Institution:
University of Cambridge

Unit of Assessment:
UoA6

Title of case study:
Improving use of available controls against bovine tuberculosis

1. Summary of the impact (indicative maximum 100 words)

Despite increasing surveillance, outbreaks of bovine tuberculosis (bTB) in the UK have steadily increased over the past two decades, with the disease now costing an estimated £100 million per annum in test and slaughter costs, and compensation payments.

Research by Professor Wood and Drs McKinley and Conlan has determined that successful control efforts will depend upon within-herd surveillance and also on reducing reintroduction from external sources; these results have directly altered the Department of Environment, Food and Rural Affairs' (Defra) new (July 2013) bovine TB strategy for England, which directly cites Dr Conlan's research when justifying changes in proposed regulations. On publication this research prompted questions during bovine Tuberculosis debates in both Westminster and the Scottish Parliament by Andrew George (MP, St. Ives) and Helen Eadie (MSP, Cowdenbeath) respectively. The work has also received national and specialist media coverage raising public awareness and understanding of bTB control in cattle.

2. Underpinning research (indicative maximum 500 words)

The research was led by Professor James Wood (employed Jan 2005, Professor since Oct 2008), in the Disease Dynamics Unit (DDU) of the Department of Veterinary Medicine, University of Cambridge, into the dynamics of infectious disease spread and control. Dr McKinley joined DDU in 2006, and Dr Conlan in 2008, both initially as research associates; both have now gained independence since 2011 having written successful grant applications as named post-doctoral scientists. Dr Brooks-Pollock joined the department/ Wood's group in 2011 funded by the EPSRC post-doctoral fellowship above. The underpinning research focussed on the dynamics of and the role of demography in the silent spread of bTB in cattle in the UK, in the face of stringent statutory controls in British cattle herds, and how this could best be addressed.

Wood's work on bTB began when he was approached by the then Veterinary Laboratories Agency to participate in the DEFRA-funded project 'Bovine Tuberculosis: the problem herd' and built on a long-standing interest in the dynamics of disease transmission and control. As part of this project, which ran from 2007 to 2011, Professor Wood's team initially undertook a series of statistical epidemiological analyses using previously collected farm management data, with the aim of determining why bTB persisted in approximately one third of herds for at least 240 days following an initial positive test[1]. Earlier published studies had attempted to identify bTB risk factors, but had not considered whether farm-level characteristics had an impact on the duration of an outbreak ('breakdown'). McKinley and Wood's novel approach, focussing on why some breakdowns persist, demonstrated that confirmation of infection (via post-mortem following culling after a positive test) was a strong indicator for breakdowns that became prolonged[1]. Further analyses explored likely risk factors for within-herd recurrence within 12 months of release from controls (23% of breakdowns were recurrences within this period); this demonstrated that the number of initial positive test reactors and the herd's prior bTB history were the most important factors in predicting recurrence, and concluded that effective control measures needed to consider the possible contribution of local residual infection (via within-herd persistence in cattle or re-introduction from external sources such as wildlife)[2]. Previously, controls had not assumed that some infection was missed. The team also established, by reanalysing data from the Randomised Badger Culling Trial (RBCT), that 'proactive' badger culling was associated with a reduction in disease recurrence on cattle farms[5].

In parallel, McKinley led a study that re-examined the sensitivity of the primary bTB screening test used in Britain and Ireland; previous studies had compared positive reactors to the test with post-mortem data from the same, but had not included post-mortem data from skin test negative animals, which complicated interpretation of test characteristics. The inclusion of test-negative data

in McKinley's study provided results consistent with previous published estimates, confirming that the live animal test failed to detect 5-25% of all 'confirmed' infected animals[3], and illustrated that recurrent breakdowns could originate from undetected infected cattle within the herd, with associated implications for the overall national testing regime; currently, ~50% of released herds suffer a recurrence of infection within 3 years. The significance of missed infection is evident from the fact that 25% of herd breakdowns are now detected in slaughterhouses in carcases from apparently healthy animals at routine meat inspection; this figure has increased substantially over the last 15 years.

Conlan, McKinley and Wood developed robust within-herd mathematical transmission models[4] to quantify the contribution of such undetected infected cattle on rates of recurrence within herds. Novel Bayesian methods were developed and used to estimate this hidden burden of infection from measures of within-herd bTB persistence using data from all newly infected herds in Britain in different incident areas. The models suggest that up to 21% of herds might harbour undetected infection, providing a first true estimate of the quantity of infection missed by cattle testing and the possible contribution of this to within-herd persistence[4]. The work also established a non-linear increase in transmission rate of bTB with herd size, suggesting that control is likely to be more difficult in these herds. Conlan concluded that up to 50% of recurrent breakdowns were attributable to missed infection in cattle[4]. However, the work also identified that rates of re-introduction from external sources were sufficiently high that eliminating the hidden burden of infection would not noticeably reduce rates of recurrence.

3. References to the research (indicative maximum of six references) (Cambridge DDU members in bold)

1. **Karolemeas, K., McKinley, T.J**., Clifton-Hadley, R.S. Goodchild, A.V., Mitchell, A., Johnston, W.T., **Conlan, A. J. K.,** Donnelly, C. A. & **Wood, J.L.N.** (2010) Predicting prolonged bovine tuberculosis breakdowns in Great Britain as an aid to control. *Preventive Veterinary Medicine* **97**:183-90
2. **Karolemeas, K., McKinley, T.J.,** Clifton-Hadley, R.S. Goodchild, A.V., Mitchell, A., Johnston, W.T., **Conlan, A. J. K.,** Donnelly, C. A. & **Wood, J.L.N.** (2011) Recurrence of bovine tuberculosis breakdowns in Great Britain: risk factors and prediction. *Preventive Veterinary Medicine* **102**:22-29
3. **Karolemeas, K.,** de la Rua-Domenech, R., Cooper, A.V., Goodchild, A.V., Clifton-Hadley, R.S., **Conlan, A.J.K.,** Mitchell, A., Hewinson, G., **Wood, J.L.N., McKinley, T.J.** (2012) Estimation of the *relative* sensitivity of the comparative tuberculin skin test in tuberculous cattle herds subjected to depopulation. *PLoS ONE* **7**: e43217
4. **A.J.K. Conlan, T. J. McKinley, K. Karolemeas, E. Brooks-Pollock,** A.V. Goodchild, A. P. Mitchell, C.P.D. Birch, R.S. Clifton-Hadley, **J.L.N. Wood** (2012) Estimating the hidden burden of bovine tuberculosis in Great Britain. *PLoS Computational Biology* **8**: e1002730
5. **Karolemeas, K., McKinley, T.J., Conlan, A. J. K.,** Clifton-Hadley, R.S., Mitchell, A., Upton, P., Donnelly, C. A. & **Wood, J.L.N.** (2012) The effect of badger culling on breakdown prolongation and recurrence of bovine tuberculosis in cattle herds in Great Britain. . *PLoS ONE* **7** (12), e51342

Major relevant sources of funding: (all to Wood as PI unless otherwise indicated)

- *Bovine Tuberculosis: the problem herd* (2007-2011). DEFRA (joint with Clifton-Hadley, VLA) £195,000
- *A longitudinal model for the spread of bovine tuberculosis* (2011-2014). BBSRC, £294,133 (currently provides salary support for McKinley)
- *How do life histories and changing demographics affect tuberculosis dynamics and control?* (2011-2014) Personal EPSRC post-doctoral fellowship to Dr Ellen Brooks-Pollock
- *A study to model vaccination of cattle with BCG at a herd level*. (2011-2013) DEFRA (joint with VLA) £271,246 (currently provides salary support for Conlan)
- *A study to identify factors associated with the detection of new TB breakdowns via abattoir surveillance in GB (2013-2015)* Defra £323,596

4. Details of the impact (indicative maximum 750 words)

Impact on Defra policy

The greatest research impact achieved by this work has been the provision of evidence-based scientific advice to HM Government that has led to a modification in Government Policy and increased awareness of the efficacy of current cattle-based controls for bTB[A]. Providing a first estimate of the contribution of missed infection to the on-going epidemic has stimulated the debate and public understanding of cattle controls, leading to questions being raised in both the Scottish Parliament[B] and Westminster[C,D]. The draft strategy for Achieving "Officially Bovine Tuberculosis-Free" status for England[E] (Published 4th July 2013) uses our research to justify strengthening herd level control policies in both high and low risk areas – and in the edge area between them.

The close working relationships fostered between the DDU, Defra and the Animal Health and Veterinary Laboratories Agency (AHVLA) from the outset of 'the problem herd' project, based around a 'pathways to impact' approach, has enabled the group's subsequent scientific outputs to be tailored towards the needs of policy development from the start. Thus, the combined research outcomes of the work described in section 2 have provided the robust body of evidence that has quantified the effectiveness of Defra's cattle control strategies for bTB clarifying where improvements need to be focussed. It also demonstrated that outbreak persistence has most likely resulted from reintroduction of infection from extrinsic sources. DEFRA has recognised the profound implications for policy. For example, much bTB research in the UK in recent years has been focused on the development of new diagnostic tests in order to increase bTB detection rates within affected herds, e.g. the gamma-interferon test. These results have demonstrated that the potential for improvement in the resolution of bTB incidents from novel tests is severely constrained by a high rate of re-introduction of infection into herds. Clearing infection from herds will therefore only have limited impact if we do not also reduce the exogenous exposure of herds to infection.

In terms of overall engagement with policy makers, Professor Wood and colleagues have presented to the following Defra TB committees:

- TB Eradication Group, 16/11/2011 (at the time the highest non-ministerial Defra TB committee, but now superseded by TBEAG). Public minutes are available [F]
- Defra's Epidemiology and Wildlife Risks Policy Advisory Group, 5/08/2011[G]
- Defra's Vaccines Programme Advisory Sub-Group 15/11/2011[G]
- Defra's Diagnostics Programme Advisory Sub-Group, spring 2011[G]
- The TB Eradication Advisory Group for England (TBEAG)[H]

The models developed in this research have further translational benefits beyond the confines of GB policy, being easily adaptable when applied to novel populations in order to quantify the differences in bTB epidemiology in different ecological contexts. This has been demonstrated by Wood and Conlan being commissioned by Northern Ireland (NI) policy makers to model within-herd and extrinsic transmission of bTB in NI; this work is due to start in spring 2014[J].

Public understanding of bTB control in cattle

This work, especially that published by Conlan *et al* (2012), has stimulated significant public debate and thereby increased public understanding of the disease and its control. As well as direct questions in Westminster and the Scottish parliament, the paper was the subject of press releases from Defra, the Badger Trust[I], PLoS and the University of Cambridge. In addition to the subsequent media coverage there was discussion on social network sites, including Twitter (with the paper being tweeted over 50 times).[K,L,M,N]

Experts taking up specialist advisory roles

The importance of the DDU's work in a policy-making context has been further exemplified by the invitation extended to Professor Wood to sit as the sole independent scientist on Defra's new TB Eradication Advisory Group for England (TBEAG)[H]. TBEAG's remit is to advise the Animal Health and Welfare Board for England and Defra ministers on the development and implementation of the strategy for eradicating bTB; it was set up following a review of its predecessor (TBEG), which found, amongst other things, that scientific input into bTB eradication policy should be

strengthened.

This continuous process of engagement has been central to the use of our research in the formulation of the new Defra strategy for bTB control in cattle in England and Wales[D] (published July 2013), which draws extensively on our work (particularly Conlan *et al*. 2012).

5. Sources to corroborate the impact (indicative maximum of 10 references)

[A] Letter of support from Head of Bovine TB Science, Animal Health and Veterinary Laboratories Agency (AHVLA), Department for Environment, Food and Rural Affairs (Defra).
[B] http://www.scottish.parliament.uk/S4_ChamberDesk/WA20121109.pdf
[C] http://www.publications.parliament.uk/pa/cm201213/cmhansrd/cm121025/debtext/121025-0002.htm
[D] http://www.publications.parliament.uk/pa/cm201213/cmhansrd/cm121026/text/121026w0001.htm
[E] https://consult.defra.gov.uk/farming/tb/supporting_documents/Draft%20%20Strategy.pdf
[F] http://archive.defra.gov.uk/foodfarm/farmanimal/diseases/atoz/tb/partnership/eradication-group/meetings/documents/tbeg-highlight-report-111116.pdf
[G] http://archive.defra.gov.uk/foodfarm/farmanimal/diseases/atoz/tb/tb-sab/members.htm
[H] https://www.gov.uk/government/policy-advisory-groups/bovine-tb-eradication-advisory-group-for-england
[I] Letter of support from a veterinary epidemiologist, Department of Agriculture and Rural Development, Northern Ireland (filename)
[J] http://www.badger.org.uk/DocFrame/DocView.asp?id=725
[K] http://www.fwi.co.uk/articles/19/10/2012/135812/scientists-reveal-the-hidden-burden-of-bovine-tb.htm
[L] http://www.healthline.com/health-blogs/study-roundup/england-cattle-bovine-tuberculosis-101812
[M] http://www.rethinkbtb.org/blog.html#home
[N] Archive of Tweets from 24th October 2012 (Tweets24thOctober2012.xls)