Institution: University of Warwick

Unit of Assessment: B10 Mathematical Sciences

Title of case study: Mathematical modelling of livestock infection to inform policy for future epidemics and control of disease outbreaks.

1. Summary of the impact

Mathematical modelling of livestock infections and disease control policies is an important part of planning for future epidemics and informing policy during an outbreak of infectious disease. Researchers in the Mathematics Institute, University of Warwick, are considered to be at the cutting-edge of developing policy-orientated mathematical modelling for a number of livestock infections. Such models have been used to inform government policy for foot-and-mouth disease (FMD) and a range of other infections including bovine tuberculosis (bTB) and bee infections. From 2008, their work with responsible national and international agencies has focused on statistical inference from early outbreak data, formulating models and inferring parameter values for bTB infection spread within and between farms, developing predictive models of FMD outbreaks in the USA, and extending such models to areas where FMD is endemic. This research has helped to shape policy and determined how policy-makers perceive and use predictive models in real-time.

2. Underpinning research

Livestock infections represent a serious threat to the farming industry, national economic prosperity and food security. In the UK alone it has been estimated that livestock infections have cost the economy over £15 billion; hence a quantitative understanding of infection and an ability to predict the impact of control measures is vital. Since the 2001 outbreak of FMD in the UK (which directly affected over ten thousand farms), mathematical modelling and statistical analysis have been viewed as important tools in scenario planning and outbreak control for a range of infectious diseases of livestock. Often, mathematical models are required to untangle the complex trade-offs between control (culling potentially infected animals) and minimising the size of an epidemic – too little culling and the epidemic is uncontained, too much culling and the effect of control could be worse than the infection. Researchers in the Mathematics Institute and Statistics Department at the University of Warwick (Keeling, Tildesley and Roberts) have been involved in the development of new mathematical and statistical tools for tackling such issues. Here, we primarily highlight their work on the transmission dynamics of FMD [1,2,4,5,9,10,13], although we have also worked on, and provided policy-makers with information about, other important livestock infections including bovine tuberculosis [8], avian influenza in poultry [3] and foulbrood in bees [12]. FMD is one of the most highly transmissible of all livestock infections, so rapid, targeted control is required to minimise economic losses. FMD is a worldwide problem and our primary results focus on controlling novel outbreaks in the UK (based on experience in 2001 and 2007 [1,2,4,5] and the USA (where data are more limited) [9,10].

The research from Warwick has pioneered two separate, but related, approaches. First, we have developed Bayesian MCMC (Markov Chain Monte Carlo) techniques to infer underlying model parameters [4,7,11,12]; and second we have constructed a range of mathematical models to elucidate the expected epidemic behaviour and the implications of different control options [1,2,6,12]. Inference of model parameters is vital if models are to be accurately fitted to available data, and confidence in the subsequent predictions is to be assessed. To infer model parameters, and hence plausible mechanisms, for the spread of FMD [4,7] and avian influenza [7,11], we developed novel MCMC methodology. In particular, for a range of diseases it is vitally important to determine occult (undetected and potentially undetectable) infections, and the methods we developed are formulated around determining these hidden case. These techniques are now becoming the accepted state-of-the-art for inference of spatial epidemic data, and we have been applying them to other infections [12].

Mathematical models, by necessity, are formulated to reflect the perceived biological reality and, therefore, differ between particular livestock infections and between different locations. However, work by Warwick researchers from 2008 onwards has focused on two main transmission pathways: local spatial transmission [1,2,5,9] and transmission through the movement of livestock

[6]. Models of local spatial transmission (primarily related to FMD) have been used to investigate a range of control measures (including localised culling [5,10,13,14] and vaccination [1,2]) which provide clear insights into the role of targeted control in livestock disease outbreaks and highlight the importance of local culling as a rapid means of containment. These models have also been used to demonstrate that knowing the exact location of farms may often be unnecessary to determine near-optimal control policies [9] – this has clear importance to countries (like the USA) where such location data is unavailable. Network models have been extensively used to study the spread of infection by movements; our research has highlighted that the dynamic nature of the movements (and the identity of the individual moving) cannot be subsumed in a static network approach but has important epidemiological consequences [6]. These local and network transmission models have been combined to allow us to study the spread and control of avian influenza [11] and foulbrood [12].

Key Researchers at Warwick: Prof. Matt Keeling (Lecturer 2002-05, Reader 2005-08, Professor, 2008-), Prof. Gareth Roberts (Professor, 2006-), Dr Michael Tildesley (Post-doctoral researcher 2003-2008, Warwick Zeeman Lecturer, 2011-2013).

3. References to the research

Publications:

1. **Keeling, M.J.,** Woolhouse, M.E.J., May, R.M., Davies, G. and Grenfell, B.T., Modelling Vaccination Strategies against Foot and Mouth Disease. Nature 421 136-142 (2003) DOI: 10.1038/nature01343
2. **Tildesley, M.J.,** Savill, N.J., Shaw, D.J., Deardon, R., Brooks, S.P., Woolhouse, M.E.J., Grenfell, B.T. & **Keeling, M.J.,** Optimal reactive vaccination strategies for an outbreak of foot-and-mouth disease in Great Britain, *Nature* **440**, 83-86. (2006). DOI: 10.1038/nature04324
3. Savill, N., St. Rose, S., **Keeling, M.,** Woolhouse, M., Silent spread of H5N1 in vaccinated poultry. Nature 442 757-757 (2006) DOI: 10.1038/442757a
4. **Jewell, C.P., Keeling, M.J. and Roberts, G.O.,** Predicting undetected infections during the 2007 foot-and-mouth disease outbreak. J. R. Soc. Interface. 6 1145-1151 (2009) DOI: 10.1098/rsif.2008.0433
5. Tildesley, M.J., Bessell, P.R., **Keeling, M.J.** and Woolhouse, M.E.J., The role of pre-emptive culling in the control of foot-and-mouth disease. Proc. Roy. Soc. Lond. B. 276 3239-3248. (2009) DOI: 10.1098/rspb.2009.0427
6. **Vernon**, **M.C**. and **Keeling, M.J.,** Representing the UK's cattle herd as static and dynamic networks. Proc. Roy. Soc. B. 276(1656) 469-476. (2009) DOI: 10.1098/rspb.2008.1009
7. Jewell, C.P., Kypraios, T., Neal, P. and **Roberts, G.O.,** Bayesian Analysis for Emerging Infectious Diseases. *Bayesian Analysis* 4(3) 465-496 (2009) DOI: 10.1214/09-BA417
8. Brooks-Pollock, E. and **Keeling, M.J.** Herd size and bovine tuberculosis persistence in cattle farms in Great Britain. *Prev Vet. Med*. 92 360-365 (2009)DOI: 10.1016/j.prevetmed.2009.08.022
9. Tildesley, M.J., **House, T.A.,** Bruhn, M.C., Curry, R.J., O'Neil, M., Allpress, J.L., Smith, G. and **Keeling, M.J.,** Impact of spatial clustering on disease transmission and optimal control. Proc Natl Acad Sci USA 107 1041-6 (2010) DOI: 10.1073/pnas.0909047107
10. **Tildesley, M.J.** Smith, G. and **Keeling, M.J.,** Modeling the spread and control of foot-and-mouth disease in Pennsylvania following its discovery and options for control, Prev Vet Med 104, 224–239. (2012) DOI: 10.1016/j.prevetmed.2011.11.007
11. **Jewell, J.C. and Roberts, G.O.,** Enhancing Bayesian risk prediction for epidemics using contact tracing. *BioStatistics* 13(4) 567-579. (2013)DOI: 10.1093/biostatistics/kxs012
12. **Datta, S., Bull, J.,** Budge, G. and **Keeling, M.J.**, Modelling the spread of American Foulbrood in honey bees. *J. Roy. Soc. Interface* 10(88) 20130650 (2013) DOI: 10.1098/rsif.2013.0650

Peer-reviewed grants/awards to Warwick researchers (unless stated otherwise):

13. PI: Keeling “Quantitative analysis of the spatio-temporal dynamics and control of foot-and-mouth disease” Wellcome Trust Oct 2002–Sep 2005 £82,931.
14. PI: Keeling “Preliminary modelling of AI epidemiology and control in the UK” Department for Environment, Food and Rural Affairs (Defra) RMP/2910 Dec 2005–Jun 2006 £40,000.
15. PI: Smith (Penn State University) Co-Investigator: Keeling “Hierarchical models for the spatio-temporal dynamics of infectious diseases” NIH MIDAS Feb 2006–Jan 2010 £217,000 (Warwick component).

16. PI: Keeling "Spatio-temporal dynamics of livestock infections" Wellcome Trust Apr 2006–Mar 2009 £166,432.
17. PI: Roberts "InFER: Likelihood-based Inference for Epidemic Risk" BBSRC BB/H00811X/1. Oct 2009–Jun 2013 £589,005.
18. PI: Keeling "Modelling systems for managing bee disease: the epidemiology of European foulbrood" BBSRC BB/I000615/1 Oct 2010–Sep 2013 £165,362 (Warwick component).
19. PI: Webb (Colorado State) Co-Investigator: Tildesley "Spread of animal disease within US Livestock: improving decisions and interventions" US Department of Homeland Security July 2011-Apr 2013 £126,842 (Warwick component).

4. Details of the impact

The mathematical models and statistical inference techniques developed by researchers at Warwick have been used by the UK government - through Defra and Animal Health and Veterinary Laboratories Agency (AHVLA) - to underpin policy relating to the control of FMD infection, particularly by vaccination. Models of other infections by Warwick researchers have added to the public debate [20] and UK government policy surrounding bTB control transmission and control [21,22,]; the control and containment of avian influenza [21]; and the spread and management of bee infections by the Food and Environment Research Agency (FERA). Since 2008, the FMD modelling framework has been extended to the USA and other countries, and has been presented to different policy groups (such as the US Department of Homeland Security [23] and the European Commission [24]), helping to shape the expectations of what mathematical modelling can achieve during a disease outbreak. We will discuss these three cases in turn.

FMD in the UK

Keeling has worked on mathematical models to predict the spread of FMD in the UK since the devastating FMD outbreak of 2001. Together with Tildesley, these early models have been refined and used to address numerous applied questions about the optimal control of outbreaks. Work since 2008 has focused on the potential benefits of control by localised (contiguous premise) culling and control by vaccination bringing the most impact, and suggested how the optimal use of these methods will vary regionally. Predictions for optimal culling [5] suggest that the number of farms losing livestock could be reduced by over 30%, while targeted vaccination [2] could reduce losses by over 75%; these insights have helped to shape government policy and are factored into current contingency planning. A statement from the Head of Epidemiology at AHVLA/Defra states "their research provides important scientific underpinning of our current FMD contingency plan" [21]. This plan now contains vaccination as a key control measure against new outbreaks and local reactive culling as an important potential method of control as a result of its unpopularity with the farming community in 2001.

Following on from methodological developments in Warwick [4,7], the above modelling is now being underpinned by more rigorous and systematic Bayesian (MCMC) parameter inference, which enables Keeling and Tildesley to rapidly tailor models more readily to any new outbreak. This important innovation means that we can rapidly respond to requests for model predictions from AHLVA/Defra, leading to Keeling being made a member of Defra's Quantitative Modelling Standing Capacity from 2011. In addition, as a component of the inference software Keeling and Tildesley have been working on GIS interface to display current cases and potential future scenarios; AHVLA are "hoping to use the GIS epidemic inference and visualisation software directly produced from the InFER project in [their] livestock epidemic planning and emergency procedures" [21].

bTB in UK

The control of bTB is complicated by the emotive arguments about the role of badgers in its transmission compared to transmission between cattle; despite scientific uncertainty of the role of badgers 2013 saw a large-scale cull of these animals. This contention necessitates a mathematical model that is robustly fitted to data and can elucidate the underlying transmission mechanisms and hence help determine adequate control strategies. Work by Keeling has developed the first national-scale predictive model of bTB that captures the spatial and temporal patterns of bTB in the UK. This model has been under development for several years and Defra have been kept fully informed of its findings; these outcomes have "shaped how Defra consider planning future control options" [21]. Owing to this work, Keeling has been invited to be a member of Defra's 'bTB modelling initiative' (see website and agenda papers where the terms of reference of the group are minuted [22, 25]).

The continuing work in Warwick on modelling livestock epidemics in the UK "forms a valuable part of the scientific underpinning for the policy decisions made on the control of livestock infections" and has been "recognised by Keeling being a member of 'Defra Quantitative Modelling Standing Capacity', to be called upon to provide timely advice in case of an outbreak situation." [21].

FMD in USA and Europe

Previous work on FMD in the USA primarily focused on localised results using complex, parameter-rich models, and hence policy was based around a limited set of potential scenarios. Keeling and Tildesley's parsimonious model with its simpler mathematical formulation has enabled the development of national-scale models that can be parameterised from early epidemic data. Modelling results have been presented to policy-makers at the US Department of Agriculture and Department of Homeland Security (DHS). As a Program Manager at the DHS says [23], "Tildesley and Keeling through their academic publications and willingness to interact with policy makers, have revolutionized the way in which DHS considers the use of mathematical modelling for future outbreaks of livestock diseases".

This modelling methodology is also being extended to Turkey where FMD is endemic and therefore acts as a reservoir for infection into Europe. As such "the work of the Warwick group has had a high impact on our European Member States and may provide the breakthrough needed in modelling control efforts in affected countries" states the Executive Secretary of the European Commission for the Control of Foot-and-Mouth Disease (EuFMD) [24]. The EuFMD is an intergovernmental body with 37 member states, operating under the auspices of the UN Food and Agriculture Organisation. [24] notes member states particularly use the Warwick group papers to decide when and where to vaccinate and produce reactive strategies. The Warwick group has led member states to recognise the importance of national policies, "...their willingness to address issues affecting confidence in use of models is of huge importance and has been a major contributor to the increased international acceptance of the use of modelling to assist with FMD emergency planning" as well as a "tool kit for predictive impact of changing movement controls, of enormous importance to emergency planners in FMD free countries" [24].

In summary, the mathematical modelling and statistical work in the University of Warwick Mathematical Sciences Departments has left the agencies responsible for infectious livestock disease control far better prepared for future outbreaks and with a far better understanding of what modelling and statistics can offer in terms of optimising control strategies and responses.

5. Sources to corroborate the impact

20. Open letter by leading scientists on the proposed badger cull. http://www.theguardian.com/theobserver/2012/oct/14/letters-observer

21. Statement from Head of the Epidemiology, Surveillance and Risk Group in the Veterinary Directorate of the AHVLA, an Executive Agency of Defra, UK.

22. Cross Departmental Review on 'Detection and Identification of Infectious Diseases', chapter S9: http://www.bis.gov.uk/foresight/our-work/projects/published-projects/infectious-diseases/reports-and-publications"

23. Statement from Program Manager of the Chemical Biological Division for the Department of Homeland Security, Science and Technology Directorate, USA.

24. Statement from the Executive Secretary of the European Commission for the Control of Foot-and-Mouth Disease (EuFMD).

25. Minutes of the SAC(13)024 on Bovine TB meeting, 26 June 2013 (p23) http://www.defra.gov.uk/sac/files/sac-13-june-agenda-papers.pdf