

Imperial College
London

MRC

Centre for
Outbreak Analysis
and Modelling



MRC Centre for
Outbreak Analysis and Modelling
www.imperial.ac.uk/medicine/outbreaks

ANNUAL
REPORT
2011



Director's message

It is four years since the founding of the MRC Centre for Outbreak Analysis and Modelling. The Centre's five-yearly review is already underway and our plans for the next five years have been submitted. In recent months, we have been reflecting on what we have achieved since 2007, and looking towards the future. The time has flown by, but not without substantial progress towards our mission: to become an international resource and centre of excellence for translational research on the epidemiological analysis and modelling of infectious disease outbreaks.

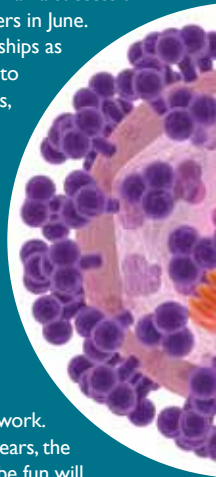
While there is much innovative research to point to, I am most proud of the translational aspects of our work. We have built long-term, sustainable partnerships with public health agencies and are working in priority areas for those organisations. Two of our senior, and most intrepid, postdoctoral research fellows, Maria Van Kerkhove and Manoj Gambhir, have taken lead roles in our collaborations with the World Health Organization (WHO) and the US Centers for Disease Control (CDC), respectively. They have worked hard to develop relationships with key groups in both organisations and facilitate introductions to Centre colleagues to kickstart new projects. These relationships have also resulted in some of the highest impact science the Centre has yet produced, reflected by papers in the *New England Journal of Medicine* and *Proceedings of the National Academy of Sciences*. Collaborations closer

to home are also bearing fruit – a recent highlight being the award of a significant MRC research grant jointly to Steven Riley at the Centre and Liz Miller and colleagues at the Health Protection Agency (HPA). Together, they will try to better understand the evolution of population immunity to influenza.

Looking forward, I feel we have a good basis on which to broaden and deepen our external partnerships. Our focus for the next five years will be on developing similar strong ties with public health researchers and agencies in low and middle income countries, notably in China and India, where we have existing links. We also aim to expand our scientific capabilities in two key areas: first, genomics and evolutionary analysis, which are increasingly vital tools in epidemiology; and secondly, health economics, which can help us to understand the impacts of the interventions that we study. Our priorities for specific disease areas – and our research successes over the last 18 months – are highlighted in the coming pages.

Lastly, an ongoing priority for the Centre has been training and career development. Based on feedback from our Centre away day in 2011, we ran a successful careers day for postdoctoral researchers in June. An increased focus on research fellowships as a route to scientific independence led to a new mentoring scheme for applicants, the success of which is reflected by four Centre staff gaining MRC early career fellowships over the last two years. We have also organised regular 'work-in-progress' lunchtime discussions and training sessions to support internal skills transfer and collaboration. A lively social scene at the Centre continues to enhance those collaborations and it is always gratifying to hear from colleagues and friends how rewarding they find their work. As the Centre evolves in the coming years, the ethos that doing great science should be fun will remain at the heart of what we do.

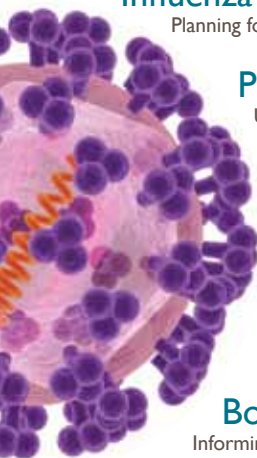
Neil Ferguson



The Centre specialises in quantitative epidemiology encompassing mathematical modelling, statistical analysis and evolutionary epidemiology, to aid in the control and treatment of infectious diseases.

RESEARCH AREAS:

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Polio



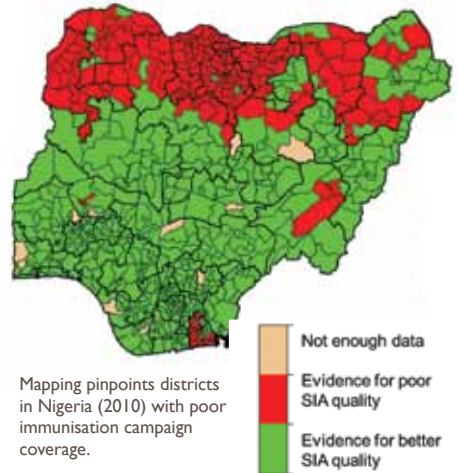
In Delhi, India, children are now routinely given the newly licensed bivalent oral poliovirus vaccine.

These are momentous times for the Global Polio Eradication Initiative. New vaccines and ongoing innovation by the polio programme in India have brought the virus to a halt; no new cases have been detected there since January 2011. However, reported cases have been

increasing in Afghanistan, Pakistan and Nigeria – the only other countries where polio remains in constant circulation – raising concerns about the virus being reintroduced to countries currently designated polio-free. Recognising the risks, in January 2012 the WHO declared polio eradication a 'programmatically emergency for global public health'. Scientists at the Centre are playing a central role in informing the critical decisions that will ultimately determine whether the eradication effort is successful.

Centre research has supported the widespread use of newly licensed polio vaccines in children. We have shown that mono- and bivalent oral vaccines, which target one and two strains of the virus respectively, are around three times more effective than the standard trivalent vaccine. Although the standard vaccine targets all three main strains, interference between these different strains reduces effectiveness. Serotype 2 wild poliovirus was eradicated in 1999. Mono- and bivalent vaccines targeting the remaining circulating serotypes have had a major impact on transmission of poliovirus since their introduction in 2005 and 2009.

Vaccination campaigns are most effective in reducing transmission of the virus if all children under five years old are immunised. In Nigeria, research by Centre scientists has helped to identify districts with poor vaccination coverage, leading to more concerted



immunisation efforts in these areas. Methods developed in the Centre have also been applied to identify African countries that are at high risk of polio outbreaks. Our risk maps, based on immunisation statistics and patterns of movement between countries, have been important in the planning of immunisation campaigns.

Despite progress, however, current polio vaccines provide far from perfect protection. We are therefore working towards a better understanding of polio immunity and have been able to estimate, for the first time, how long protection lasts after a child receives a dose of oral poliovirus vaccine. The substantial loss of protection after one year indicates a need for frequent booster doses. With colleagues at the Christian Medical College in Vellore, India we are carrying out a trial to test the effectiveness of booster vaccines in immunised children.

Nick Grassly (second from left) leads the Polio research programme.



Human tuberculosis

TB remains an important public health concern in the UK, where annual diagnoses have risen for the past 20 years. New diagnostic tools and approaches to case-management that help patients complete lengthy treatment programmes need to be tailored to different patient groups. However, limited resources mean interventions must be cost-effective.

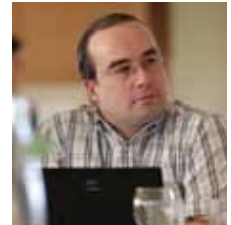
The Centre is collaborating with colleagues at the HPA, Imperial College London, University College London, Queen Mary University of London, and others, on a wide range of studies on TB, with projects examining the likely impacts and costs of a range of different screening approaches, including more expensive but more sensitive and specific diagnostic tests.

One recent project in collaboration with Imperial's Centre for Respiratory Infections focused on screening of new entrants to the UK. We found that there is a need for greater uniformity in screening practice across the country, as well as to extend screening to those arriving from regions not previously screened, notably the Indian subcontinent. In April 2011, Head of the Tuberculosis Research Unit, Ajit Lalvani, appeared on BBC Radio 4's *Today* programme to discuss Britain's immigrant screening programme and how it could be improved.

Our researchers have also examined different approaches to screening and treatment in socially marginalised groups. Although in London only a small proportion of all TB diagnoses are in homeless people, prevalence and transmission rates within this group are very high. We were commissioned by the Department of Health to evaluate

the cost-effectiveness of the London TB Find & Treat service, in which a mobile X-ray unit housed in a van takes a screening service to homeless people. The analysis, which was published in the *British Medical Journal* and discussed in Parliament, found that this targeted screening approach was highly cost-effective when followed by active case management. It may also be cost-effective in other cities with a high TB burden. In ongoing work we are studying the cost-effectiveness of testing the homeless and prisoners for asymptomatic (latent) TB, and strategies to improve adherence to treatment in these groups.

A new test for active TB called Cepheid GeneXpert MTB/RIF offers quicker, simpler diagnosis but is expensive. Centre researchers are undertaking several UK studies to try to establish strategies for cost-effective use, in both hard-to-reach groups and the general population.



Peter White leads the Human TB research programme.

Users of the London Find & Treat Service.



Image: Kevin Gorman

Malaria

Our malaria research programme is continuing work on a wide variety of projects including those exploring immunity and vaccine response, transmission dynamics, and the impact of traditional and novel control measures.

Seasonal malaria chemoprophylaxis (SMC) is an approach to malaria prevention that involves giving children under five years of age three or four courses of anti-malarials at monthly intervals during the peak transmission season. It aims to clear current infections and prevent new infections, with a number of trials demonstrating substantial reductions in episodes of clinical disease. However, seasonal variations in malaria transmission are more pronounced in some regions than others. Over the past year, we have worked as members of a working group convened by the WHO Global Malaria Programme to identify areas where transmission is sufficiently seasonal to warrant SMC. We have also been evaluating cost-effectiveness of SMC in these areas, and its likely impact, in terms of lives saved. Our results formed part of the evidence submitted to the first meeting of the Malaria Policy Advisory Committee in January 2012.

As malaria declines, connections between affected and less affected regions are becoming increasingly important. People travelling from places where infection rates are still high may risk re-introducing the disease elsewhere. Through surveys studying

Burkina Faso Survey Team.



Azra Ghani (fourth from left) leads the Malaria research programme.

movement patterns in people, we are improving our understanding of these connections and are working with local partners in Africa to collect information about where, how and why people travel. We have also recorded information on the use of mobile phones on these trips so that comparisons can be made with movement patterns estimated from mobile phone usage data. Surveys in Mali and Burkina Faso have been completed, with further surveys planned in Zambia and Tanzania in 2012.

We continue to work closely with the WHO Global Malaria Program, Clinton Health Access Initiative and UCSF Global Health Group in developing tools to assist National Malaria Control Programmes (NMCPs) in Africa. Our user-friendly 'Malaria Tools' modelling software platform can help NMCPs to understand the likely impacts of combining different intervention approaches. Our work in this field has involved collating data and developing models to fit many different locations across Africa. The range of interventions covered by the software has been extended to include bed nets, mass treatment approaches, indoor spraying, the new RTS,S vaccine, and drug treatment approaches based on intermittent prophylactic therapy (IPT) in infants and children. Users can compare the potential impacts of different intervention policies on multiple measures of malaria transmission and disease burden, over a range of timescales. The software will be piloted with NMCPs in the coming months.

HIV

Scientific progress in HIV prevention has reached a turning point. The last year has seen several major international clinical trials demonstrate that antiretroviral medicines have the potential to reduce both the risk of becoming infected with HIV and the risk of transmitting it to others. These breakthroughs raise important research questions and decision-making dilemmas. Could new antiretroviral drugs reduce the size of HIV epidemics? Are these medicines affordable? And what would be their long-term impacts? Within the Centre, the work of the HIV research programme endeavours to answer these questions.

Studies by Centre scientists show that in countries with the largest treatment programmes, antiretrovirals are already beginning to reduce the rate of HIV infection. Mathematical modelling from our own and other groups suggests that resources should be spent increasing coverage among those who are already infected before expanding use to protect healthy individuals. These results are feeding into international policy discussions and have in the last year featured in high profile journals including *The Lancet* and *Science*.

In addition, the Centre was delighted to be involved in a successful bid to conduct a large multicentre clinical trial, known as PopART, funded by the US National Institutes of Health (NIH) and The Bill & Melinda Gates Foundation. Although treatment should be prioritised, in many sub-Saharan African countries, the only feasible strategy for a sustainable, long-term response to the HIV/AIDS epidemic is prevention of new infections. The PopART trial will test strategies for preventing new infections through large-scale prophylactic use of antvirals. Led by Christophe Fraser, Centre researchers will be responsible for mathematical modelling using trial data.



The research groups of Tim Hallett (top, second from left) and Christophe Fraser (bottom, third from left) contribute to the HIV research programme.

Major research efforts are also being devoted to verifying the robustness of modelling results. We are taking a systematic approach to comparing results across many international research groups and models used by international agencies. Thus far, this effort has identified key areas of disagreement and uncertainty, helping to inform further studies by highlighting remaining gaps in the data, and bringing us closer to defining the intervention strategies that will make the greatest impact on HIV transmission.



Influenza

Influenza remains a major research priority. While we continue to analyse data collected during the 2009 H1N1 pandemic, we are also monitoring current infections and working to understand the evolution of seasonal influenza, to help focus vaccine development for future outbreaks.

Influenza surveillance is challenging. Cases are hard to track because only a small proportion of those infected visit their GPs, and symptoms associated with other influenza-like diseases are often mistaken for influenza. Infection rates can be estimated based on serological studies, which measure antibody levels in blood and can indicate past exposure to different strains. However, interpretation of serological results is complex. Centre scientists are involved in studies on influenza that address these challenges. Simon Cauchemez, in collaboration with Peter Horby's group at Oxford University, has made major strides in redefining how serological data are analysed and interpreted.

In southern China, Steven Riley is also taking a serological approach – to assess the differences between influenza rates in urban and rural areas. Separate studies are underway in Hong Kong, investigating multiple aspects of influenza transmission, including how rates of severe disease vary between strains and how infection with one subtype of influenza protects from infection with another.

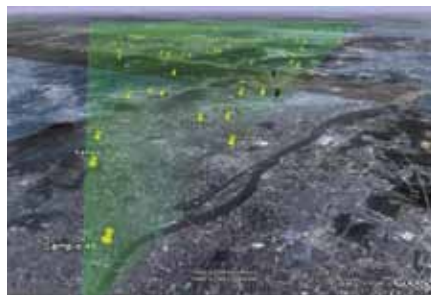
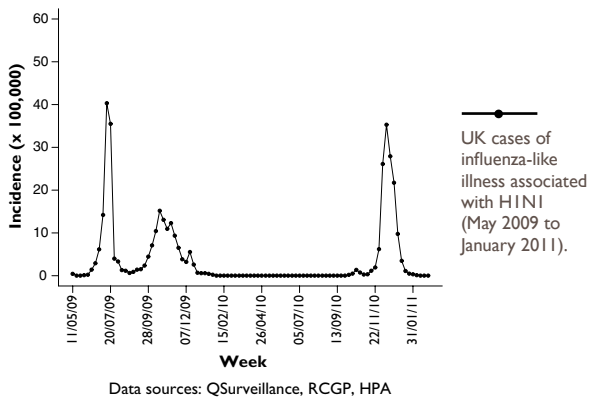
The aims of these studies dovetail with modelling led by Neil Ferguson which is examining how different assumptions about the ecology and evolution of influenza would be expected to affect transmission dynamics and patterns

seen in genetic data. This work also examines the extent to which sequence data can be used to predict the molecular characteristics of new seasonal influenza strains – work that, crucially, may offer the potential to improve strain selection for influenza vaccines in the future.

Substantial efforts are still underway in analysing the wealth of data collected from around the world during the 2009 H1N1 pandemic. One particular focus is in trying to understand why the UK – almost uniquely – experienced a third wave of pandemic H1N1 infection in the winter of 2010.



The research groups of Steven Riley (above), Simon Cauchemez and Neil Ferguson contribute to the Influenza research programme.



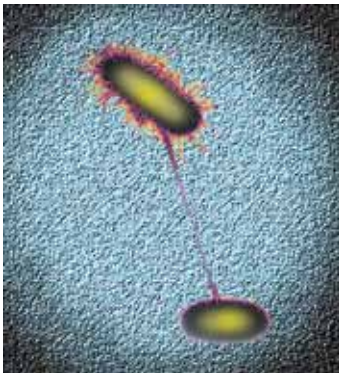
Urban and rural study sites in and near Guangzhou in southern China, viewed with Google Earth.

Pathogen evolution

Epidemiology is being transformed by our ability to rapidly sequence the genomes of pathogens, and thus study outbreaks and epidemics in far more detail than before. We can use this information to track individual chains of transmission, and to work out how pathogens are evolving over time. The Centre has a rapidly growing presence in this area. Our approach integrates epidemic surveillance data and genetic sequence data to track the emergence of new strains of influenza, HIV and multi-drug resistant bacteria.

Next-generation sequencing can now be used to obtain reliable sequences of whole genomes consisting of over two million base pairs. Centre scientists have been involved in work that showcases these cutting-edge technologies, demonstrating the extraordinary ability of bacterial pathogens to evolve under pressures exerted by antibiotic use and vaccines.

Since 2007, Christophe Fraser's group has been gathering evidence in support of a controversial hypothesis about HIV evolution – that the virus plays a more prominent role in determining the severity of infection than was

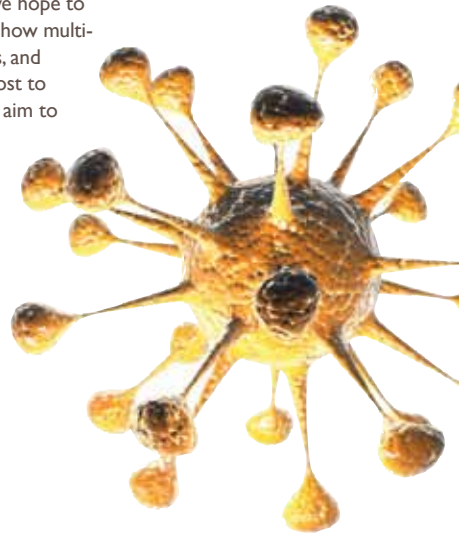


previously thought. Recent work in the Centre tested this hypothesis directly by showing that severity was similar in couples where one partner transmitted the virus to the other, hinting that viral genetic factors, as opposed to host factors, are key. This finding was confirmed by four other publications in 2011. We are now exploring the consequences for our understanding of the mechanism of disease and evolution in HIV, using a combination of epidemiological and genetic approaches.

The growing global problem of antiviral and antibiotic drug resistance is also a major focus of our work in the Centre. Using novel methods to analyse routine epidemiological and clinical data collected by agencies such as the HPA, CDC and WHO, we hope to understand more about how multi-drug resistance develops, and whether it comes at a cost to bacteria and viruses. We aim to inform drug use policies that minimise the rate of evolution and spread of resistance.



The research groups of Christophe Fraser (above) and Neil Ferguson contribute to the Centre's work on evolution and genetics.



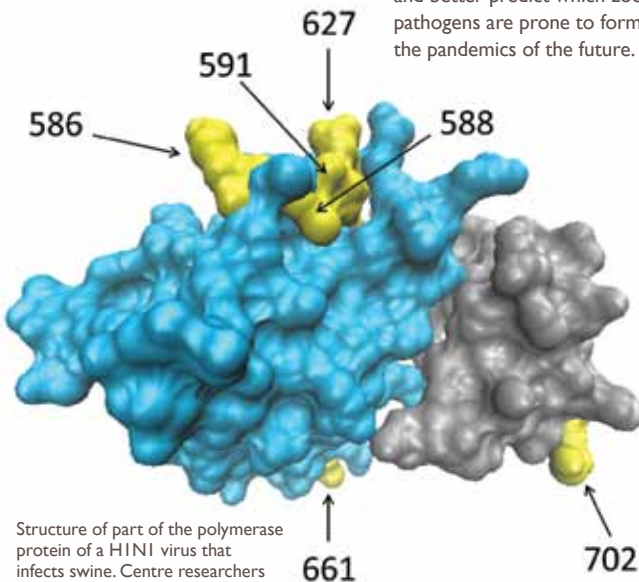
Bacterial cells exchanging genes. Recent work on conjugation or 'sex' between bacteria indicates important public health consequences.

Emerging infectious diseases

The Centre maintains an active research programme in emerging infectious diseases, funded by the European Union and NIH. Our work in this field falls under three main areas: analysing the genetic factors that enable some viruses to jump from one species to another; improving methods for characterising new disease threats based on surveillance data and applying mathematical models to compare the potential effects of different control options. Viruses capable of crossing from animal reservoirs into human populations (zoonoses) can pose major public health problems, as SARS outbreaks in 2003 and the H1N1 influenza pandemic in 2009 demonstrated.

Researchers at the Centre are developing new methods that use routine surveillance data to monitor zoonotic diseases and assess their epidemic potential. We are also developing simple analytical tools for use in outbreak investigations. These tools will help field epidemiologists with no in-depth knowledge of mathematical modelling to predict how a disease will spread, and the effects of different control measures, based on raw surveillance data.

More fundamental research is using viral genomics to probe the evolution of emerging infections, applying machine learning techniques first developed in computer science to better understand how viruses adapt to particular host species, and better predict which zoonotic pathogens are prone to form the pandemics of the future.



Structure of part of the polymerase protein of a H1N1 virus that infects swine. Centre researchers identified amino acids (numbered) that distinguish it from versions of the virus that infect humans.



The research groups of Neil Ferguson, Christl Donnelly and Simon Cauchemez (top to bottom) contribute to the emerging infectious diseases research programme.

Dengue fever

Working closely with stakeholders at the WHO and the Bill & Melinda Gates Foundation, the Centre has recently initiated a substantial research programme on the mosquito-transmitted virus, dengue fever. Global infection rates for dengue have risen dramatically in the last decade, with over 50 million people now infected every year. The disease causes major epidemics in much of the tropical and subtropical world.

Historically, intervention options for dengue fever have been limited. No treatment or vaccine exists, and the mosquitoes that transmit the virus are difficult to control. However, a number of vaccine candidates are now in the later stages of clinical trials and innovative biological control methods targeted at mosquitoes are starting to show promise. The Centre's work on dengue fever focuses on biological control, exploring two different approaches that make use of biotechnology to target mosquito populations. The first involves the release of genetically modified male mosquitoes that mate with wild females. Their offspring inherit genes that cause them to die before they can transmit infection.

The second technique uses a bacterium called *Wolbachia*, which inhibits replication of the dengue virus in mosquitoes. We are assisting the groups developing these technologies with trial design and data analysis.

Genetically modified mosquitoes released in a trial in Grand Cayman significantly suppressed mosquito numbers, and the results from the *Wolbachia* research are encouraging. Using models to extrapolate from data gathered in the field and laboratory, it appears that some *Wolbachia* strains

have the potential to substantially reduce dengue transmission, perhaps below levels required for the virus to sustain itself in some areas. Our unique approach to this work integrates human and mosquito models of infection into one population-level model of transmission.

New work beginning at the Centre this year will use modelling to examine how integrated dengue intervention programmes – combining novel vaccines and mosquito control methods – can be designed to achieve optimal control with limited resources.



Neil Ferguson's research group. Neil (back row, second from left) and Christl Donnelly's groups work on the Dengue research programme.

A field worker releasing transgenic male mosquitoes to reduce dengue transmission risk.



Image: Kevin Gorman

Bovine tuberculosis

While the number of UK farms affected by bovine TB continues to rise, controversy surrounds the package of measures appropriate for controlling the disease. Bovine TB infects wild animals as well as livestock and its circulation in badger populations makes it harder to control in cattle.

Research conducted in the Centre has been at the heart of the ongoing debate about the likely effectiveness of badger culling as a control strategy. Christl Donnelly played a key role in the advisory group overseeing the Randomised Badger Culling Trial (RBCT), which estimated the impact of culling of badgers on bovine TB incidence in cattle. The trial provided clear evidence that repeated widespread culling could reduce bovine TB in targeted areas, but suggested that the disease risks increased among cattle herds on neighbouring land.

In December 2011, the UK government announced two badger-culling pilots. Given results from the RBCT, which revealed that trapping and shooting of badgers would not be cost-effective, the Government has proposed the shooting of free-ranging badgers. However, whether this method of culling will yield similar reductions in cattle TB remains to be seen.

Our bovine TB team frequently meets with Defra scientists and policy advisors, politicians and stakeholders to discuss new results from the RBCT and other TB work. Centre scientists are evaluating various cattle vaccination strategies,

as well as methods for reporting of cattle testing results that allow for more frequent testing of high risk herds. Following on from the RBCT, we are continuing to compare the incidence of bovine TB in culled and uncultured areas. We are also working in collaboration with the Institute of Zoology to understand the impact that low-level social perturbation has on badger populations.



Image: Zoe Sumner

Christl Donnelly leads the Bovine TB research group.

Bovine TB is maintained in the wild by badgers.



Images: Richard Yarnell

Partnerships

A key focus of the Centre is building strong partnerships with national and international public health agencies. We work closely with colleagues at the **HPA** and **Department of Health** in the UK, **CDC** in the US, **WHO**, and many others.

Holding an external position as head of the HPA Modelling and Economics Unit, Centre researcher Peter White is well placed to facilitate Centre collaborations with the Agency. Joint projects focus on mathematical modelling of the epidemiology of influenza, TB and sexually-transmitted infections, including HIV, and the impact of healthcare interventions. The recent award of a substantial MRC grant to support joint research on influenza serology should see the collaboration flourish in future work.

As an official WHO Collaborating Centre for Infectious Disease Modelling, we are committed to developing projects to support WHO activities and policy making for influenza and other emerging diseases. During the 2009 influenza H1N1 pandemic, our dedicated liaison officer Maria Van Kerkhove linked directly with several WHO departments, working groups and outside organisations to coordinate the WHO informal mathematical modelling network for pandemic influenza. Since the pandemic, Centre scientists have provided technical assistance to and are coordinating research for the Global Influenza Programme, Global Alert and Response Network and Initiative for Vaccine Research, through the interpretation of global data, often in collaboration with many other scientists around

the world. The Centre also provides technical support in the areas of polio, malaria, yellow fever and meningitis.

Another key relationship is with the CDC in Atlanta. As the world's largest public health agency, the CDC has a profound influence on US and international infectious disease health policy in the areas of vaccination, disease mitigation, and epidemiological analysis. Building on a close working relationship before and during the 2009 H1N1 influenza pandemic, Centre researcher Manoj Gambhir has taken up residence at the CDC. Based within the National Center for Immunization and Respiratory Diseases since early 2011, he has been developing collaborations on projects that are viewed as both critical to public health and amenable to novel modelling approaches. One project uses modelling to make sense of the upwards trend in whooping cough infections in the US; despite high levels of vaccination coverage, 2010 saw the worst outbreak since the 1940s. In another project, Centre and CDC staff are examining the potential impacts of a new cytomegalovirus vaccine in babies who contract the disease from their mothers.



Maria Van Kerkhove collaborates internationally with partners at the WHO.



Manoj Gambhir liaises with the CDC in the US.



Image: James Gathany, Centers for Disease Control and Prevention, Atlanta, GA, USA



OTHER WORK ON DISEASE CONTROL STRATEGIES

- In collaboration with the WHO, scientists at the Centre are analysing outbreak data in Africa to inform optimal meningitis and yellow fever vaccination strategies.
- In collaboration with the London School of Hygiene and Tropical Medicine, the Task Force for Global Health and other partners, several Centre researchers are involved in modelling work that is informing control of trachoma, the leading infectious cause of blindness. Models have helped to shape community drug treatment regimes as well as non-pharmaceutical interventions in Africa.
- Uptake of the measles mumps and rubella (MMR) vaccine is influenced by parental concerns about vaccine safety. Diane Pople, an MRC Centre researcher, is working with childcare facilities and parent websites to understand how advice-sharing and contacts between parents affect patterns of infection in vaccine-preventable diseases. Our models could inform planning of public health responses to future vaccine scares.



Image: Mark Oliver

INSPIRING LEARNING

- As part of the Next Generation project, Kath O'Reilly and Azra Ghani from the Centre visited primary schools to talk to children about their work as scientists, elaborating on elements of the Key Stage 2 syllabus through examples of their research on diseases and microorganisms, and supporting practical work.
- Centre scientist Tom Churcher acted as Scientific Advisor for a play called *Bind*, which explored the impact of vaccination on communities. Produced by Ice and Fire, the play was funded by a Wellcome Trust Arts Award and toured London schools to reach over 2,000 young people.



Wellcome Trust-funded production *Bind* focused on vaccination.



MRC Centre Researchers at annual Away Day.

The MRC Centre for Outbreak Analysis and Modelling is an international resource and centre of excellence for research on the epidemiological analysis and modelling of novel infectious disease outbreaks.

If you are interested in studying with us, carrying out research with us or funding our work, please contact:

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The MRC Centre for Outbreak Analysis and Modelling is a Centre at Imperial College London. As the only UK university to focus entirely on science, technology, engineering, medicine and business, Imperial College London offers a critical mass of international research expertise to improve quality of life for people throughout the world.

