Institution: University of Warwick

Unit of Assessment: B10 Mathematical Sciences

Title of case study: Mathematical modelling informing policy on human infectious diseases, particularly pandemic influenza

1. Summary of the impact

Researchers in the Epidemiology Group at the University of Warwick have an international reputation for high-quality mathematical modelling of human infectious diseases, with particular emphasis on population heterogeneity and variability. Such formulations and insights are an important component of predictive modelling performed by Public Health England (PHE), and are helping to shape national policy for a range of vaccine-preventable infections.

The Warwick group was instrumental in providing a range of real-time analyses and advice to UK authorities during the 2009 H1N1 (swine-flu) pandemic, acknowledged by the Department of Health (DoH) to be "fundamental to the construction of the UK's pandemic response" and making an important contribution to the overall programme which "led to the saving of many hundreds of millions of pounds of taxpayers money, while greatly increasing the health of the Nation". Modelling and analysis carried out at Warwick continue to provide insight into the control and containment of future pandemics and are considered "essential in determining UK pandemic policy".

2. Underpinning research

Statistical analysis of data and mathematical modelling of controls are key tools in the modern public-health arsenal. Many decisions on health policies must be shown to be cost-effective through mathematical and economic modelling. Work within the Mathematics Institute at the University of Warwick (performed by Keeling, House and Danon) has led to both fundamental and applied insights in public health epidemiology. Here, we highlight research on pandemic influenza, which addressed many pressing issues during the 2009 pandemic and continues to influence policy planning for future outbreaks.

One important component of the group's work has been methodological, and the developments of mathematical techniques underlying modelling are used extensively. Keeling's textbook [1] has become a standard text on modelling infectious diseases (cited over 700 times), and as such is developing the next generation of public-health researchers and career academics.

During the 2009 influenza pandemic, there was considerable international collaboration to understand the early infection dynamics. Danon worked closely with researchers in the USA who were interested in the public-health impacts in Mexico and the United States and published several papers during that period. In particular, the number of influenza incidents among foreign travellers was used to estimate the true burden of disease in Mexico [2]. This work was one of the first to indicate that there was a huge undiagnosed level of infection and that most infections were mild.

A key issue in infectious disease policy is optimal use of a limited vaccine supply. Work by Keeling, arising directly from a collaboration with the health protection agency (HPA) during the pandemic, addressed the trade-offs in vaccination between targeting of an epidemiologically important group (such as primary school children) and a group in which the outcomes of infection are severe [3]. Mathematical modelling verified the decisions taken during the pandemic to first target vaccination at those with severe health-risks and then at young children.

The hospital-based healthcare system was under severe stress in particular localities during 2009, and it was suggested that localized school closures might reduce transmission and, hence, relieve the local burden. Our modelling and spatial statistics showed in 2011 that only widespread extensive closure of schools (which is economically extremely costly) would have had a substantial impact on cases of H1N1 [4].

As shown in [3], early case ascertainment (determining how many people are infected when not all are severely ill) is key to understanding the progression and control of an infection. In 2012, the group developed techniques to quantify case ascertainment using the theory of non-Markovian epidemic final outcomes and Bayesian MCMC (Markov Chain Monte Carlo) together with household information on early cases in Birmingham [5]. This work suggested that over 50% of

cases were undetected during the early stages of the 2009 pandemic, and provided a novel framework for analysis of household data that our colleagues in the PHE are considering for future outbreaks.

Clinical trials indicated that antivirals were effective against H1N1, but their impact at the population level was not realized during the 2009 pandemic. In 2013, the group used Bayesian methods in conjunction with the theory of path integrals for continuous time Markov chains to model antiviral effects in a household-structured epidemic model [6]. This showed that delays in delivery might account for the discrepancy between clinical trials and population-level efficacy.

Key researchers at University of Warwick:
Prof. Matt Keeling (Lecturer 2002-05, Reader 2005-08, Professor, 2008-), Dr. Leon Danon (Post-doctoral researcher & Leverhulme fellow, 2006-2013), Dr Thomas House (Post-doctoral researcher & EPSRC CAF fellow, 2006-).
***Key collaborators*:**
Dr Andrew Black & Dr Josh Ross (University of Adelaide), Prof. Pej Rohani (University of Michigan), Prof. Marc Lipsitch (Harvard University).

3. References to the research

Key publications

1. 1. **Keeling, M.J.,** & Rohani, P., Modeling Infectious Diseases in Humans and Animals. Princeton University Press. 408 pp. (2007) ISBN: 9780691116174
2. Lipsitch M, Lajous M, O'Hagan JJ, Cohen T, Miller JC, Goldstein E, **Danon L,** Wallinga J, Riley S, Dowell SF, Reed C & McCarron, M., Use of cumulative incidence of novel influenza A/H1N1 in foreign travellers to estimate lower bounds on cumulative incidence in Mexico PLoS ONE, 4 (9) e6895. (2009) DOI: 10.1371/journal.pone.0006895
3. **Keeling, MJ**, & White, PJ, Targeting vaccination against novel infections: risk, age and spatial structure for pandemic influenza in Great Britain. *J. R. Soc. Interface* **8**(58) 661–670. (2011) DOI: 10.1098/rsif.2010.0474
4. **House T,** Baguelin M, van Hoek AJ, White PJ, Sadique Z, Eames K, Read JM, Hens N, Melegaro A, Edmunds WJ & **Keeling, M.J.,** Modelling the impact of local reactive school closures on critical care provision during an influenza pandemic. *Proc. R. Soc. Lond. B* **278**(1719) 2753–2760 (2011) DOI: 10.1098/rspb.2010.2688
5. **House T,** Inglis N, Ross JV, Wilson F, Suleman S, Edeghere O, Smith G, Olowokure B & **Keeling, M.J.,** Estimation of outbreak severity and transmissibility: Influenza A(H1N1)pdm09 in households. *BMC Medicine* **10**117 (2012) DOI: 10.1186/1741-7015-10-117
6. Black A, **House T, Keeling MJ** & Ross, J.V., Epidemiological consequences of household-based antiviral prophylaxis for pandemic influenza. *J. R. Soc. Interface* **10**(81) 20121019. (2013) DOI: 10.1098/rsif.2012.1019

Key peer-reviewed grants and awards

7. Leach (HPA, PI), Grenfell (Cambridge), Keeling (Warwick) “Application of HE computing to public health” EPSRC GR/S43214/01 Oct 2003 – Sept 2005 £90,776.
8. Keeling (Warwick, PI), Read (Liverpool) “Social contact survey and modelling the spread of influenza”. MRC G0701256 Oct 2008 – Sept 2011 £669,233.
9. Keeling (Warwick, PI) “State of the art models for infectious disease spread”. Wellcome Trust Jan 2010 – Sept 2013.
10. Keeling (Warwick, PI) “Implications of clustering (motif-structure) for network-based processes”. EPSRC EP/H016139/1 Jan 2010 – Jun 2013 £290,372.
11. Leverhulme Trust “Mobile phone data and infectious diseases”. Dec 2010 – Nov 2013. Danon (Warwick, Early Career Fellowship)
12. House (Warwick, Career Acceleration Fellowship) “Disease Transmission and Control in Complex, Structured Populations” EPSRC EP/J002437/1 Oct 2011 – Sep 2016 £632,534
13. House (Warwick, PI) “Robust Mathematical Modelling of Household-Stratified Epidemic Time-Series”. EPSRC EP/K026550/1 Oct 2013 – Sep 2016 £216,448

4. Details of the impact

When the outbreak of H1N1 influenza was first identified in Mexico there was worldwide concern that this might signify the start of a pandemic with levels of mortality comparable to those of the 1918 flu outbreak. Keeling, House and Danon have a reputation for both cutting-edge

mathematical modelling and applied quantitative epidemiology; this has led to their research being used to advise and inform policy and decision-making for pandemic influenza (in 2009 and for future outbreaks), as well as for other infections such as the recent measles outbreak in Swansea.

Informing UK policy through membership of DoH Advisory Committees. Keeling became an active member of the government's Joint Committee on Vaccination and Immunisation (JCVI-influenza) [16] and during 2009 was the designated independent chair of the Scientific Pandemic Influenza Subgroup on Modelling (SPI-M) [15, 17]. He remains a member of both. In both these roles Keeling has provided, and continues to provide, detailed mathematical/modelling advice to the DoH, based on his research described above [1,2,14-16, 18, 19]. He has provided SPI-M with real-time modelling updates on control and containment of pandemic influenza "which played an important and often critical role in formulating the Group's [SPI-M's] consensus forecasts of what was happening and what would happen later in the pandemic" [15]. Both during and after the pandemic, Keeling has provided analysis that "has been essential in determining UK pandemic policy" [15]. As acknowledged by a Senior Principal Analyst at DoH and HPA, Keeling "played a very significant role in generating the SPI-M consensus view which has been fundamental to the construction of the UK's pandemic response and the management of the 2009 pandemic" [15]. Since 2009, SPI-M has continued to meet and provide updated advice to the Civil Contingencies Committee (commonly known as COBRA) in light of recent scientific evidence.

A key issue during the early stages of any pandemic is determining the true scale of the outbreak (whether all cases are severe and the outbreak is currently small, or the outbreak is larger but fewer cases have severe symptoms). This knowledge is vital in terms of effective public-health planning. Danon and a team of researchers from around the world (USA, Mexico, Hong Kong and the Netherlands) together with the CDC (Centres for Disease Control, USA) provided early evidence that H1N1 was a mild infection [1] in distinct contrast to all earlier reports. This precipitated a change worldwide in the way the infection was considered. The retrospective analysis undertaken with members of the HPA shows how data from infected households during the early stage of any pandemic could be used to infer the answers to many of these fundamental questions about case severity [5]. As such, this strategy is being considered as part of future planning both in the UK and overseas [14].

In addition to providing a quantitative estimate of the current epidemiology, mathematical models were used to provide information about the potential effect of control [3, 6]. During the pandemic there was considerable debate around the optimal use of vaccination, in part driven by poorly-posed findings in the early literature. Once vaccines were available in the later stages of the pandemic, preliminary results (later published as [3]) supported the general medical advice that vaccination should be targeted first to those with severe health risks and then to young children. Antivirals form the other pharmaceutical arm of control, but they did not perform as well in practice during 2009 as indicated by controlled tests; our results [3] showed that prompt antiviral treatment was key to reducing population-level transmission and have informed debate about future antiviral drug usage. A Senior Principal Analyst at DoH and HPA, referring to the 2009 pandemic, acknowledged that Keeling's work "formed an important contribution to the overall analytical programme which led to the savings of many hundreds of millions of pounds while greatly increasing the health of the Nation" [15].

Outreach to Public, Practitioners and Pupils. Our work in this area has led to substantial impact in term of public interest and engagement (impacts on society), impacts on practitioners and the enhancement of science knowledge in school children both locally and internationally. In all of these policy engagement events we highlight the importance and significance of the impact of our mathematical models in underpinning policy, and how we have substantially informed public debate and stimulated public interest and engagement. Examples of public activities include:

- Interviews with newspapers and media related to both H1N1 influenza and subsequent research, including [20]:
  Keeling's and Danon's Guardian interview (October 2011) (average daily circulation of 265,000 in 2011) that linked their research work with the film Contagion [20a];
  Promoting the importance of childhood vaccination against influenza through The Times of

India [20b], the Mail Online (averages more than 8 million daily browsers) [20c], House interviewed by Reuters (January 2013) [20d], Danon on BBC Coventry & Warwickshire radio (November 2011) and House (January 2013) on WAMC Northeast Public Radio (public radio station in New York) [20e].

- Presentations and interviews for NHS practitioners and coordinators and associated services: For example, House presented at a public policy exchange symposium (for public health officials, from NHS practitioners and pandemic coordinators to local government officers in community services and the Metropolitan Police) in April 2013 [21]. The company Wellards, which provides training on all aspects of the sales environment for professionals in the pharmaceutical and biotech industries with over 16,000 users from 300 companies, has used the research as one of its case studies on 'Vaccines in the NHS' [22].
- Presentations to Maths 'A'-level students: Keeling presented how we predict epidemics and control to "two capacity audiences, each of 900 students engaging them with the significance of mathematics in his research and the significance of his research to the general public" in a Mathematics in Action programme (2011-12) organised by The Training Partnership [23] (who provide events complementary to the A-level curriculum).

5. Sources to corroborate the impact

14. Letter by Head of Bioterrorism and Emerging Disease Analysis, Public Health England
15. Letter by Senior Principal Analyst, Department of Health, Health Protection Analytical Team

Membership in DoH Advisory Committees

16. Member of Joint Committee on Vaccination and Immunisation: https://www.gov.uk/government/policy-advisory-groups/joint-committee-on-vaccination-and-immunisation

17. Member of Scientific Pandemic Influenza Subgroup on Modelling: https://www.gov.uk/government/policy-advisory-groups/scientific-pandemic-influenza-subgroup-on-modelling

Informing UK Government

18. Foresight Review "Detection and Identification of Infectious Diseases" by Keeling commissioned by the Department for Business, Innovations & Skills of the UK Government, section S9: http://www.bis.gov.uk/foresight/our-work/projects/published-projects/infectious-diseases/reports-and-publications

Underpinning UK policy

19. House and Keeling cited as evidence in UK Influenza Pandemic Preparedness Strategy (p 39): https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/134747/dh_131040.pdf.pdf

Outreach to Public, Practitioners and Pupils

20. a http://www.guardian.co.uk/education/2011/oct/17/kate-winslet-contagion-fight-disease
b. http://articles.timesofindia.indiatimes.com/2009-06-18/health/28191041_1_vaccinate-kids-new-vaccine-potential-pandemic
c. http://www.dailymail.co.uk/health/article-1193839/All-children-offered-swine-flu-vaccine-autumn-contain-spread-pandemic-say-researchers.html
d. http://uk.reuters.com/video/2013/01/22/data-model-could-improve-future-pandemic?videoId=240644097&videoChannel=4000
e. http://www.wamc.org/post/dr-thomas-house-university-warwick-mathematics-and-mapping-epidemics

21. http://publicpolicyexchange.co.uk/events/DD23-PPE.php

22. http://www.wellards.co.uk/courses/vaccines_in_the_nhs/screen28_case.html

23. Letter received from Managing Director of The Training Partnership