Imperial College London

MRC Medical Research Council

MRC Centre for Outbreak Analysis and Modelling

Annual Report

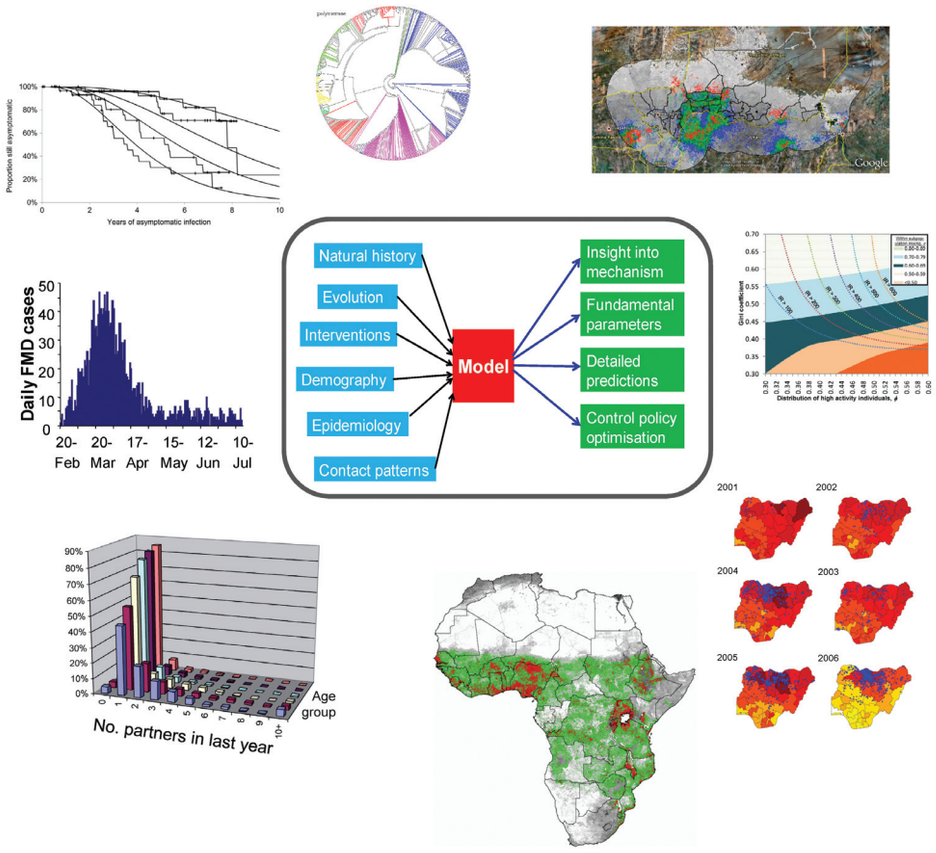
2008

Introduction

The first year of the MRC Centre for Outbreak Analysis and Modelling has been a busy one. Our mission is to be an international resource and centre of excellence for research on the epidemiological analysis and modelling of infectious disease outbreaks, and the research output of the Centre in 2008 has lived up to those goals. Highlights include groundbreaking work published in the New England Journal of Medicine examining the efficacy of polio vaccination in Nigeria[1], one of the last refuges of the polio virus. Reducing the uncertainty surrounding the likely impact of public health interventions in a flu pandemic was also a priority, with Centre staff publishing in Nature the first estimates of the likely impact of closing schools on virus transmission in a pandemic[2]. Other significant work included an analysis of evolutionary trade-offs between virulence and transmissibility in HIV[3], and an examination of the potential impact of artemisinin-based combination therapies on malaria transmission[4].

We have had a very successful first year attracting new research funding, with a $10m award from the Bill and Melinda Gates Foundation to found the Vaccine Modelling Initiative, collaboration between the Centre, Penn State University and the University of Pittsburgh. Close to £900k in additional MRC funding was raised to work on outbreak analysis methods and malaria eradication modelling. Additional substantial projects were funded by the EU, WHO and Defra.

Key to the aims of the MRC Centre is making our work 'translational' – which in the public health context means working with public health agencies and policy makers to use the research of the Centre to improve preparedness and responses to disease outbreaks. This year has seen the Centre working closely with the World Health Organisation (WHO) in a number of areas, and we have initiated negotiations to become a WHO Collaborating Centre. Staff in the MRC Centre continue to advise the UK and other governments in a large number of disease areas, and in the coming year we will be focussing on building closer collaborative links with the UK Health Protection Agency (HPA), following a period of significant organisational change at the HPA Centre for Infections.



Staff profiles

Professor Neil Ferguson OBE FMedSci – Director
Neil Ferguson is Director of the MRC Centre. His research interests focus on the use of mathematical models of disease transmission coupled with rigorous statistical analysis to understand epidemic dynamics and assist in planning for and responding to novel infectious disease outbreaks. He has worked on a wide range of diseases, including pandemic and seasonal influenza, SARS, foot and mouth disease and bioterrorist threats.

Professor Christl Donnelly
With an ongoing research programme in TB in British cattle and badgers, Prof Donnelly maintains a strong interest in diseases affecting livestock and wildlife, with key collaborations to improve understanding of the infectious cancer which threatens the Tasmanian Devil with extinction and to better characterise the spread of avian influenza between chickens.

Professor Geoff Garnett
As the Co-Chair of the UNAIDS Epidemiology Reference Group, Prof. Garnett's research focus is the use of antiretroviral treatments in the epidemiology of HIV. This includes analyses of the impact of different strategies for initiating treatment in resource poor settings, the role of pre-exposure prophylaxis on reducing incidence and the potential impact of antiviral treatment on the transmissibility and subsequent control of HIV.

Professor Azra Ghani
Professor Ghani's research combines the use of mathematical models and statistical methods to understand the transmission dynamics and control of a range of infectious diseases of humans and animals. Her recent malaria research includes the identification of loss of immunity as a determinant of patterns of intervention success. Other areas of interest include the dynamics of gonorrhoea transmission in the UK and H5N1 avian influenza in poultry in SE Asia.

Francois Balloux
With a fundamental interest in evolutionary genetics, Dr. Balloux's work within the Centre involves the development of a coherent and flexible framework for "eco-geographic" analyses of genetic data in space and time. This toolkit will be employed to investigate questions surrounding the origin of tuberculosis and the annual cycle of influenza.

Simon Cauchemez
As a researcher in the Centre, Dr. Cauchemez has estimated a range of key parameters critical for pandemic planning including the impact of school closure on influenza epidemics, the efficacy of facial masks to reduce transmission, and viral generation times. He is currently investigating the efficacy of antiviral drugs and developing methods for real-time outbreak monitoring.

Christophe Fraser
Dr. Fraser's research centres on the development of simple analytic models and their application to real epidemics. His group has recently focused on epidemic models including households and workplaces and applied these to influenza and SARS. He is also working on modelling resurgent HIV epidemics and antiretroviral treatment.

Nicholas Grassly
Dr. Grassly and his group are focused on poliovirus transmission during the end stages of global eradication, sexually transmitted infections in developed and developing countries, and trachoma dynamics as the international target of eliminating blindness due to this infection by 2020 is pursued. Recent topics of research include: the effectiveness of gut mucosal immunity induced by oral poliovirus vaccine, the limits to herd immunity and effective drug-sparing strategies for mass distribution of antibiotics to treat trachoma.

Chris Rhodes
As an RCUK Fellow in the Institute for Mathematical Sciences, Dr. Rhodes researches mathematical models for understanding the spread of communicable disease. He has recently researched the effects of heterogeneity of transmission in communicable diseases, a kinetic theory approach to basic epidemic models and transmission of wireless worms between mobile devices (in collaboration with BT Research).

Peter White
Dr. White is interested in the modelling of infectious disease epidemics, including HIV and TB, and the impact of health-care interventions. In collaboration with the Health Protection Agency, University College London and others, Dr White has developed a model to assess the impact of targeted screening of high-risk groups for TB (including prisoners and homeless people) in London using a mobile X-ray unit, funded by the Department of Health.

Emily Lyons
Dr. Lyons is the Scientific Manager for the MRC Outbreak Centre. Prior to joining the Centre she conducted research in infectious disease genetics. Specifically, she has investigated diversity in malaria parasites and human susceptibility to TB. As Centre Manager, she is responsible for grant management, communication with collaborators and funders, web development and annual reporting.

Pandemic influenza

Continued research on preparing for the next flu pandemic has been a key emphasis of the first year of the Centre. Work has focussed on two areas: statistical analysis of historical data to better understand the transmission and epidemiology of influenza, and using large-scale simulation models of the spread of pandemic flu to help inform policy planning around the world. In an innovative paper published in the journal Nature[2], Simon Cauchemez, Neil Ferguson and collaborators reported the first reliable estimates of the extent of school-based transmission in influenza epidemics. This allowed them to conclude that deliberately closing schools in a pandemic might prevent 1 in 5 cases in children, but only 1 in 7 in the population as a whole. Another collaborative study with multiple US-based modelling groups compared the predictions from different models of the likely impact of public health measures (such as quarantine, 'social-distancing' and school closure) on a flu pandemic[5]. Ongoing work includes collaboration with the China Center for Disease Control and Prevention on modelling pandemic mitigation strategies in China, and work with the US CDC on understanding spatial patterns of seasonal influenza spread. In addition, Centre researchers have attended numerous government and international meetings to advise on pandemic planning policy.

Livestock diseases

Bovine tuberculosis (TB) remains a major problem for farmers in Britain, and there has been much debate over the last decade as to whether culling badgers (a natural reservoir of infection) would reduce the number of cases in cattle. Centre researchers, led by Christl Donnelly, were heavily involved in the long-running Randomised Badger Culling Trial which concluded in 2007 that widespread culling of badgers reduced cattle TB inside the culled areas, but increased it around the boundaries of the area[1]. Following this study, the UK Government decided that badger culling would not be used to control bovine TB. Prof Donnelly continues to monitor cattle TB incidence in trial areas to quantify the longer-term effects of badger culling on cattle TB incidence.

Work also continues on foot-and-mouth disease (FMD), continuing a long-running research programme starting with Centre researchers' work on the 2001 FMD epidemic in Britain. Current research is focussing on developing generic methods for estimating transmission parameters from epidemic data[6], applying these to the data from 2001 to better understand that epidemic, and embedding these methods into software designed to improve real-time analysis of future outbreaks.

Further afield, H5N1 avian influenza has had a devastating impact in much of South East Asia. In collaboration with local institutions, government departments and the UN Food and Agriculture Organization, Centre staff are investigating the dynamics and control of H5N1 avian influenza in poultry in the region. In Cambodia, this includes evaluation of human exposure to high risk poultry practices and characterisation of poultry movement networks. In Vietnam, work is ongoing to estimate the effectiveness of vaccination against H5N1 in poultry and evaluate the role of live-bird markets in H5N1.

Malaria

In October 2007 the Bill and Melinda Gates Foundation joined forces with other major funders and global health organizations such as the WHO to call for a new ambitious goal of malaria eradication. This paradigm shift from control of disease toward local elimination and eventual global eradication of the parasite requires a re-evaluation of current and potential future intervention strategies for which the role of mathematical models has been recognized. With this in mind, over the past year we have substantially increased our focus on developing transmission models that can be used to guide policy decisions, including published work exploring the potential impact that roll-out of ACTs could have on transmission[4], the evaluation of IPTi (Intermittent Preventative Treatment in Infants) studies[10] and the impact of loss of immunity on intervention effectiveness[11]. Research is currently underway exploring the influence of the movement of people and migration patterns on the success of intervention strategies, the potential impact of IPTi on the development of drug resistance and in developing models to estimate transmission intensity from serological data.

On the basis of this work, additional MRC Centre funding has been awarded to develop a full-scale spatially-explicit individual-based simulation model for malaria transmission and control in Africa. This will be informed by the simpler model structures explored to date and parameterised using the most recent data available on the current status of malaria, more detailed studies from specific research field sites on aspects of the full transmission cycle, and preliminary studies on human migration and movement studies. In the longer term, the full range of intervention strategies, including vector control, treatment and prophylaxis and vaccines will be incorporated within this framework to provide a scientifically-robust tool to aid decision making.

Polio

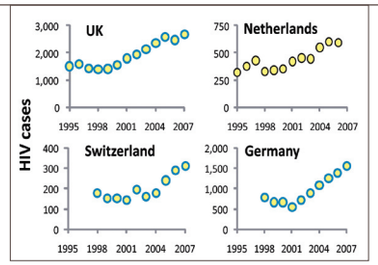
Our research in 2008 focused on estimating the effectiveness of oral vaccines in inducing immunity against poliovirus in those countries that have yet to eradicate polio. We have also been examining the epidemiology of both wild and vaccine-derived poliovirus outbreaks to better understand the risk factors for transmission, including levels of immunity, environmental conditions and population movements. Highlights include the publication of a paper in the New England Journal of Medicine describing the effectiveness of immunisation in Nigeria. In addition to demonstrating the impact of the newly licensed monovalent oral on population immunity, this work found very low levels of vaccine coverage in northern Nigeria, which have allowed wild poliovirus to persist. These results contrast with the severe biological constraints on vaccine efficacy that we previously found to explain the persistence of polio in northern India, despite good vaccine coverage[7,8]. These different challenges presented by India and Nigeria, two of the remaining four endemic countries, are highlighted in the recent report from the Advisory Committee on Polio Eradication[9]. We try to ensure that our work is informative to the Global Polio Eradication Initiative and to national governments. For example, we have recently developed a simple method to predict vaccine-induced immunity under different immunisation strategies and this was used during the development of immunisation plans for 2009 by the Government of India. Despite the fact that the oral (Sabin) and inactivated (Salk) poliovirus vaccines were developed 50 years ago, many important questions about the systemic and mucosal immunity induced by these vaccines and the epidemiology of poliovirus remain unanswered.

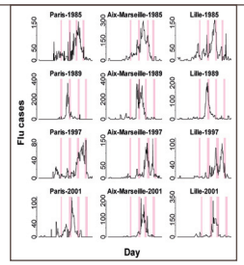
Basic research

Centre researchers are at the forefront of developing new methods for analysing infectious disease data and simulating transmission dynamics. A particular emphasis in 2008 was the development of efficient and statistically rigorous methods for estimating epidemiological parameters – such as disease transmissibility or the impact of control measures – from data collected during an epidemic[12]. Ongoing work is tackling the challenges of real-time (rather than retrospective) analysis of epidemic data, namely delays in reporting surveillance data, and the noisy and incomplete of such data.

A second focus has been on epidemic models which incorporate households, workplaces and other social units. Work in this area has deepened our understanding of the dynamics of such models, and developed new statistical methods for estimating transmission parameters for such complex models[2].

Last, the evolution of infectious diseases remains a major research interest for several Centre researchers, with active research programmes examining antigenic variation[13] and the evolution of transmissibility and virulence in HIV[3].





Selected Publications

1. **Jenkins HE; Woodroffe R; Donnelly CA. (2008)** The effects of annual widespread badger culls on cattle tuberculosis following the cessation of culling. International Journal of Infectious Diseases. 12:457-465

2. **Cauchemez S; Valleron AJ; Boëlle PY; Flahault A; Ferguson NM. (2008)** Estimating the impact of school closure on influenza transmission from Sentinel data. Nature. 452:750-754.

3. **Fraser C; Hollingsworth TD; Chapman R; de Wolf F; Hanage WP. (2007)** Variation in HIV-1 set-point viral load: epidemiological analysis and an evolutionary hypothesis. Proc Natl Acad Sci USA. 104:17441-17446

4. **Okell L, Drakeley C, Boema T, Whitty C, Ghani AC (2008)** Potential impact of artemisinin-based combination therapies on the transmission of malaria in endemic settings. PLoS Medicine, e226.

5. **Halloran ME; Ferguson NM; Eubank S; Longini IM; Cummings DAT; Lewis B; Xu SF; Fraser C; Vullikanti A; Germann TC; et al. (2008)** Modeling targeted layered containment of an influenza pandemic in the United States. P Natl Acad Sci USA. 105:4639-4644.

6. **Chis-Ster, I; Singh, ; Ferguson, NM. (2008)** Epidemiological inference for partially observed epidemics: The example of the 2001 FMD epidemic in Great Britain. Epidemics. In Press

7. **Grassly NC, Fraser C, Wenger J, Deshpande JM, Sutter RW, Heymann DL, Aylward, RB. (2006)** New strategies for the elimination of polio from India. Science. Nov 17; 314(5802):1150-3.

8. **Grassly NC, Wenger J, Durrani S, Bahl S, Deshpande JM, Sutter RW, Heymann DL, Aylward RB. (2007)** Protective efficacy of a monovalent oral type 1 poliovirus vaccine: a case-control study. Lancet. Apr 21;369(9570):1356-62.

9. **WHO (2009)** 17 Conclusions and recommendations of the Advisory Committee on Poliomyelitis Eradication, November 2008. Weekly Epidemiology Record. 16 January 2009, vol. 84, 3 (pp 17–28)

10. **Gosling R, Ghani AC, Deen J, von Seidlein L, Greenwood B, Chandramohan D (2008).** Can changes in malaria transmission intensity explain lack of rebound and high protective efficacy of intermittent preventive treatment for malaria in infants? Malaria Journal 7:54.

11. **Ghani AC, Sutherland CJ, Riley EM, Drakeley CJ, Griffin JT, Gosling R, Filipe JAN (2009).** Loss of population levels of immunity as a result of exposure-reducing interventions: consequences for interpretation of disease trends. PLoS One 4(2) e4383.

12. **Cauchemez S; Ferguson NM. (2008)** Likelihood-based estimation of continuous-time epidemic models from time-series data: application to measles transmission in London. J R Soc Interface. 5:885-897

13. **Abu-Raddad LJ; van der Ventel BIS; Ferguson NM. (2008).** Interactions of multiple strain pathogen diseases in the presence of coinfection, cross immunity, and arbitrary strain diversity. Phys. Rev Lett. 100.

Wellcome Collection images: Dan Salaman, Hugh Sturrock
Avian Flu image: Maria Van Kerkhove, Bovine TB image: Richard Yarnell
Nigeria Polio images are reprinted with permission from ref 1: (Jenkins et al., 2008)

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