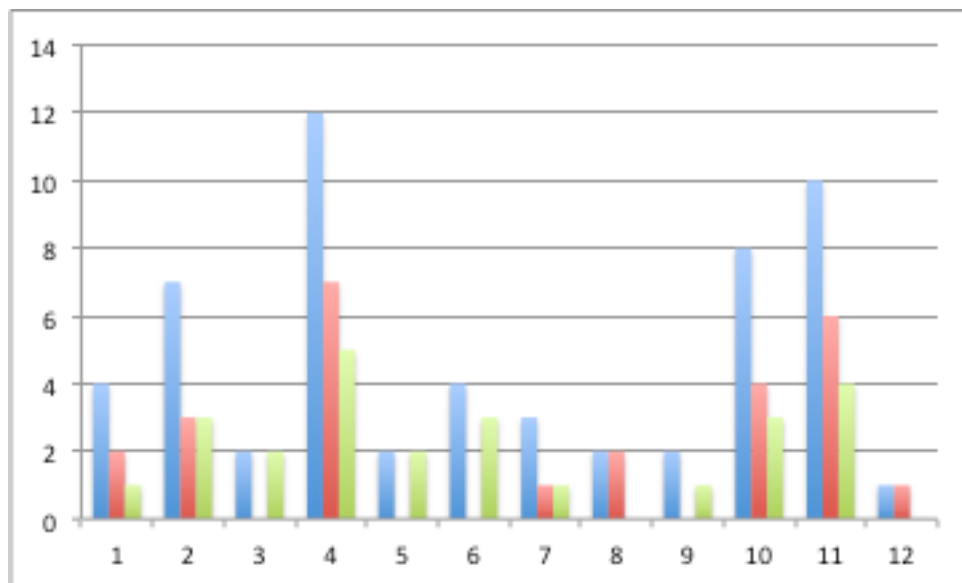
vi) What types of data are available and useful to you now?

1. Wildlife demography
2. Wildlife movements
3. Cattle movements
4. Contact rates between wildlife and cattle
5. Farm locations
6. Abattoir surveillance data
7. Herd test data
8. Herd health/purchase policy
9. Bacterial genotype (e.g. spoligotype and/or VNTR type)
10. Bacterial whole genome sequences
11. Farmer behavioral/economic attitudes
12. Other (please specify)



vii) What additional types of data that could be made available now or in the near future would be most useful to you?

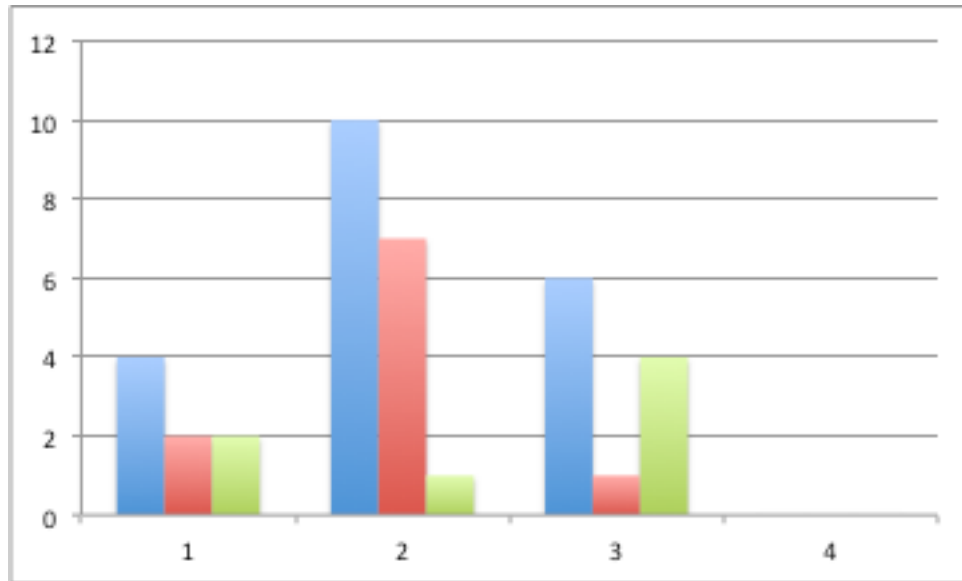
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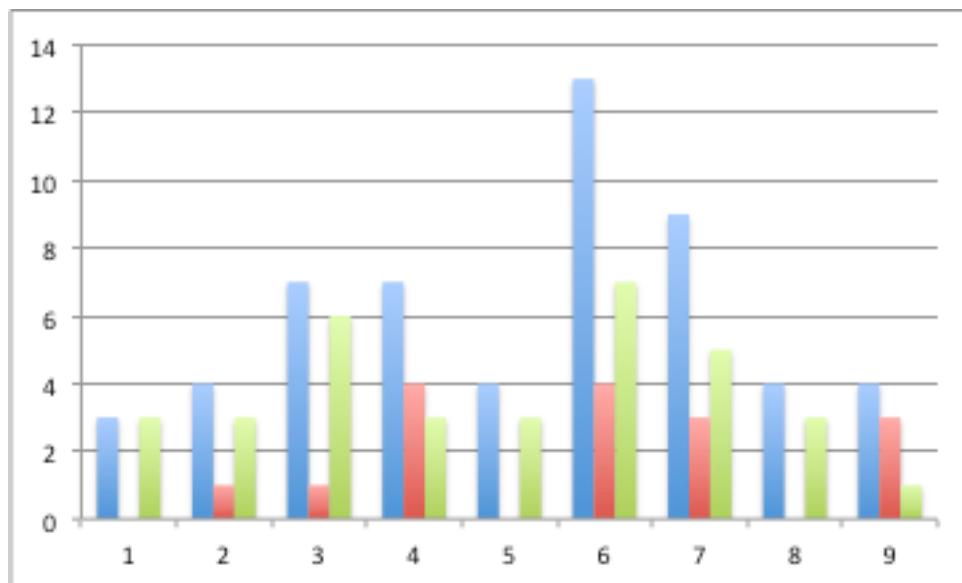
viii) In terms of cost/benefit, what is the primary improvement that could be made regarding bTB *surveillance* in your country?

1. Better testing regime
2. Improved test sensitivity
3. Abattoir surveillance
4. Other (please specify)



ix) In terms of cost/benefit, what is the primary improvement that could be made regarding bTB eradication in your country

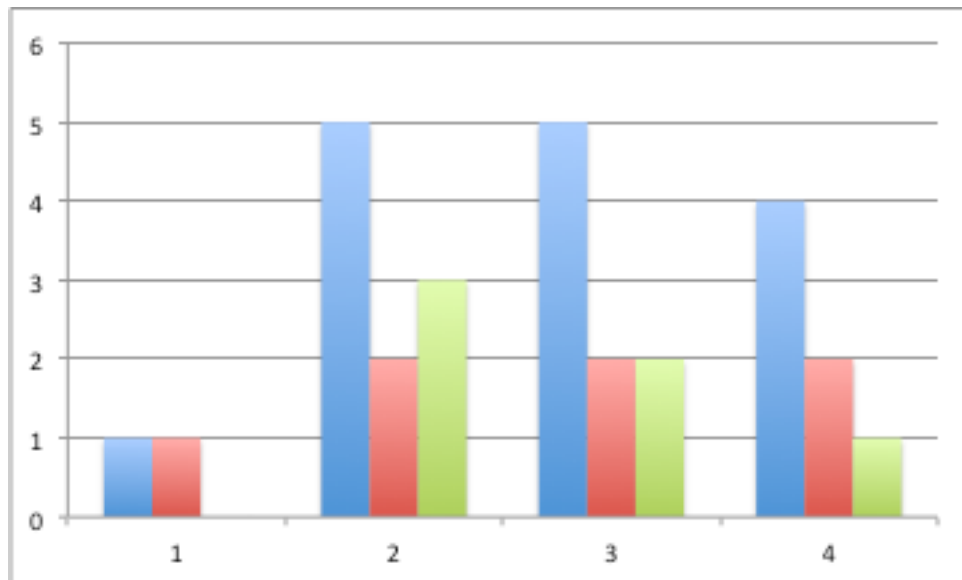
1. Testing regime
2. Biosecurity (on-farm)
3. Biosecurity (between-farm)
4. Biosecurity related to cattle
5. Biosecurity related to people
6. Biosecurity related to wildlife
7. Test sensitivity
8. Abattoir surveillance
9. Other (please specify)



x) In your view, cattle vaccination will be a viable epidemiological tool in

1. 1 year
2. 5 years
3. 10 years
4. 10+ years?

(please also state any key issues)



Key issues stated:  
Legislative  
DIVA tests

xi) Open responses (answer up to all 4): what technological advances do you most anticipate as being useful to you in the next

- a. 1 year
- b. 5 years
- c. 10 years
- d. 10+ years?

**1 year**

WGS (five)

Better diagnostics (three)

Unified/better databases (two)

**5 years**

vaccines (four)

data manipulation/integration (three)

transcriptomics/proteomics (metabolomics?)

**10 years**

vaccines (four)

DIVA

Breeding resistant cattle

**10+ years**

None

xii) Open response: if you were to identify the single most important scientific question you would have regarding bovine TB epidemiology or related bTB issues, what would that be?

Relative roles of cattle and wildlife better defined (4)

Understanding of the ecology of bTB (2)

The role of the farmer (socio-economic factors) (2)

Development of early detection methods

bTB is only a problem because we've made it one (various people in various places)