Imperial College London

MRC Centre for Outbreak Analysis and Modelling

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ANNUAL REPORT 2012

Director's message

April 2013 sees the Centre renewed for a second 5-year term, after we received an unprecedented 10 out of 10 score from the MRC subcommittee, which assessed the performance of the Centre over its first term. Just as the work of the Centre over that time has been very much a team effort, so was the success of the renewal.

The last few months have seen us start to drive through our strategy for the next 5 years. A crucial aspect of this is to boost capacity in key research areas. It is therefore my pleasure to welcome new academic staff into the Centre. Xavier Didelot joined us last year as a lecturer in pathogen genetics, and our expertise in evolutionary and genetic research will be further boosted this year by the recruitment of at least one additional member of academic staff in this area. Developing research at the interface of economics and epidemiology is another priority, and so we are delighted that Nimalan Arinaminpathy will also be joining us from Princeton (as a senior lecturer). We look forward to the new ideas and perspectives that these researchers will bring to the Centre.

In last year's report I highlighted the Centre's work with the World Health Organization and the US Centers for Disease Control; these partnerships continue to flourish, but the last year has also seen rapid development of our long-term relationship with another key global health body, the Bill and Melinda Gates Foundation. Nick Grassly's work to support polio eradication and to understand the basis of immunity for that infection continues to grow with the Foundation's support, encompassing both analytical research and field studies. In malaria, Azra Ghani was awarded a large grant by the Foundation in late 2012 to provide modelling support for their strategy for malaria eradication. This year, a further two major Foundation-supported initiatives in the Centre – the HIV Modelling Consortium (led by Tim Hallett) and the Vaccine Modelling Initiative – are up for renewal. However, grants are only one aspect of the relationship. As important are the close working relationships between staff in the Centre and the Foundation, which sees our research increasingly used to inform Foundation strategy and delivery.

Despite its title, the Centre's mission rapidly evolved to encompass delivering innovative epidemiological analysis not only of novel infectious disease outbreaks, but also of endemic diseases of major global health significance. Our work on polio, malaria and HIV reflects this. However, the last few months have highlighted the ongoing relevance of our original mission to enhance preparedness and response to emerging disease threats. Centre researchers in London and at CDC in Atlanta have been at the forefront of analysing data on a new H3N2 swine influenza virus, which has caused significant outbreaks in people in the US. As I write this, we are also tracking and analysing the outbreaks of the novel coronavirus that has generated cases in the Middle East and now the UK.

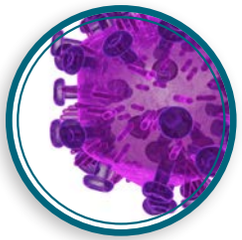
Lastly, I'd like to acknowledge and thank the superb team of administrative and technical staff whose work supports the Centre largely from behind the scenes. Susannah Keeling (Scientific Manager), James Hayward (Centre Administrator), Ruth Tipples (Departmental Manager), Wes Hinsley (Technical Computing and Database Manager) and Francesca Tracey (my Personal Assistant and organiser of my working life!) have made an enormous contribution to making the Centre a success and continue to do so.

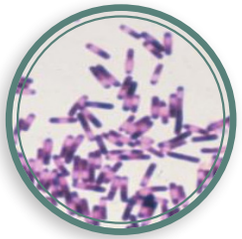
Neil Ferguson

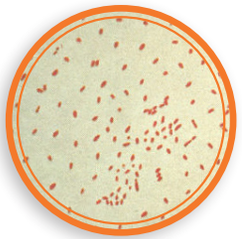
2012

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

Research







Polio

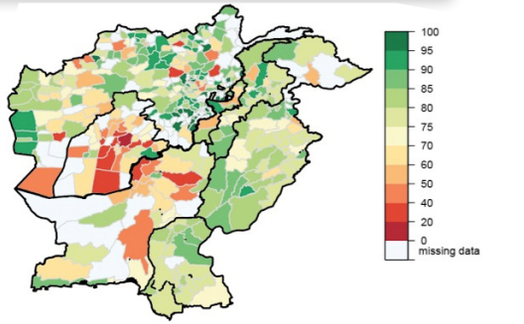
Supporting global eradication efforts

Nick Grassly

At the World Health Assembly in May 2012, polio eradication was declared: "a programmatic emergency for global public health". This statement was largely driven by the recent resurgence of poliovirus in Afghanistan and Pakistan. Researchers from the Centre play an important role in combatting polio by providing estimates of vaccination campaign coverage, vaccine performance and the impact on poliovirus transmission to the Global Polio Eradication Initiative (GPEI). This is in addition to research on fundamental immunology and epidemiology of poliovirus.

In India, for example, the team identified poor efficacy of trivalent oral vaccine as a major cause of polio persistence, and provided the first estimates of the efficacy of a newly licensed monovalent vaccine. This work supported the widespread adoption and use of this vaccine by the GPEI.

India recorded its last case of polio due to indigenous virus in January 2011 and was declared polio-free in 2012. Just three countries have yet to interrupt transmission: Afghanistan, Pakistan and Nigeria, and in 2012 case numbers were at the lowest ever level. Kath O'Reilly has worked to understand why polio was resurgent in Afghanistan and Pakistan; in collaboration with the World Health Organization (WHO), Kath analysed data on the vaccination history of children reported with acute flaccid paralysis in these countries. The majority of these children are paralysed by causes other than poliovirus and so these data provide a valuable insight into vaccination coverage. By comparing the vaccination status of children with and without paralysis caused by poliovirus it is possible to estimate the effectiveness of different vaccines using 'case-control' methods. Kath found that newly licensed monovalent and bivalent vaccines were more effective than the standard trivalent vaccine. However, despite the use of these superior vaccines, population immunity to poliovirus had declined because of substantial drops in vaccination



The proportion of Pakistani and Afghani children under three years old with immunity to serotype 1 poliomyelitis

coverage between 2006 and 2011 (notably in Federally Administered Tribal Areas (FATA) and Balochistan in Pakistan and in southern Afghanistan). Substantive and fundamental changes to the programme in these countries were made in 2012 and clear national emergency action plans put in place.

In 2012 Kath travelled to Afghanistan alongside an independent review team to directly assess the progress being made in implementing these changes. It was discovered that children were not being vaccinated because of basic managerial deficiencies at the district level, rather than due to security or access issues. This was an important realisation and these problems are now being addressed.

Kath O'Reilly (centre)

In 2012 polio case numbers declined in both Afghanistan and Pakistan. There is every reason to hope that this will be polio's last stand in Asia.

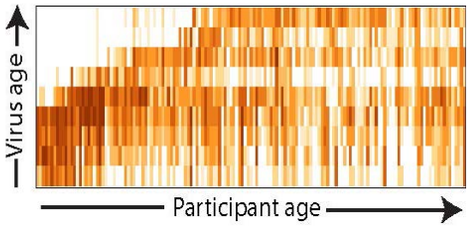
Tara Mangal, Ed Parker, Nick Grassly, Saurabh Johri, and Isobel Blake

Influenza

The Centre conducts a wide range of research into influenza to provide evidence to governments and policy-makers on planning and preparedness for flu pandemics. Research themes include real-time epidemiologic analysis of emerging outbreaks; inter-pandemic patterns of spatial spread and dynamics of genetic and antigenic evolution of influenza for the purpose of analysing historical illness, mortality, and strain surveillance data; and evaluation of intervention measures (including drugs, vaccines and non-pharmaceutical interventions) for containment.

Identifying infection history

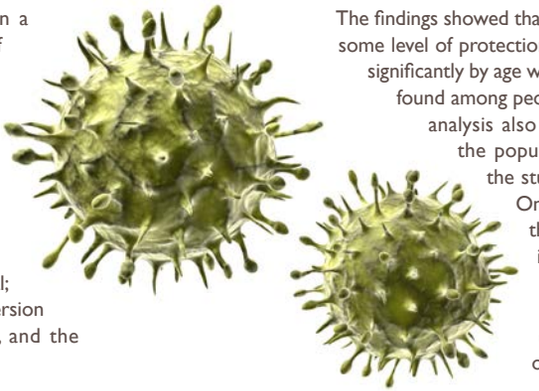
Influenza is different from most other viral infections because individuals can get infected many times over the course of a lifetime. Each time an individual gets infected, the immune system creates antibodies to fight the virus, but, despite making antibodies to fight off the infection, influenza repeatedly infects us year on year. This is a consequence of the way the virus continually evolves to evade the immune system.



Younger people had stronger antibodies (dark colours) to recent strains

Because the body falls into repeated sequences of antibody production for different versions of influenza, Steven Riley and colleagues hypothesised that blood might contain a record of all previous infections. If confirmed, this would enable the infection histories of entire communities to be studied and compared. For example, it might be possible to test whether people living in cities have experienced more flu than those in rural areas.

In their pilot study, the FluScape team collected serum samples from 151 residents of Guangdong Province in China between the ages of seven and 81 years and found that their blood did contain a relatively accurate record of their infection history. It is not a perfect record for any specific individual. However it was possible to make a good estimate of the strength of antibody response to a particular version of flu if three facts were known about an individual; current age, age when this version of the virus first circulated, and the community they lived in.

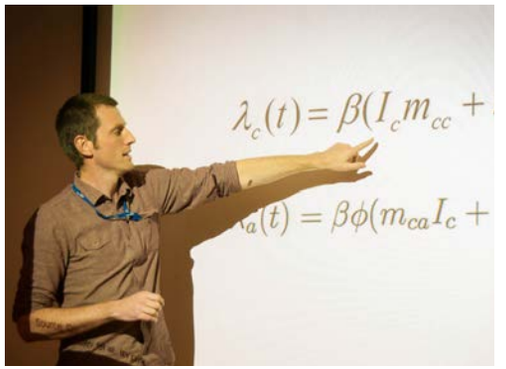


Going forwards, the FluScape team wants to use this knowledge to study the historical patterns of infection and also to think about how to optimise the use of vaccines.

Estimating global incidence of H1N1 pandemic

In June 2009 the WHO announced the first pandemic of the 21st Century: H1N1 influenza. Subsequently, Centre researchers, Maria Van Kerkhove, Artemis Koukounari, Steven Riley, Christl Donnelly and Neil Ferguson participated in a global WHO-Imperial-led collaboration to estimate the number of H1N1 infections during the pandemic's first year.

The first of its kind, the study produced a global summary estimate of the proportion of the population infected by the pandemic virus, by using original serological data from 19 low, middle, and high-income countries.



Steven Riley

The findings showed that 5 per cent of the population had some level of protection against the virus, but this varied significantly by age with the highest rates of protection found among people of 65 years old and older. The analysis also found that 24 – 27 per cent of the populations (of countries included in the study) were infected with the virus. Once again, this varied by age; however this time the highest proportion of infections were reported in school children aged between five and 19 years (47 per cent), followed by children from birth to four years old (36 per cent).

These findings provide vital insight into the previously under-appreciated impact and severity of the H1N1 pandemic and add value to planning and preparation for future pandemics. In particular, the results highlight the need for standardised seroepidemiological studies, and the critical importance of age-specific infection rate data for public health decision makers and mathematical modellers.

Epidemic potential of zoonotic diseases

In February 2012, Lyn Finelli (Surveillance and Outbreak Response Team Lead, Influenza Division, CDC) reported that while half of the 12 people infected with swine influenza A (H3N2) in 2011 had been in close contact with swine, the other half of infected individuals had acquired the infection via human-to-human transmission. At that time, this relatively high proportion of human-to-human transmissions raised concerns in public health agencies.

Initially, viruses are often poorly adapted for sustained human-to-human transmission, but due to strong selective pressure they can evolve to acquire this trait. For an efficient public health response, it is important to quickly and reliably evaluate the extent to which a virus has acquired the ability to transmit from person to person. This is usually measured by the reproduction number 'R': the mean number of persons infected by a human case.

Until now, estimating R required detailed outbreak investigations of human clusters;

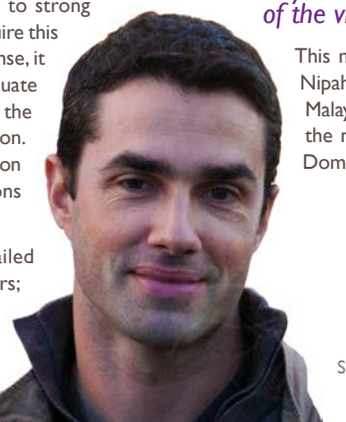
Epi-Aid in PA, USA (courtesy of Karen Wong)

however, such investigations are resource intensive, prone to selection bias and may suffer from imperfect detection of cases. A breakthrough was made when Simon Cauchemez and colleagues realised that knowing the likely source of infection (for example, animal reservoir or human-to-human) of detected cases was sufficient to estimate R. The team developed a simple estimation method that only required data collected through routine surveillance and standard case investigations. This was used to assess the transmissibility of the novel H3N2 variant in the US. Simon's estimates of the transmissibility of the novel H3N2 variant were presented at a briefing to Tom Frieden, the director of the CDC, in February 2012.

Dr Finelli, provided comment on the work:

"Outbreaks of the H3N2v-M virus largely took place at livestock exhibitions with thousands of visitors every day. It is very hard to perform detailed outbreak investigations and effectively trace cases in such settings since visitors are widely dispersed. The approach presented in the paper, is simple, requires few data, and was very useful in assessing transmissibility of the virus from the data available."

This method has now also been applied to Nipah virus (an emerging zoonotic virus) in Malaysia and Bangladesh, and even applied to the non-zoonotic cholera outbreak in the Dominican Republic.



Simon Cauchemez

HIV

Researchers within the Centre conduct a wide range of modelling studies to tackle questions relating to the HIV / AIDS epidemic.

Xavier Didelot, Marcus Shepheard, Katrina Lythgoe, Christophe Fraser, Thibaut Jombart, Anne Cori, Michael Pickles, Diane Pople, Oliver Ratmann, Rafal Mostowy, and David Aanensen

BEEHIVE

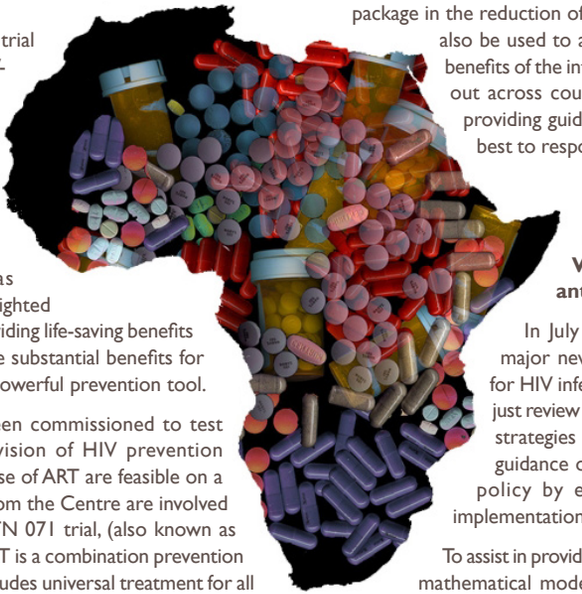
Christophe Fraser and his team have recently started a new project that will investigate HIV biology, evolution and epidemiology: Bridging the Evolution and Epidemiology of HIV in Europe (BEEHIVE). Advanced genomic technologies and bioinformatics will allow the 'deep' genomes of viruses from approximately 3,000 clinically well-characterised HIV-infected patients with known dates of infection to be sequenced. The primary objective of this study is to discover the viral genetic determinants of severity of infection. The project is technologically ambitious and will result in new cutting-edge approaches to viral genome association studies; this is the first time such a study has been attempted with a hyper-variable virus such as HIV. If successful, the findings could lead to a substantial shift in the understanding of HIV disease.

The study also hopes to address a number of critical questions in HIV epidemiology and evolution. Mathematical models and molecular epidemiology will together be used to help understand the resurgence of the HIV epidemic seen in high-risk groups, such as men who have sex with men. The aim will not just be to establish who is at risk of infection, which is known from conventional epidemiological approaches, but to characterise the epidemiological (and possibly virological) risk factors for onwards transmission of the virus.

The MRC Centre has funded pilot studies for this project, which have established that the experimental protocols are feasible and suitable for a large scale-up. Funding for the project is currently being sought.

PopART

In 2011 a landmark clinical trial (HPTN 052) found that HIV-infected heterosexuals offered early antiretroviral therapy (ART) were 96% less likely to transmit the virus to their uninfected partner, than individuals treated under standard guidelines. The study was ground breaking as it highlighted that ART, in addition to providing life-saving benefits to individuals, may also have substantial benefits for the wider population as a powerful prevention tool.



Several trials have now been commissioned to test whether widespread provision of HIV prevention packages that include the use of ART are feasible on a larger scale. Researchers from the Centre are involved in one such study, the HPTN 071 trial, (also known as PopART). Central to PopART is a combination prevention package that includes universal treatment for all infected individuals. The package combines community-wide house-to-house universal voluntary testing for HIV, the offer of medical circumcision to men who test HIV-negative, and immediate initiation of antiretroviral therapy for all those testing HIV-positive. The primary aim is to reduce incidence of new infections during a three-year intervention. The study will assess the impact of these strategies in 21 large communities in Zambia and South Africa with total population 1.2 million. This trial will be the largest HIV prevention study ever carried out.

Christophe Fraser

Christophe Fraser and his team have developed a mathematical model to assist protocol design and optimise the delivery of the intervention during the trial. The model provides insight into which part of the intervention will be crucial for the success of the trial and as such requires careful monitoring. At the end of the trial, the model will be used to aid interpretation of the results by evaluating the relative roles of the different components of the prevention package in the reduction of HIV incidence. The model will also be used to assess the long-term costs and benefits of the intervention if it were to be rolled out across countries. This will be critical for providing guidance to policy makers on how best to respond to the findings of the study.

Modelling recommendations for WHO guidelines on antiretroviral treatment

In July 2013, the WHO will release major new guidance on the use of ART for HIV infection. These guidelines will not just review the optimal clinical management strategies but also include programmatic guidance on how best to implement the policy by either staged or prioritised implementation.

To assist in providing long-term recommendations, mathematical modelling was introduced into the development of the guidelines for the first time. The HIV Modelling Consortium, directed by Tim Hallett, was enlisted to lead a large collaboration of over 60 mathematical modellers and health economists to answer a number of specific questions raised by the WHO. The group included leading researchers from over 20 international institutions, including Imperial College London, the London School of Hygiene and Tropical Medicine, Stellenbosch University, Princeton University, and Harvard School of Public Health.

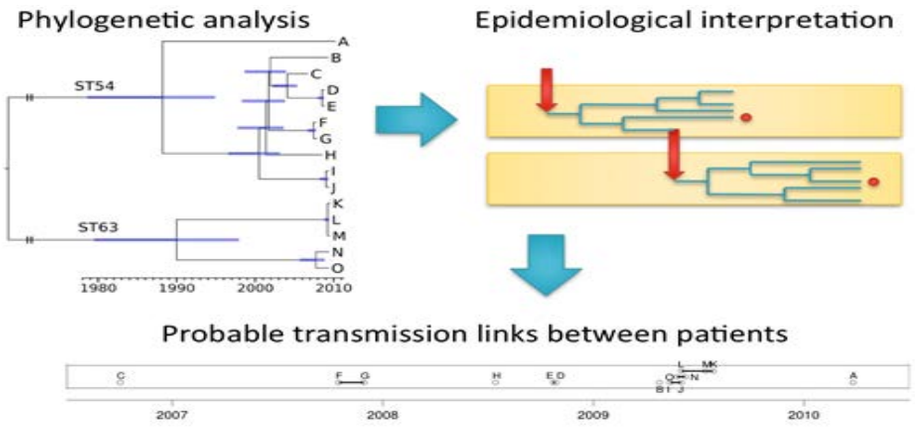
Tim Hallett, Jack Olney, Daniel Keebler, Ellen McRobie, Jeff Eaton, Paul Revill; members of the HIV Modelling Consortium at a meeting with the International epidemiologic Databases to Evaluate AIDS (IeDEA) network in Kampala, Uganda

The modelled scenarios included the impact of earlier ART eligibility, prioritised treatment of special populations, cost and impact of alternative strategies for monitoring patients on ART (adults and children) and they will provide guidance on how programme managers should respond to these findings. To evaluate the potential health impact and cost effectiveness of different treatment eligibility criteria, long-term (20 year) projections were provided for case studies of South Africa, Zambia, India and Vietnam.

Tim and members of the Consortium attended several planning meetings with the WHO in Geneva to review the potential recommendations from the modelling work, the outcomes of which will be incorporated into the guidelines and unveiled at the International AIDS Society conference in July 2013. In addition, the team has developed two papers providing further insight on the modelling efforts and they are co-ordinating a special edition supplement in AIDS which will include papers from collaborators on topics such as prevention of mother-to-child transmission and hepatitis co-infection.

Tim Hallett

C. difficile



Probable transmission links between patients in a subset of fifteen patients.

Genomic analysis

Understanding how human infectious diseases spread from person to person is essential when determining which containment measures will effectively limit the burden on public health. The emergence of a new genomic methodology of studying this transmission holds great promise for the advancement of the field as it complements traditional epidemiological approaches. As mutations accumulate at a relatively low and constant rate on the genome of a pathogen, if a person infected another, the genomes they carry are expected to be highly similar. This simple principle can be inverted, in order to assess the probability of transmission between two individuals given the similarity of the genomes infecting them.

Centre researchers, led by Xavier Didelot, have recently applied this technique to investigate the transmission of *Clostridium difficile*: a bacterium that can cause life-threatening diarrhoea, especially when it infects the elderly. Genomes were sequenced from hundreds of hospital patients showing symptoms of being infected in Oxfordshire between 2006 and 2010. In order to reveal probable transmission links between patients, the genomes were first compared using phylogenetic techniques, and then interpreted epidemiologically in terms of within-host evolution of the bacteria.

The study aimed to test the widely-held assumption that transmission occurs frequently in hospitals between symptomatic patients. When hospital transmission was found to be likely on the basis of the genomic comparison, it often corresponded to patients having visited the same wards on overlapping dates. The epidemiological and genomic data were therefore in good agreement. However, genomes frequently failed to match to an extent that would indicate recent transmission. This suggests that *Clostridium difficile* may often spread through other routes, for example in communities or through asymptomatic carriers.

As the speed and cost of sequencing whole bacterial genomes continue to fall, a genomic approach to studying transmission is likely to become increasingly widespread, not only for *Clostridium difficile* but also for a variety of pathogens. In order to make the most of this new stream of information, Xavier and his team are developing novel analytical tools and preparing new applications to investigate the transmission of other pathogens, such as *Staphylococcus aureus* or *Helicobacter pylori*.

Xavier Didelot

Rabies

Making the most of surveillance data

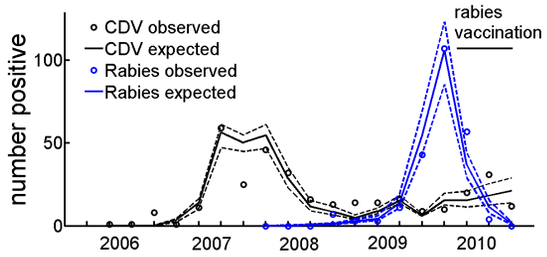
It was recently estimated that human rabies causes 70,000 deaths worldwide each year. This is despite the disease being entirely preventable by vaccine. The control of rabies is particularly challenging because the virus can infect virtually any mammal; thus, a detailed understanding of the transmission dynamics within and between various species is critical to target control efforts most effectively.

Ana Bento, Nick Beckley, Picha Suwannahitatorn, Jon Bielby, Christl Donnelly, Pete Winskill, Pierre Nouvellet, and Eve Miguel

Researchers from the Centre, in collaboration with the Istituto Zooprofilattico Sperimentale delle Venezie (IZSVe), recently studied the reintroduction of fox rabies in Italy, after a thirteen-year absence. The aim of this collaboration was to estimate the incidence of the disease and the underlying rate of transmission among foxes, allowing the team to assess the impact of a fox oral vaccination campaign.

A key challenge of the study was to make full use of data collected from both dead and living foxes; as infected animals die at a higher rate than uninfected ones, the prevalence of infection among the dead is clearly biased. A basic mathematical model was developed to allow statistical inference in this challenging setting, which is common in surveillance data on wildlife. After assessing the incidence of infection, it was estimated that a rabid fox would infect a susceptible fox on average once every three days. The team also estimated that the vaccination campaign in 2010 immunised roughly 70 per cent of foxes: a level sufficient to impede further spread of the disease within this population.

At the same time as the resurgence of rabies, a Canine Distemper Virus (CDV) epidemic also affected the Italian fox population. The incidence and the rate of transmission were again estimated. Each of these cocirculating diseases can modify the structure of the fox population, thus 'ecologically interfering' with the transmission dynamics of the other disease.



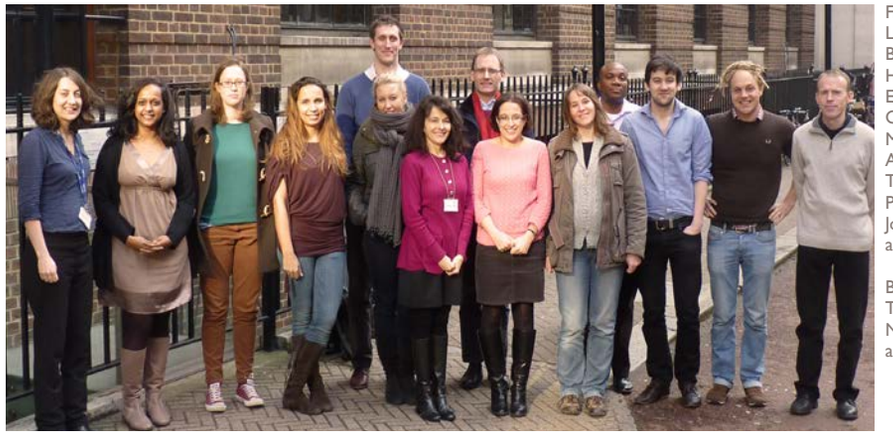
Observed and expected detected cases of CDV and rabies in Italian foxes from 2006 to 2010

Beyond this study, the research team is working to improve the understanding of the dynamics of rabies transmission both within and between species.

The team is collaborating with Rosie Woodroffe (London Institute of Zoology and honorary Imperial College London Professor) to quantify rabies transmission among African wild dogs (*Lycaon pictus*) and to assess whether domestic dogs act as a reservoir of rabies for transmission to wildlife species. In complementary work with the Pasteur Institute, the team is also working to understand the dynamics of rabies among urban domestic dogs, a principal threat to human health, using data from Algiers (Algeria) and Bangui (Central African Republic).

Christl Donnelly

Malaria



Front:
Lucy Okell,
Bharghavi Rao,
Hannah Slater,
Emilie Pothin,
Celine Christiansen-Jucht,
Maria-Gloria Basanez,
Azra Ghani,
Tini Garske,
Patrick Walker,
John Marshall,
and Jamie Griffin

Back:
Tom Churcher,
Neil Ferguson,
and Ndukwe Ukoha

Understanding the role of malaria vaccines in reducing malaria burden and transmission

More than a third of the world's population is at risk of contracting malaria, with the majority of severe cases affecting young children in sub-Saharan Africa. A vaccine for preventing malaria would be an invaluable tool for reducing the burden of disease in young children. The RTS,S vaccine is the most advanced vaccine candidate against any human parasite and is currently being tested in phase III trials in African children. Over the past year, Azra Ghani and colleagues have collaborated with GlaxoSmithKline Biologicals, the developers of RTS,S, to investigate how vaccine efficacy varies between individuals according to age, transmission intensity and the magnitude of the vaccine-induced immune response. To explore how these factors affect vaccine efficacy the team has used mathematical models to analyse data from multiple phase II trials, ranging from laboratory-based trials where healthy adults are exposed to the bites of infectious mosquitoes, to field-based trials in African children living in malaria endemic areas. Through collaboration with the Program for Appropriate Technology in Health (PATH) Malaria Vaccine Initiative, these insights are being integrated into transmission models to estimate the public health impact and cost-effectiveness of the vaccine across a broad range of epidemiological settings in Africa. This work takes into account the ongoing distribution and scale-up of other anti-malaria interventions, including bed nets and house spraying. The team is also working closely with the WHO to ensure that the outcomes of this work are relevant to the decision-making process following the submission of the final phase III trial results in 2014.

Photo credit: Dave Poland, PATH Malaria Vaccine Initiative

The malaria research group is also investigating how restricting transmission of malaria from humans to mosquitoes can be used to control the disease. In collaboration with Bob Sinden and Andrew Blagborough from the Department of Biological Sciences at Imperial College London, the team has developed a laboratory-based model that simulates malaria transmission in a mouse population. This allows the impact of a transmission-blocking drug upon both insect and host populations over multiple transmission cycles to be investigated. The experiments show that restricting the development of parasites in individual mosquitoes can reduce the probability of transmission to the next mammalian host. By changing the number of mosquitoes biting the mice it is possible to simulate different intensities of transmission. This demonstrates that partially effective transmission blocking interventions may eliminate malaria in low transmission settings but not high ones. These studies will be used to test the impact on transmission of a range of different drugs and vaccines before the most promising candidates are taken forward into human trials.

Dengue and Yellow Fever

Dengue is an important viral mosquito-borne infection which is estimated to infect 50 million people a year across much of the tropical and subtropical world. The last 12 months have seen a substantial increase in the resources the Centre is committing to dengue research, with the principal aim of informing the continuing development of vaccines and novel vector control measures.

We continue to work with the 'Eliminate Dengue' team who are developing the insect pathogen *Wolbachia* as a biological control to reduce vector competence and with Oxitec Ltd who are developing genetically modified sterile insects (using the RIDL technology). With collaborators, Christl Donnelly published a paper last year that compared trial designs which might be used to evaluate the effectiveness of *Wolbachia* in suppressing dengue transmission. Neil Ferguson and members of his group have been continuing their work to predict the potential impact of *Wolbachia* infected mosquitoes on transmission of dengue. In collaboration with Cameron Simmons' group in Vietnam, they have used novel clinical and experimental data to derive serotype specific estimates of the reductions in transmission different strains of *Wolbachia* may induce, together with insights into the pathogenesis of dengue in mosquitoes.

Aedes aegypti is a mosquito that can spread the dengue fever

The last year also saw publication of unexpectedly disappointing results from the first (phase IIB) efficacy trial of the Sanofi-Pasteur dengue vaccine candidate. The results of the trial call into question established wisdom about dengue pathogenesis and transmission, and open up a number of interesting and important research avenues. Over the next few years, we are planning to work with a consortium of collaborators spanning both academia and the vaccine industry to try and gain a better quantitative understanding of the human immune response to both natural dengue infection and vaccine – work which we hope will improve understanding of the epidemiology of dengue and inform vaccine development and use. Our work in this area will build on our ongoing research, modelling the dynamics of the interaction between virus and the human immune response during dengue infection.

Dengue epidemics vary dramatically from year to year and place to place in their intensity. Planning for use of novel interventions requires a better understanding of the causes and magnitude of this variation in dengue transmission intensity. Therefore other work in the Centre is developing new methods for quantifying this variation from both serological data and routine surveillance of clinical dengue cases. Other new sections of work will look at dengue characteristics determining transmission such as immunity over time, and understanding and modelling the spatial aspects of dengue.

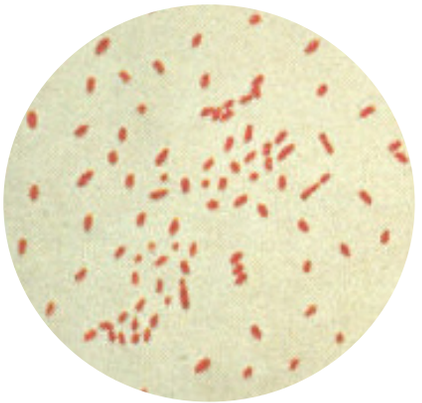
An Oxitech researcher releases mosquitos

Finally, 2012 also saw work begin on Yellow Fever, a relative of dengue virus and an important cause of morbidity and mortality in West and Central Africa and South America. In collaboration with colleagues from the World Health Organisation and the CDC, we have generated the new estimates of the burden of disease caused by Yellow Fever in Africa. These will be used to inform decisions on investments in Yellow Fever vaccination programmes to be made in the coming months.

Pertussis

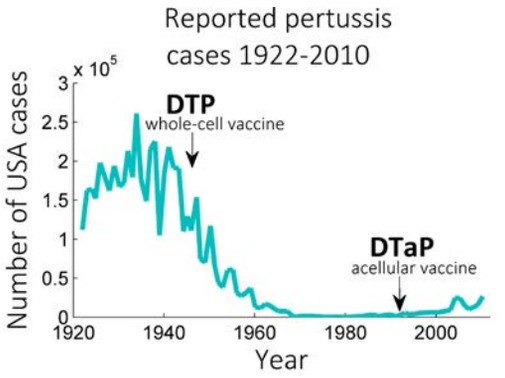
Modelling the pertussis resurgence in the US at the Centers for Disease Control (CDC)

Over the past 20 years, the incidence of whooping cough (pertussis) in the United States has risen, with particularly sharp increases in disease during 2004-2005, 2009-2010 and in 2012. 2010 saw the highest reported disease incidence since the pre-vaccination era, and there were an even larger number of cases in 2012. Pertussis can be a severe disease, particularly in infants and very young children who account for most of the disease-related deaths. The recommended vaccination schedule in the United States is five doses of pertussis vaccine; three to be delivered before the age of one and the following two given by six years of age. In addition to the overall rise in disease that has occurred over the past decade, a shift in the age distribution of cases has also been observed, with a greater number in those between seven and 10 years of age.



Bordetella pertussis bacteria

Several explanations have been put forward to account for this resurgence. Centre researchers Manoj Gambhir, Simon Cauchemez and Neil Ferguson have collaborated with the Meningitis and Vaccine Preventable Diseases Branch within the National Center for Immunization and Respiratory Diseases at CDC to construct a nationwide suite of mathematical models. Regular consultations were held with the epidemiology and outbreak investigation teams to devise these models and to fit them to National Notifiable Disease Surveillance System (NNDSS) incidence data from 1990-2009 and time series incidence data from 1950-1989. It was found that the clearest explanation for the rise in disease comes from a model in which the vaccine efficacy of a relatively new 'acellular' pertussis vaccine is slightly lower than that of the 'whole-cell' vaccine that had been previously recommended. This is in agreement with a small number of vaccine effectiveness studies that have been performed by CDC and others. However, this drop in efficacy is small, and the team is currently investigating ways in which disease might be controlled by administering booster doses to adolescents and adults.



Source: CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System and 1922-1949, passive reports to the Public Health Service

This project is illustrative of the continued close collaboration with CDC on health policy issues of the highest public importance, that began with H5N1 avian influenza preparedness planning and continued most notably with the 2009 H1N1 influenza pandemic. The team provides a unique service within CDC, giving insight into the complex dynamics of infectious disease in a clear, responsive and sophisticated way.

Manoj Gambhir

Tuberculosis

Refining testing strategies

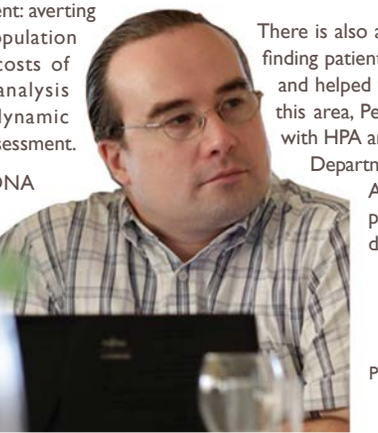
The Centre works closely with the Health Protection Agency (HPA, soon to become Public Health England) through the joint appointment of Peter White, who heads the HPA Modelling and Economics Unit. Work with HPA focuses on the mathematical modelling of the epidemiology of influenza; tuberculosis (TB); sexually transmitted infections, including HIV; and the impact of healthcare interventions.

TB is a major cause of mortality worldwide and has been increasing in the UK for the last two decades, with resistance to antibiotics a growing cause for concern. Dame Sally Davies, Chief Medical Officer at the Department of Health has identified antibiotic resistance as a key threat to health. Combating drug resistance in TB requires rapid diagnosis of infection and identification of drug-resistance, followed by successful administration of treatment. This is challenging and it is necessary to develop services that are tailored to patients' needs, while ensuring that they provide value for money. For example, TB is concentrated in particular patient groups, many of whom are socially excluded, making access to care difficult. In addition, management of TB requires lengthy treatment programmes, for which maintaining adherence can be difficult. If a patient exhibits antibiotic-resistant TB then treatment can take two years.

An important part of assessing the benefit of interventions is using mathematical modelling to predict the numbers of infections averted in the future by effective control measures implemented in the present: averting infections not only improves population health but also reduces future costs of treatment. Health economic analysis integrated with transmission-dynamic modelling is used to provide this assessment.

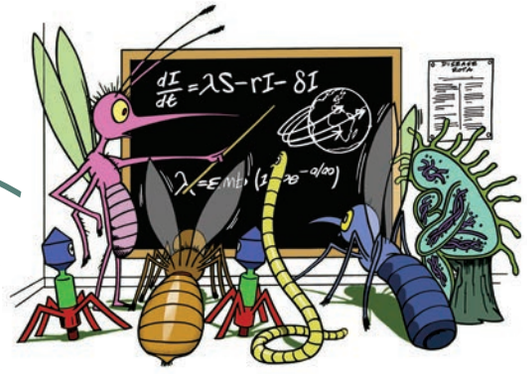
New diagnostic tests, based on DNA testing rather than microbiological laboratory culture, that are better at rapidly identifying TB and detecting drug resistance are available. However, they are expensive and in an era of constrained budgets it is necessary to determine the most cost-effective way to use them. Peter and colleagues are working on the most cost-effective arrangement of testing services for drug-resistant TB, with collaborators at University College London (UCL), Queen Mary and Brunel University, funded by the National Institute for Health Research (NIHR). As diagnostic tests continually improve and the number available increases, it is important to assess cost-effectiveness of novel TB diagnostics.

There is also a requirement for better methods of finding patients so that they can be tested, treated and helped with adhering to their medication. In this area, Peter and colleagues are collaborating with HPA and UCL, with funding from NIHR, the Department of Health, and the Wellcome Trust. An example of this work is the recent publication of an economic analysis of different testing strategies for immigrants.



Peter White

IN BRIEF



SHORT COURSE

Each year, centre researchers contribute to the organisation and running of a 2-week introductory course to Mathematical Models of the Epidemiology and Control of Infectious Diseases, which attracts participants from all over the world. A highlight of the 2012 session was the invited lecture that Prof. Harald zur Hausen, 2008 Nobel Prize in Physiology or Medicine, gave on the role of infectious agents in the causations of human cancers.

www.infectiousdiseasemodels.org

GLOBAL PARTNERSHIPS

Global Polio Eradication Initiative

• Global polio eradication is entering the 'endgame'. Centre staff provide surveillance data analysis and mathematical models of polio risks that contribute to strategic planning and evaluation of innovations to accelerate eradication, including assessing the potential impact of expanding the target age group for vaccination campaigns.

Consortium for the Standardization of Influenza Seroepidemiology (CONSISE)

• In collaboration with several international organisations, including the WHO, European Centre for Disease Control (ECDC), HPA and CDC, Centre staff are key members of CONSISE: a global partnership aiming to develop influenza investigation protocols and standardise seroepidemiology to inform health policy.

WHO working group; Yellow Fever

• As part of a WHO working group to explore modelling techniques and review surveillance systems data to measure the Yellow Fever disease burden in Africa, Centre scientists recently presented their results to WHO and GAVI and demonstrated the impact of the GAVI vaccine investment implemented in 2005.

Maria Van Kerkhove

Elimination Scenario Planning Workshop, The Gambia

• Participating in a workshop led by the Clinton Health Access Initiative and WHO with the National Malaria Control Programs of The Gambia and Senegal, Azra Ghani and Jamie Griffin ran a session on the Centre-developed Malaria Tools software to assist country programmes to explore scenarios for future intervention packages. One participant commented;

"I loved the practical session… we went from one scenario to another and saw the impact of various interventions and the value added of combining interventions".

Malaria Tools software in use

PUBLIC ENGAGEMENT

Science Uncovered

• Centre researchers presented and discussed information about HIV/AIDS at Science Uncovered - the Natural History Museum's biggest after hours event attended by 8,500 visitors.

Jenny Smith, Erica Pufall, and Sarah Gerver

Imperial Fringe Event

• At the Imperial College Fringe Event for Halloween, Centre staff used a simplified interactive version of their Global Epidemic Simulator computer modelling software to show the behaviour of an infectious outbreak of Halloween-esque figures including zombies, werewolves, witches and vampires. Disease characteristics, mobility and intervention policies are key factors in predicting the spread of real outbreaks.

Wes Hinsley at the Imperial Fringe

Café Scientifique, The Royal Society

• Azra Ghani led a debate at The Royal Society's 'Café Scientifique', addressing questions such as '*does taking the bus make you ill?*', and '*are your friends challenging your immune system?*'. They discussed the importance of travel and social contact in spreading infectious diseases, and how you can minimise your risk of getting sick, without becoming a hermit.

Cambridge Science Festival

• Christl Donnelly spoke in a session entitled "*Outbreak: how epidemiologists work to protect you*", explaining the race against the clock to limit the spread of a newly identified infectious disease.

FELLOW FOCUS

• Centre researchers John Marshall and Kath O'Reilly each received MRC fellowships in 2012.

• Wellcome Trust postdoctoral fellow Oliver Ratmann returned from Duke University to continue work on evolutionary epidemiology focusing on the analysis of HIV transmission dynamics in Europe from clinical and molecular genetic data.

Oliver Ratmann

John Marshall

IN BRIEF

media

The Observer

Adam Kucharski

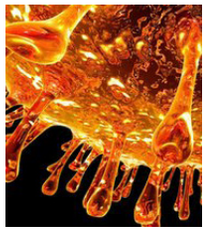
In 2012, an MRC Centre researcher was awarded the Wellcome Trust Science Writing prize.

Adam Kucharski, who works on influenza with Steven Riley, was winner of the professional scientist category for an article about the importance of estimates in science. Almost 600 entries were submitted in total.

The winning piece, entitled 'In need of a number', was published in the Observer last autumn.

BBC NEWS

Swine flu infected 'fifth of people'



"At least 20% of people, including half of school children, were infected with swine flu during the first year of the pandemic in 2009,"

Centre researcher, Maria Van Kerkhove, one of the lead authors of the corresponding Influenza-published article, said;

"This study is the result of a combined effort by more than 27 research groups worldwide, who all shared their data and experience with us to help improve our understanding of the impact the pandemic had globally."

BBC NEWS MAGAZINE

'The flu virus that nearly killed me'

The BBC News Magazine featured a story about the journalist, Michael Moseley, who gave a sample of his blood to Centre Investigator, Steven Riley. The sample was analysed and the results compared to a database of antibody data, thus enabling a picture of his exposure to historical viruses to be painted.

Michael Moseley was born in India shortly after the Asian flu of 1957 emerged. The analysis was able to show traces of antibodies to the Asian flu along with antibodies to the flu pandemic of 1968 that he had caught while living in Hong Kong as an 11 yr old, and finally the Russian flu of 1977 that he had caught as a student at Oxford university

Steven Riley

theguardian

Centre Investigator, Christl Donnelly, was a key member of the government's Independent Scientific Group which designed, oversaw and analysed the Randomised Badger Culling Trial (a study that measured the extent to which badger culling could reduce bovine TB in cattle). Guardian environment reporter Damian Carrington published a letter to Nature from Christl and collaborator Rosie Woodroffe demonstrating the implications of difficulties in counting badgers. He wrote;

"... the culls have to wipe out at least 70% of the animals to avoid making matters worse, but it's impossible to know whether you've hit this target if you don't really know how many there were to start with."

Selected Publications

Boily MC, Mâsse B, Alsallaq R, Padian NS, Eaton JW, Vesga JF, Hallett TB. HIV treatment as prevention: considerations in the design, conduct, and analysis of cluster randomized controlled trials of combination HIV prevention. *PLoS Med*. **2012**;9(7):e1001250.

Bousema T, Griffin JT, Sauerwein RW, Smith DL, Churcher TS, Takken W, Ghani A, Drakeley C, Gosling R. Hitting hotspots: spatial targeting of malaria for control and elimination. *PLoS Med*. **2012**;9(1):e1001165.

Cauchemez S, Horby P, Fox A, Mai LEQ, Thanh LET, Thai PQ, Hoa LENM, Hien NT, Ferguson NM. Influenza infection rates, measurement errors and the interpretation of paired serology. *PLoS Pathog*. 2012;8(12):e1003061.

Chis Ster I, Dodd PJ, Ferguson NM. Within-farm transmission dynamics of foot and mouth disease as revealed by the 2001 epidemic in Great Britain. *Epidemics*. **2012**;4(3):158-69.

de Silva E, Ferguson NM, Fraser C. Inferring pandemic growth rates from sequence data. J R Soc Interface. **2012**;9(73):1797-808.

Delva W, Eaton JW, Meng F, Fraser C, White RG, Vickerman P, Boily MC, Hallett TB. HIV treatment as prevention: optimising the impact of expanded HIV treatment programmes. *PLoS Med*. **2012**;9(7):e1001258.

Didelot X, Bowden R, Wilson DJ, Peto TE, Crook DW. Transforming clinical microbiology with bacterial genome sequencing. *Nat Rev Genet*. **2012**;13(9):601-12.

Dorigatti I, Cauchemez S, Pugliese A, Ferguson NM. A new approach to characterising infectious disease transmission dynamics from sentinel surveillance: application to the Italian 2009-2010 A/H1N1 influenza pandemic. *Epidemics*. **2012**;4(1):9-21.

Eaton JW, Johnson LF, Salomon JA, Bärnighausen T, Bendavid E, Bershteyn A, Bloom DE, Cambiano V, Fraser C, Hontelez JA, Humair S, Klein DJ, Long EF, Phillips AN, Pretorius C, Stover J, Wenger EA, Williams BG, Hallett TB. HIV treatment as prevention: systematic comparison of mathematical models of the potential impact of antiretroviral therapy on HIV incidence in South Africa. *PLoS Med*. **2012**;9(7):e1001245.

Grassly NC, Jafari H, Bahl S, Sethi R, Deshpande JM, Wolff C, Sutter RW, Aylward RB. Waning intestinal immunity after vaccination with oral poliovirus vaccines in India. *J Infect Dis*. **2012**;205(10):1554-61.

Karolemeas K, Donnelly CA, Conlan AJK, Mitchell AP, Clifton-Hadley RS, Upton P, Wood JLN, McKinley TJ. The Effect of Badger Culling on Breakdown Prolongation and Recurrence of Bovine Tuberculosis in Cattle Herds in Great Britain. *PLoS ONE*. **2012**;7(12).

Lessler J, Riley S, Read JM, Wang S, Zhu H, Smith GJD, Guan Y, Jiang CQ, Cummings DAT. Evidence for Antigenic Seniority in Influenza A (H3N2) Antibody Responses in Southern China. *PLoS Pathogens*. **2012**;8(7).

Lythgoe KA, Fraser C. New insights into the evolutionary rate of HIV-1 at the within-host and epidemiological levels. *Proc Biol Sci*. **2012**;279(1741):3367-75.

Namouchi A, Didelot X, Schöck U, Gicquel B, Rocha EP. After the bottleneck: Genome-wide diversification of the Mycobacterium tuberculosis complex by mutation, recombination, and natural selection. *Genome Res*. **2012**;22(4):721-34.

Okell LC, Bousema T, Griffin JT, Ouédraogo AL, Ghani AC, Drakeley CJ. Factors determining the occurrence of submicroscopic malaria infections and their relevance for control. *Nat Commun*. **2012**;3:1237.

O'Reilly KM, Durry E, ul Islam O, Quddus A, Abid N, Mir TP, Tangermann RH, Aylward RB, Grassly NC. The effect of mass immunisation campaigns and new oral poliovirus vaccines on the incidence of poliomyelitis in Pakistan and Afghanistan, 2001-11: a retrospective analysis. *Lancet* **2012**;380(9840):491-8.

Ratmann O, Donker G, Meijer A, Fraser C, Koelle K. Phylodynamic inference and model assessment with approximate bayesian computation: influenza as a case study. *PLoS Comput Biol*. **2012**;8(12):e1002835.

Truscott J, Ferguson NM. Evaluating the adequacy of gravity models as a description of human mobility for epidemic modelling. *PLoS Comput Biol*. **2012**;8(10):e1002699.

Wolbers M, Kleinschmidt I, Simmons CP, Donnelly CA. Considerations in the design of clinical trials to test novel entomological approaches to dengue control. *PLoS Negl Trop Dis*. **2012**;6(11):e1937.

Yu H, Cauchemez S, Donnelly CA, Zhou L, Feng L, Xiang N, Zheng J, Ye M, Huai Y, Liao Q, Peng Z, Feng Y, Jiang H, Yang W, Wang Y, Ferguson NM, Feng Z. Transmission Dynamics, Border Entry Screening, and School Holidays during the 2009 Influenza A (H1N1) Pandemic, China. *Emerging Infectious Diseases*. **2012**;18(5):758-66.

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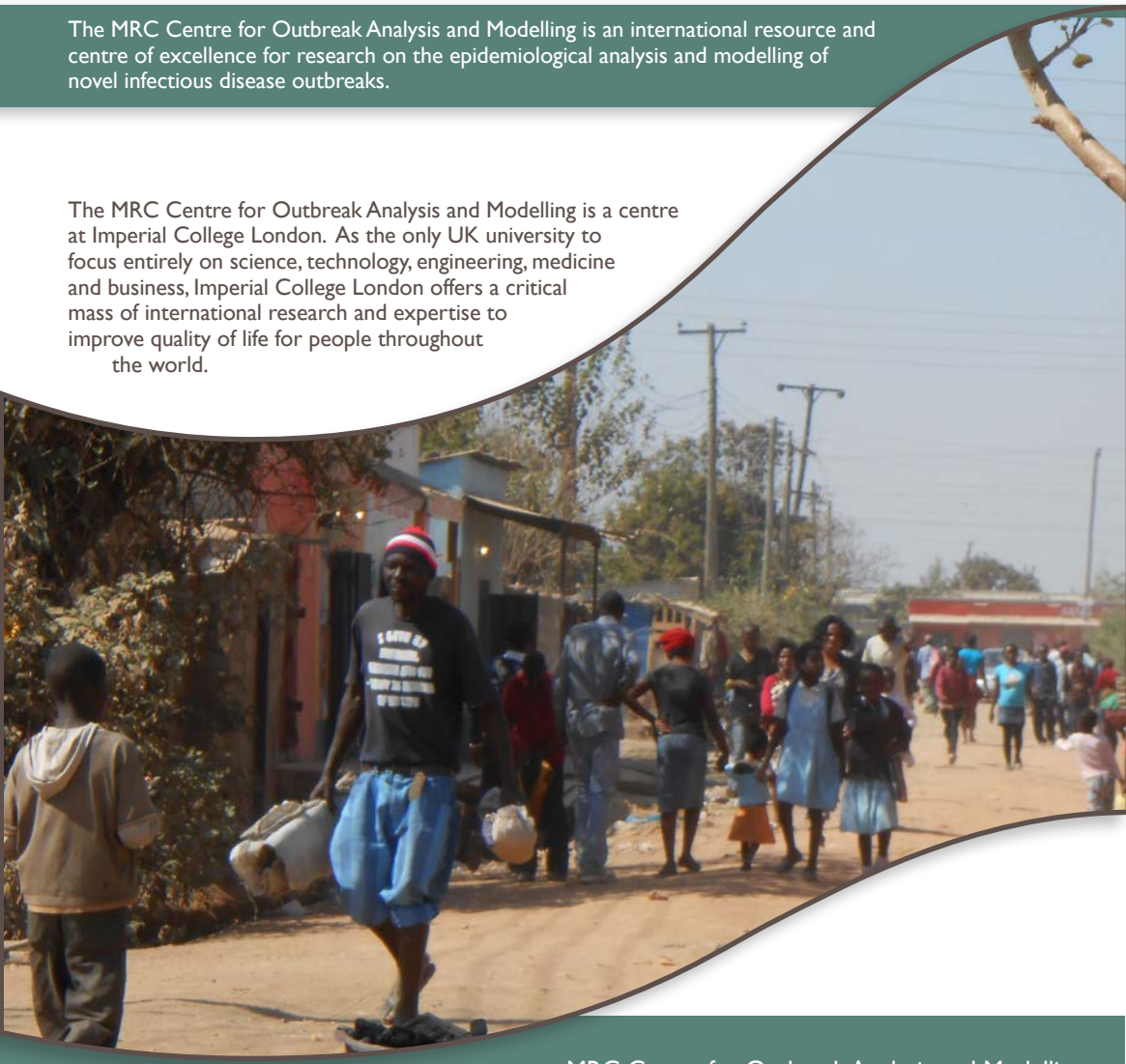

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