Institution: University of Cambridge

Unit of Assessment: 6

Title of case study: Changes in policy for the control of bovine tuberculosis

Period when the underpinning research was undertaken: 2007-2019

Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Andrew JK Conlan	University Senior Lecturer in Epidemiology	2006 – present
James LN Wood	Head of Department of Veterinary Medicine and Alborada Professor of Equine and Farm Animal Science	2005 – present

Period when the claimed impact occurred: 01 August 2013 – present

Is this case study continued from a case study submitted in 2014? N

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

Bovine tuberculosis (bTB) is a global disease that is economically draining to control and threatens human health. Research at the University of Cambridge has directly informed policy decisions relating to the control and surveillance programmes of bTB in the UK and Ethiopia. The research sculpted the future direction of vaccination policy and delayed the implementation of cattle vaccination in the UK, which saved at least GBP120,000,000 of public money. The work has also led to improved surveillance of bTB in English slaughterhouses. Through sustained engagement and collaboration, Cambridge research has contributed to greater availability of high quality bTB testing in Ethiopia, through specially trained staff and testing teams, and establishment of the country's first ministerial group to lead national efforts in overcoming bTB.

2. Underpinning research (indicative maximum 500 words)

Bovine tuberculosis (bTB) is a significant bacterial disease in the UK and globally. It is infectious and contagious, with two main reservoirs (cattle and badgers). The disease threatens the cattle industry and presents risks to other livestock, wildlife and domestic pets. bTB in animals can also threaten human health, although the widespread pasteurisation of cows' drinking milk and milk products largely protects the public from undisclosed cases of bTB in cattle (source: UK Government Animal and Plant Health Agency, online). Globally, no bTB vaccine is licensed for use in cattle. The problem is that at present it is impossible to distinguish between a vaccinated and TB-infected cow and a positive result in the standard diagnostic skin test acts as the legal definition of a TB infection, even if induced by vaccination.

Modelling the suitability of cattle vaccination as a supplement to existing test-and-slaughter control
Conlan and Wood have worked closely with bTB policy teams in Defra since 2007 with a series of Defra-funded projects; since 2012 they have developed mathematical models for the transmission of bTB within herds in Great Britain, providing a shift in the level of statistical rigour applied to policy approaches and offering insights into the epidemiology of bTB. These models were used to publish the first estimates of cattle-to-cattle transmission of bTB in the UK [R1].

Between 2011 and 2013, the cattle-to-cattle transmission models developed by Conlan and Wood were extended to explore cattle vaccination as a supplement to existing test-and-

slaughter control. Vaccination is known to interfere with the standard diagnostic tests for bTB because it is impossible to tell whether a positive result is due to the vaccine or a true infection. There was an acknowledged need for a test that Distinguishes Infected from Vaccinated Animals (DIVA); none are currently licenced.

Developing cattle vaccination is central to UK government strategy for bTB control. However, under current national and international trading regulations the UK government will only consider vaccination as a supplement, rather than a replacement, to test-and-slaughter. Most of the economic costs associated with bTB in the UK come from testing and restrictions, rather than disease losses, therefore Conlan and Wood's models demonstrated that there was no economic benefit of vaccination without an accurate DIVA test [R2].

Subsequently, in 2014 Conlan and Wood were part of a Defra-funded tender led by Triveritas management (a commercial organisation providing veterinary good clinical practice regulatory studies) to calculate the size and scale of field trials necessary to satisfy the EU's requirements for allowing use of a cattle vaccine. The models showed that demonstrating a protective benefit from the vaccine in individual cattle could be achieved by a trial of ~100 herds. However, satisfying the EU's requirement that trials could estimate an impact of vaccination on reducing transmission of infection would require far larger, and frankly unaffordable, trials (of the order of ~1000 herds). As an invited member of a follow-on working group, Conlan developed cheaper experimental designs to evaluate this key requirement from the EU, namely a three arm design which includes fully vaccinated, partially vaccinated and unvaccinated control herds [R3].

Operational models to rank the effectiveness of slaughterhouse surveillance for bTB in Great Britain
In 2018 Conlan, Wood and collaborators developed the first operationalised model to rank the effectiveness of slaughterhouse surveillance for bTB in Great Britain [R4]. The model identified large geographic variations in the effectiveness of slaughterhouse surveillance and offered the ability to prioritise further investigation to slaughterhouses that had unusually high or low rates of bTB.

Bovine tuberculosis in Ethiopia
Since 2014, Conlan and Wood have led major programmes of underpinning research on the epidemiology, spread and control, including social and political aspects, of bTB in Ethiopia using mathematical modelling and analyses of whole genome sequences of *Mycobacterium bovis* from cattle and humans. Their research has demonstrated that the prevalence is high, if highly variable between regions, with a herd prevalence of 22.4% (95% CI: 17-29%) outside Addis Ababa in Ethiopia [R5].

3. References to the research (indicative maximum of six references)

R1. *****Conlan, A. J. K.**, McKinley, T. J., Karolemeas, K., Pollock, E. B., Goodchild, A. V., Mitchell, A. P., . . . **Wood, J. L. N**. (2012). Estimating the hidden burden of bovine tuberculosis in Great Britain. *PLoS Comput Biol*, *8*(10), e1002730. doi:10.1371/journal.pcbi.1002730

R2. *****Conlan, A. J. K**., Brooks Pollock, E., McKinley, T. J., Mitchell, A. P., Jones, G. J., Vordermeier, M., & **Wood, J. L. N**. (2015). Potential benefits of cattle vaccination as a supplementary control for bovine tuberculosis. *PLoS Comput Biol*, *11*(2), e1004038. doi:10.1371/journal.pcbi.1004038

R3. *****Conlan, A. J. K.**, Vordermeier, M., de Jong, M. C., & **Wood, J. L**. (2018). The intractable challenge of evaluating cattle vaccination as a control for bovine Tuberculosis. *Elife*, *7*. doi:10.7554/eLife.27694

R4. *McKinley, T. J., Lipschutz-Powell, D., Mitchell, A. P., **Wood, J. L. N., & Conlan, A. J. K**. (2018). Risk factors and variations in detection of new bovine tuberculosis breakdowns via slaughterhouse surveillance in Great Britain. *PLoS ONE*. **13** (6), e0198760

R5. *Mekonnen, G.A., **Conlan, A.J.K.,** Berg, S., BT Ayele, A Alemu, S Guta, M Lakew, Tadesse,B., Gebre, S., **Wood, J.L.N.** & Ameni, G. (2019) Prevalence of bovine tuberculosis and its associated risk factors in the emerging dairy belts of regional cities in Ethiopia. *Preventive veterinary medicine* **168**, 81-89

*The above publications were peer reviewed

Competitive funding secured
- ETHICOBOTS – Ethiopian control of bovine tuberculosis strategy. Wood, Hewinson, Conlan *et al*, ZELS (DfID, BBSRC, ESRC), 2014-2020, GBP2,900,000
- ETHICOBOTS2, Research to Impact. Wood, Hewinson, Conlan *et al*, ZELS (DfID, BBSRC, ESRC), 2019-2021, GBP476,000
- Accelerating Bovine TB Control in Developing countries, Kapur (PI), Conlan, Wood et al, Bill & Melinda Gates Foundation, 2017-2022, GBP2,051,534
- A study to identify factors associated with the detection of new TB breakdowns via abattoir surveillance in GB. Wood *et al*, Defra SE3133, 2013-2016, GBP323,596
- The identification of bTB at slaughter - developing annual monitoring of Slaughterhouse performance Conlan *et al*, Defra SE3137 - 2016-2017, GBP56,671

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

Bovine tuberculosis is a substantial economic and animal welfare problem. The UK government spends ~GBP100 million annually on bTB control, with costs to industry estimated to be a further GBP50 million [E1, page 13]. As a member of OIE (World Organisation for Animal Health), the UK is required to have a bTB eradication plan. Modelling work undertaken at the University of Cambridge has led to the following impact:

Influencing high-level policy direction in the UK
Conlan and Wood have engaged closely with government advisory bodies that formulate or challenge government policy in England: Wood as part of Defra's TB Eradication Advisory Committee the independent review committee in 2018, chaired by Professor Sir Charles Godfray [E2], and Conlan on a group examining vaccination strategies. In 2014, their research was cited as part of the evidence for the government's epidemiological rationale in the Defra's Strategy for achieving Officially Bovine Tuberculosis Free status for England [E3, page 57], which rejected a "one size fits all approach" and set targets to measure progress. Wood's research was also cited in a Parliamentary debate on 13 March 2014 by a Liberal Democrat MP, highlighting the issue of latent TB in cattle and suggesting a change in focus regarding strategies [E4]. At this point, badger culling as a means to tackle TB was not seen as publicly acceptable, with the government looking to vaccination as a desirable alternative.

Changes to vaccination strategy in England
Conlan and Wood's evaluation of BCG vaccination in cattle (R2) suggested that field trials would have to be on a massive scale, but at the point when Defra commissioned their analysis in 2014, led by Triveritas, extensive field trials were still expected to start in 2015. This was in line with the 2014 Strategy for achieving Officially Bovine Tuberculosis Free status for England, in which the Secretary of State for Environment, Food and Rural Affairs committed to an investment of GBP24.6 million in the development of effective TB vaccines for both cattle and badgers [E3]. The Triveritas study estimated that the cost of the field trial then proposed would be as much as GBP120,000,000, with additional costs of [text removed for publication] for implementing any vaccination programme [E5].

These results had an immediate impact on Defra policy: to indefinitely delay implementation of cattle vaccination. This saved public money through stopping impossibly large field efficacy trials and through providing clear evidence that DIVA tests had to be improved before vaccination could be rolled out. It also prompted a longer-term change of focus on the specificity (the ability to detect a true negative) of the replacement DIVA test, rather than sensitivity (the ability to

detect a true positive), which had previously been the priority [E1]. In a statement on 18 December 2014, the Secretary of State for Environment, Food and Rural Affairs said, "[The] report…shows that before cattle vaccination field trials can be contemplated, we need to develop a better DIVA test. This research is likely to take a further two years." [E6]

The senior policy adviser from Defra's Bovine TB Programme states that the evaluation report, and Conlan and Wood's 2015 paper (R2), *"contributed to a change of emphasis from vaccination assessment to the validation of new diagnostic (DIVA) tests. By understanding the scale of trial needed to confirm efficacy, we were able to prevent costly, complex action that would not have resulted in demonstrable lowering of disease. In real terms, this translates as preventing government expenditure and saving an estimated* [text removed for publication] *of public money."* [E7]

The 2018 Bovine TB strategy review [E2] cited Wood and Conlan's research, noting that *"Existing surveillance regimes underestimate the prevalence of the disease in cattle in England and this hinders control."* [E2, page 32, cites (R1)]

It goes on to say: "*The* [EU] *Commission indicated the necessity of field trials... However, to obtain sufficient statistical power using this approach would likely require, given the prevalence of bovine TB in England, large-scale field trials which might involve 500 farms over 2 years. This may be unfeasible and equivalent information might be obtained more easily using vaccination and challenge experimentation with approximately 200 individual Animals.*"[E2, page 44, cites (R3)].

The Government response in March 2020 recognised that *"performance of the DIVA test is crucial in enabling BCG vaccination to realise disease control benefits. As well as identifying vaccinated cattle that are truly infected, it is essential that the DIVA test has a high specificity... Field trial designs have been developed to further evaluate the cattle BCG vaccine and DIVA skin test and provide the evidence required for applications for* [Marketing Authorisations] *to be submitted and for the DIVA test to be internationally recognised.*" [E1, page 23]

The Defra senior adviser confirms that *"Research from the University of Cambridge…has played a key role in government understanding of key factors involved in building a diagnostic and vaccination policy for bovine TB, and has directly influenced decisions that have had an important impact on public spending."* [E7]

Identification of slaughterhouses with low rates of bTB detection
The model of slaughterhouse surveillance (R4) was transferred to the Animal and Plant Health Agency (APHA), responsible for bTB control, resulting in implementation of new professional practice to monitor bTB levels. It is run on an annual basis to identify slaughterhouses with unexpectedly low rates of bTB detection, which need further investigation. The Data Systems Group Workgroup Leader at APHA says that this is now an "integral part" of reporting to Defra and enables them to "identify any poor performing slaughterhouses (in terms of their inability to identify bTB infected animals)" [E8]. The Godfray review also cited the research, noting the need for *"raising awareness of its importance with slaughterhouse workers, financial incentives for good practice and more frequent inspection."* [E2, 3.35, page 38].

Introduction of new bTB policy in Ethiopia
In Ethiopia, where the bTB burden is very high in dairy cattle, Wood has been instrumental in the establishment of a steering group, chaired by the Ethiopian state minister, on bTB control; no similar body has existed before. By engaging in a series of focus group discussions with farmers, veterinarians and human health workers in two sites in Ethiopia, Conlan, Wood and collaborators were able to show the need for investment in animal health system strengthening in Ethiopia [E9]. The terms of reference of this Ministerial group in Ethiopia include that it be chaired by the State Minister to lead on national efforts to coordinate control at the national and regional level, a highly significant symbol in the centralised Ethiopian government system. The controls now being developed have a firm base in the work published from the Cambridge

related programmes (R5). There is now much greater availability of high quality bTB testing, through specially trained staff and testing teams in the government agency National Animal Health and Diagnostic Investigation Centre (NAHDIC), which regularly offers advice to farmers around disease control [E9].

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

E1 Department for Environment, Food and Rural Affairs report: Next steps for the strategy for achieving bovine tuberculosis free status for England. The government's response to the strategy review, 2018

E2 Bovine TB Strategy Review October 2018

E3 Defra Strategy for achieving Officially Bovine Tuberculosis Free status for England 2014

E4 Hansard, 13 March 2014, Volume 577 (Badger Cull), 2.15 p.m.

E5 Feasibility study into testing and validating cattle BCG vaccine and DIVA

E6 Statement on bovine TB made by the Secretary of State for Environment, Food and Rural Affairs, 18 Dec 2014

E7 Testimonial from Defra Senior Policy Adviser

E8 Letter from APHA re: slaughterhouse model application (Oct 2020)

E9 Hodge et al. (2020), Acceptability and feasibility of proposed control and prevention strategies for bovine tuberculosis among Ethiopian dairy farmers and associated professionals. Prev. Vet. Med., 185, 105184, DOI: 10.1016/j.prevetmed.2020.105184