Imperial College London

MRC Centre for Outbreak Analysis and Modelling

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ANNUAL REPORT 2015-16

www.imperial.ac.uk/medicine/outbreaks

Contents

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

Director's message

Neil Ferguson

No sooner had the catastrophic Ebola epidemic in West Africa finally been eliminated, reports emerged of a large-scale Zika virus epidemic in Brazil. Following the World Health Organization's (WHO) declaration of the Zika epidemic as a public health emergency of international concern, Centre researchers have been at the forefront of trying to understand the epidemiology of this previously under-studied virus, and of predicting the likely future trajectory of the epidemic (see page 4).

However, while remaining a key part of its mission, outbreak response now represents only a minority portion of Centre research. In addition to outbreaks, a major ongoing theme is the application of modelling and analysis to inform Global Health planning – most notably for HIV, malaria, TB, and neglected tropical diseases. The work of Centre researchers to inform the Global Fund's (to fight AIDS, TB and Malaria) new Investment Case is a notable translational highlight and a great example of close stakeholder engagement that has become the norm across the very broad range of Global Health research undertaken within the Centre.

Vaccine research is another theme of growing importance in the Centre's research portfolio. In the last 12 months, Centre researchers have published major papers on the mode of action and/or public health impact of vaccines against polio, malaria, dengue and yellow fever. In much of this work, a growing emphasis has been on deriving maximum information from clinical trial data – and indeed, in the case of Polio, running our own trials. Both Ebola and Zika have led to renewed emphasis on vaccine research, with the Centre well-placed to add value to this effort.

Antimicrobial resistance (AMR) is another global research priority area where the Centre is increasingly consolidating and growing its research capacity. Integrated genomic and epidemiological analysis will be essential to quantifying the burden of disease from AMR, understanding drivers of the emergence and spread of resistance, and to developing innovative approaches to responding to this challenge.

The Centre has recently recruited 10 new lecturers and senior lecturers: Nim Pathy and Erik Volz in 2013, Tom Churcher in 2014, Lesong Conteh, Katharina Hauck, Pierre Nouvellet and Thibaut Jombart in 2015 and, most recently, Lucy Okell, Tini Garske and Sam Bhatt. Some have brought new skills (e.g. in health economics, phylodynamics and geostatistics), while others reinforce existing areas of excellence, but all will be vital to the continued evolution of the Centre.

Christl Donnelly discussing the Ebola outbreak with Tini Garske and Pierre Nouvellet. Photo by Thomas Angus

Emerging infectious diseases

Emerging infectious diseases include: previously unidentified "newly emerging" infections (e.g. Middle East respiratory syndrome coronavirus (MERS-CoV)); known "re-emerging/resurging" infections spreading into new geographic areas (e.g. Ebola and Zika), and "deliberately emerging" infections, re-emerging due to antimicrobial resistance or changing social conditions.

With MERS, Ebola and Zika outbreaks arising in quick succession, Centre researchers have been working on all three in parallel. Some analytical methods and tools are useful in all settings, however bespoke statistical methods have also been developed to distinguish between camel-to-human and human-to-human transmission of MERS, and between vector-borne and sexual transmission of Zika virus.

Epidemiological analysis by Centre researchers suggests the ongoing Latin American Zika pandemic may have now peaked, limiting scope for interventions having a major impact. This work also highlights that the current pandemic will generate high levels of herd-immunity in the countries affected, preventing future large-scale outbreaks for at least a decade. This gives a valuable window to develop vaccines and novel vector controls, but poses challenges for the design of efficacy trials. Many aspects of the epidemiology of Zika remain poorly understood with large uncertainties due to the mild and non-specific nature of symptoms and difficulties in assessing prior exposure. With partners in Colombia (and emerging MRC funding), the Centre is conducting serological surveys using state-of-the-art testing to characterise the local epidemiology of Zika. Statistical models will be developed to assess current herd-immunity levels, and characterise the force of infection, thus enabling researchers to predict future possible attack rates and transmissibility.

All outbreaks bring unique challenges, but the Centre can now draw on an increasingly rich library of methods based on collective experience and the analytical tools it has developed. A particular current methodological focus is on 'operationalising' the wealth of methods developed within the Centre and elsewhere into a set of code libraries that can easily be deployed worldwide by public health agencies and researchers in future outbreaks.

Tanzania zoonoses meeting participants

Photo by Helen O'Neill
(Institute of Zoology)

Animal diseases

Centre research on animal diseases has focussed on zoonotic diseases, transmissible from animal to human populations. Collaborative projects focus on bovine TB in cattle and badgers, rabies in domestic and endangered African wild dogs, and Ebola in non-human primates.

In a joint study with the Zoological Society London (ZSL), GPS tracking and proximity loggers on cattle and badgers tracked their movements within shared environments. A ZSL study site in Kenya used similar technology to quantify rabies transmission opportunities between domestic and African wild dog populations.

Collaborating with Institut Pasteur, complementary single-species work in the Central African Republic used spatial, temporal and genetic data on rabies in dogs to reconstruct the evolutionary and epidemiological dynamics of dog rabies viruses in the capital city Bangui. Similar work is underway in Algiers, Algeria.

Despite media coverage about the 2014-16 West African Ebola virus epidemic, many are unaware of the serious threat posed to great ape conservation. The Centre is collaborating with ZSL and the Wildlife Conservation Society (WCS) to understand the apparent heterogeneity in the impacts of Ebola virus on great ape populations.

HIGHLIGHT: *Tanzania zoonoses meeting*

Christl Donnelly organised a workshop in Tanzania, funded by the EU-FP7 Predemics project, aiming to strengthen strategic interdisciplinary partnerships to improve understanding and control of zoonotic diseases. 25 individuals from 9 countries, included academics, veterinarians, NGOs, research institutes, the WHO, Centers for Disease Control and Prevention (CDC), and government units. Talks discussed the human-wildlife-livestock interface in Africa, the challenges of controlling zoonoses in wildlife, the impact of wildlife trade, and risks around food safety. Breakout groups identified and evaluated current situations, key concerns, burning research questions and control needs. A Dragon's-Den-style competition for a (sadly fictional!) $1 million research grant was won by a programme for control of livestock zoonoses directly consulting the community, before developing a scalable and sustainable model.

Maasai people as captured by Harriet Mills

HIV/AIDS

Worldwide antiretroviral therapy (ART) access is increasing, resulting in a dramatic decline in AIDS-related morbidity and mortality. Yet, many people living with HIV/AIDS (PLWHIV) are unable to benefit fully from treatment, and consequently deaths continue. As attention turns to the behavioural and programmatic barriers existing between PLWHIV and durable viral suppression, many countries and the recent UN High Level Panel have signed-up to highly ambitious targets for treatment coverage.

The HIV Modelling Consortium, led by Timothy Hallett, has contributed to articulating the steps that patients need to go through to achieve successful treatment and the barriers they face, as the 'HIV care cascade'. It has worked closely with partners in Western Kenya to characterise all aspects of the cascade and identify optimal routes to strengthening it. Analyses have shown that changing the ART eligibility policy to recommend ART for all PLWHIV would remove risk of loss from the care cascade and therefore lead to substantial benefits.

Interest in understanding care cascades has since grown such that the HIV Modelling Consortium was asked by WHO to develop a user-friendly modelling tool (below), with which member states can analyse their own data and come to conclusions about how best to strengthen their own HIV treatment programmes. In 2016 this model will be used in 20 countries in collaboration with WHO and is expected to guide policy in many countries as they enter the next phase of HIV treatment scale-up.

User-friendly modelling tool

Policy impact case study: The Global Fund Investment Case

The Global Fund raises and disburses monies to countries to support their actions against AIDS, TB and Malaria. In 2015 the Global Fund developed an 'Investment Case' for its replenishment in collaboration with its partners, stakeholders and a set of modelling groups responsible for the development of disease-specific 'Global Plans'. This Investment Case is the centrepiece of the Global Fund's argument for replenishment, aimed to be $13bn for the period 2017-2019.

Timothy Hallett chaired the technical panel overseeing the modelling for the investment case, with contributions on impact and cost projections from both the ***HIV Modelling Consortium*** *and the* ***Centre's Malaria Modelling Group*** *led by Azra Ghani. These reports show that, in aggregate with other funding sources, a successful replenishment of the Global Fund could lead to 8 million deaths averted, and 300 million combined cases of malaria and TB and HIV infections averted. These results were presented by Timothy Hallett at The Global Fund's Replenishment Preparatory Meeting in Tokyo.*

HIV Modelling Consortium

The Global Fund
To Fight AIDS, Tuberculosis and Malaria

Timothy Hallett

Malaria

The Centre's Malaria group (including Azra Ghani, Tom Churcher and Lucy Okell) develops models to support malaria control and elimination planning globally. We have recently expanded our support to product development, including diagnostics (under the Diagnostics Modelling Consortium) and novel vector control tools (with the Integrated Vector Control Consortium) whilst continuing work on pre-erythrocytic and transmission-blocking vaccines (with the Malaria Vaccine Initiative) and newly registered drugs (with the Medicines for Malaria Venture). Through these we aim to identify where new products will enhance existing interventions and hence support the development of target product profiles.

From a public health perspective, we have expanded our modelling framework to incorporate costs and budgets to optimise intervention mixes. Building on work developed to support WHO Global Technical Strategy, we have explored the most efficient pathways to malaria elimination in Africa, evaluated combining the RTS,S malaria vaccine with other interventions, and supported the Global Fund investment case. We continue to use analytical tools to understand the changing epidemiology of malaria. Examples over the past year include better understanding of the transmission dynamics of Plasmodium vivax, exploration of patterns of decline in malaria over time in Senegal, and characterisation of the infectious reservoir.

Policy Influence case study: Potential public health impact of the RTS,S malaria vaccine

Phase III trial results for the first malaria vaccine – RTS,S – showed 35% efficacy against clinical malaria in children aged 5-17 months. Working with the Malaria Vaccine Initiative and GlaxoSmithKline (GSK), we analysed the relationship between antibody titres and protection. Our results demonstrated for the first time that anti-circumsporozoite titres are a surrogate of protection for the magnitude and duration of RTS,S efficacy. These results were used as evidence in the European Medicines Agency's (EMA) positive decision in July 2015.

Working with GSK, the Swiss Tropical and Public Health Institute and the Institute for Disease Modeling, we evaluated the vaccine's potential public health impact across Africa. Our results demonstrated a significant public health impact and high cost-effectiveness across a wide range of settings, and were submitted as evidence to WHO's joint Strategic Advisory Group of Experts and Malaria Policy Advisory Committee in November 2015, where pilot vaccine implementation was recommended.

The village of Dielmo, Senegal, where declines in malaria transmission have been observed.
Photo by Jean-François Trape

Tuberculosis

Peter White

Globally, tuberculosis (TB) is a leading cause of infectious disease mortality. Moreover, multi-drug resistant (MDR) TB poses an increasing concern, urgently needing diagnostic and treatment improvements. Understanding TB transmission patterns requires better intervention targeting and cost-effectiveness assessment using mathematical modelling and whole-genome sequence data must be synthesised with detailed epidemiological data to improve understanding. Centre researchers are working with collaborators worldwide towards achieving these goals.

TB also remains a public health challenge in many high-income countries, with the infection burden concentrated in particular population groups. The Centre's Peter White led analysis of different treatment regimens for the National Institute for Health and Care Excellence (NICE) to inform new guidance in 2016. Most of the UK's TB cases are in migrants, so UK visa applicants from high-burden countries must be tested (and treated if necessary) for active TB. However, since most infections remain latent for life, most would not benefit from treatment. Therefore, patient risks and benefits, treatment costs, and cost savings from averting active TB must be considered when assessing cost-effectiveness.

Novel molecular diagnostics offer faster MDR TB infection diagnosis and appropriate treatment. Peter White led transmission-dynamic modelling to assess the effectiveness of genetic screening for drug resistance to accelerate appropriate MDR-TB treatment.

India accounts for a quarter of TB's global burden. The Centre's Nimalan Arinaminpathy continues to deepen ties with public health partners in the Indian Revised National TB Control Program (RNTCP); recently leading a team, with Government of India participation, to examine data for TB treatment. The study showed roughly twice as much TB treatment in the unregulated private sector than in the RNTCP, indicating that India's TB burden is considerably greater than previously recognised.

Nimalan Arinaminpathy

Antimicrobial resistance

Antimicrobial resistance (AMR) is increasingly recognised as a major public health threat, which could cause up to 10 million annual deaths globally by 2050. Tackling AMR requires developing a better understanding of the epidemiological and evolutionary factors causing AMR to appear and spread in pathogen populations. Centre members are currently investigating resistance of malaria to the antimalarial drugs used in Africa, as well as resistance of many bacterial pathogens to antibiotics.

Xavier Didelot and colleagues work with Public Health England (PHE) on AMR of the healthcare-associated bacterial pathogens *Staphylococcus aureus* and *Clostridium difficile*. Whole-genome sequencing is applied to isolates from UK-wide surveillance programmes and these data are analysed using new purpose-built statistical and computational techniques. Nick Croucher's group have used similar approaches to investigate the international dissemination of MDR lineages of the community-associated pathogen *Streptococcus pneumoniae*, as well as experimentally investigating the spread of AMR loci in the same pathogen. This collaborative and multidisciplinary approach has been shown to reveal both the genetic mechanisms and the evolutionary processes involved in the spread of AMR. Comparing these results with past antibiotic usage trends can help inform future antibiotic stewardship programmes.

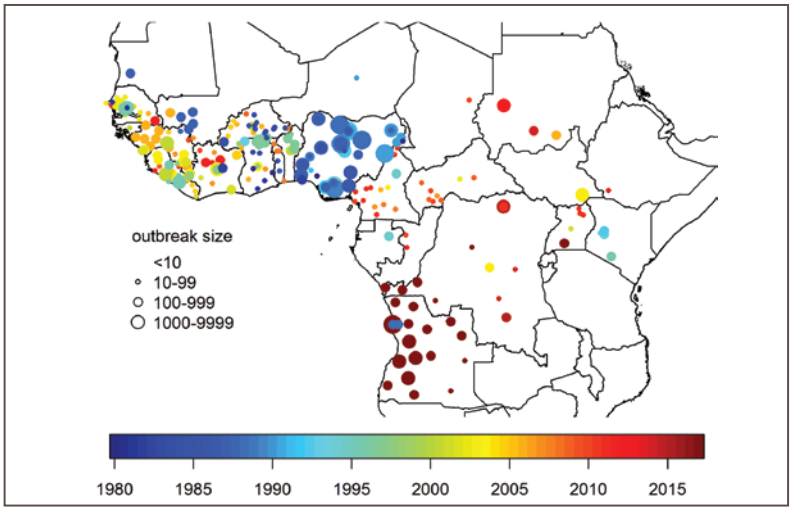
Centre staff recently contributed to the influential AMR review commissioned by the UK Government in collaboration with the Wellcome Trust. Nimalan Arinaminpathy modelled the potential impact of improved diagnosis and treatment for MDR-TB in future. TB is a leading cause of death by infectious disease, and – while most cases are curable – the emergence of MDR-TB is challenging TB control efforts worldwide. The analysis used WHO data to project global trends for MDR-TB and showed that new diagnostic technologies, combined with improved second-line TB treatments, could save over 770,000 lives over the next decade. Pierre Nouvellet, Neil Ferguson and colleagues from PHE also contributed to the AMR review by estimating the current burden of *Escherichia coli* blood stream infections in Europe at 17,000 excess deaths, one third of which were attributable to drug-resistant infections. Their analysis predicted that in the worst case, this burden of disease could increase four-fold due to increasing levels of resistance, but that the combined impact of novel diagnostics and treatments could halve this mortality.

Antimicrobial susceptibility testing in culture plate

Dengue fever and yellow fever

Centre research on **dengue** – the most common mosquito-transmitted viral infection in humans – continues to focus on the development and deployment of control measures, notably the Sanofi vaccine and Wolbachia, a novel biological control to reduce the ability of *Aedes aegypti* mosquitoes to transmit dengue. In work led by Neil Ferguson and Christl Donnelly, collaborating closely with the Eliminate Dengue initiative, Centre researchers are using models to understand the spatial spread of Wolbachia after initial release.

This work will inform the design of the first large-scale trials of Wolbachia and measure its impact on dengue transmission. The first such trials are likely to start in Colombia and Indonesia, with studies in Vietnam and Brazil starting soon after. In addition, Neil Ferguson's group has played a major role in modelling the likely public health impact of the Sanofi vaccine, informing WHO recommendations on its use. Most recently, the group started work with US colleagues to develop the first global maps of dengue transmission intensity. This work is relevant to refining assessments of disease burden and to predicting the impact of both the vaccine and Wolbachia.



Yellow fever outbreaks in Africa between 1980 and 2016.

Circle size indicates where circle radius shows outbreak size and colour indicates year.

Centre activities on **yellow fever** have expanded in the past year thanks to funding from the Bill and Melinda Gates Foundation (BMGF). Yellow fever is in the same family of viruses as dengue and is also transmitted by *Aedes aegypti* mosquitoes. Tini Garske and colleagues are working closely with WHO and GAVI (the Global Vaccine Alliance) to refine estimates of the global disease burden from yellow fever and the impact of vaccination campaigns. This work is informing GAVI's Vaccine Investment Strategy. In addition, the group has been supporting WHO in response to an ongoing outbreak in Angola, the largest outbreak in 30 years. In the face of global vaccine shortages, a key priority has been to estimate populations at risk from the Angolan outbreak in order to inform dose-sparing vaccination strategies.

Polio

Nick Grassly

Polio eradication is in its final stages. Two wild-type poliovirus serotypes have been eradicated, and the third hangs on in Afghanistan and Pakistan, but it is hoped transmission will be halted by next year.

Mass oral poliovirus vaccine (OPV) campaigns have been central to the Global Polio Eradication Initiative (GPEI) strategy, but must eventually cease because OPV can rarely evolve to regain neurovirulence and transmissibility. Poliomyelitis outbreaks caused by vaccine-derived polioviruses (VDPV) have been reported in 25 countries since 2000. The GPEI strategic plan for 2013-18 envisages globally synchronised OPV withdrawal, which began with serotype 2 in April 2016.

Members of VERG during their visit at BMGF in February 2015

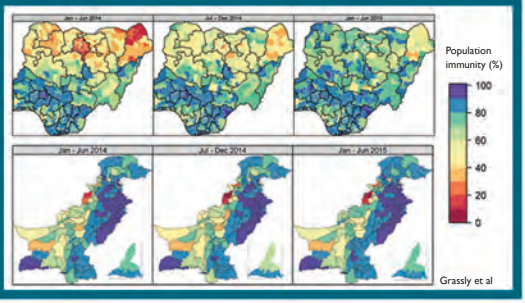
Members of VERG during their visit at CDC in November 2014

The Centre's Vaccine Epidemiology Research Group (VERG) led by Nick Grassly is a WHO collaborating institute on polio data analysis and modelling, and contributes to the GPEI strategy. In 2015-16 a focus has been illustrating the trade-offs between minimising the risk of seeding new VDPVs with trivalent OPV campaigns and ensuring population immunity against each serotype. The GPEI has since adopted a risk-based strategy that targets specific countries with multiple campaigns, and routine OPV-use boosted with the inactivated polio vaccine. The VERG works with WHO, BMGF, CDC and other GPEI partners to: optimise surveillance data usage, develop and apply methods estimating the sensitivity of environmental sample sites, quantify transmission from poliovirus genetic sequence data, and use algorithms to detect outbreak signatures before laboratory tests are complete. The responsive nature of the group to the GPEI's needs is facilitated by working groups and task team memberships, e.g. the WHO Strategic Advisory Group of Experts (SAGE) on Immunisation.

Policy Impact Case Study: *In 2015 the WHO SAGE decided to proceed with the global withdrawal of serotype 2 OPV in April 2016. The VERG contributed to the decision's evidence base by identifying the role of inactivated vaccine to mitigate withdrawal risks and by assessing progress towards ensuring maximum serotype 2 immunity at the time of withdrawal.*

Estimates of serotype 2 population immunity among children 0-2 years old in Nigeria and Pakistan; presented to WHO SAGE on Immunisation in October 2015 by the GPEI Director

Estimates for Children 0-2 years



Evolution and disease dynamics

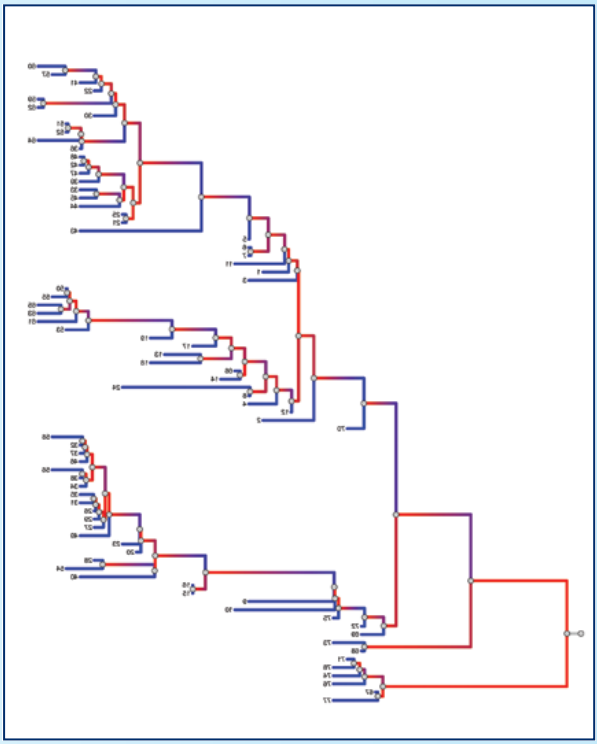
Most of the work within the Centre makes use of evolutionary theory or disease dynamic models to some degree. However, there are a number of projects that are more focused on the underlying science and epidemiology of these areas than on their application to specific public health questions. For example, this year Steven Riley helped to initiate a collaboration with Wendy Barclay and Colin Russell (Imperial College London) on the evolution of non-human influenza, and Erik Volz and colleagues developed a method to identify key sub-populations within epidemics using sequence data.

Evolution of influenza

In order to survive in humans, influenza viruses must continuously evolve and transmit efficiently from person-to-person. How efficiently viruses transmit is critical to determining how quickly an outbreak can spread and how many people it affects. Centre researchers have joined a collaborative study using an animal transmission model in which some ferrets are infected deliberately with a known virus and other ferrets are exposed. These are widely used techniques, however most use very small animal numbers and artificially severe infecting doses, meaning results are crude. Through a new collaboration supported by a Wellcome Trust Collaborator Award, Steven Riley and colleagues will simultaneously study virus evolution and transmissibility through improved experimental designs, mathematical models, and genetic sequencing. Information gained will enhance pandemic preparedness by identifying which animal viruses are most likely to cause the next pandemic, and aid the choice of viruses to be included in the annually updated seasonal flu vaccine.

Identifying key populations from sequence data

In addition to treating HIV infection, modern therapies promise to prevent transmission and reduce HIV incidence. In sub-Saharan Africa, diagnosis and treatment rates are still far below targets, but are increasing rapidly. Conventional wisdom holds that in generalised African epidemics, small high risk groups (e.g. commercial sex workers and men who have sex with men (MSM)) contribute a small proportion of transmissions, and thus focused treatment and prevention strategies are likely to be inefficient.



Phylogenetic tree of Ebola virus evolution in Sierra Leone in 2014 (from Volz E, Pond S, PLoS Currents. 2014;6)

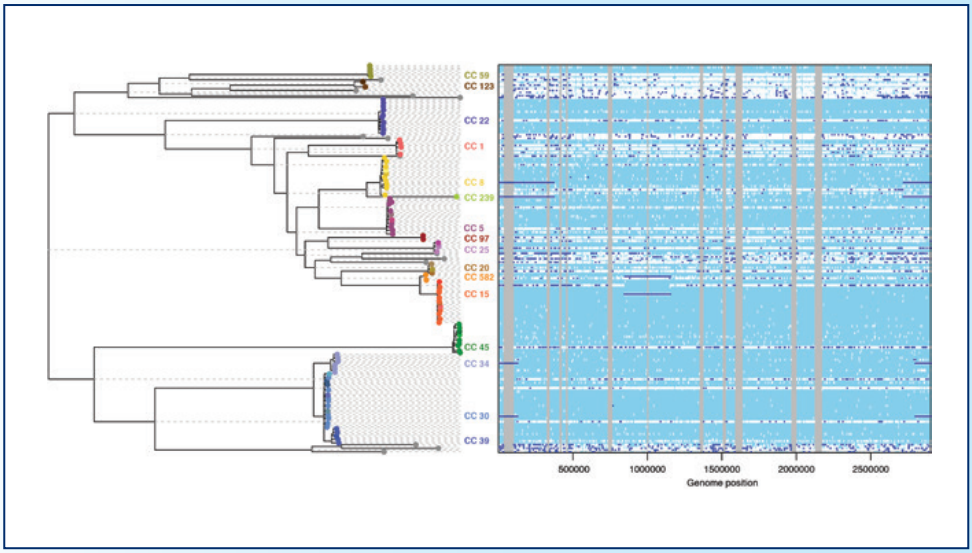
New research conducted in the MRC Centre challenges this view. A recent collaboration with the Institute of Human Virology in Nigeria (IHVN), and The Global Fund, addressed the origins of HIV infections in Abuja, Nigeria. Using a combination of traditional epidemiology, novel survey methodology, and phylogenetic analysis of HIV genomic data, researchers showed HIV incidence is rapidly rising among Nigerian MSM, but falling in the general population. Moreover, small high risk groups contribute a substantial proportion of transmissions despite comprising a small proportion of the population. Erik Volz led the phylogenetic analysis of Nigerian HIV sequence data at the Centre and developed simulations exploring the cost effectiveness of public health interventions. This has shown that focused rapid testing and early treatment of high risk groups in Nigeria prevents more transmissions at a fraction of the cost as compared to increasing general population testing and treatment rates.

New software tool: ClonalFrameML

Investigating evolution and infectious disease dynamics from genetic data typically requires building accurate frequently undergo recombination, disrupting the phylogenetic signal of vertical inheritance.

To circumvent this problem, Xavier Didelot and colleagues have developed a new software tool, called ClonalFrameML (freely available from https://github.com/xavierdidelot/ClonalFrameML). ClonalFrameML is based on an evolutionary model explicitly accounting for mutation and recombination, so that it builds accurate trees even in the presence of recombination. It is also able to reconstruct where and when recombination has happened, which is often an important evolutionary mechanism, e.g. in the evolution of antimicrobial resistance.

ClonalFrameML was designed specifically to deal with large amounts of genomic data, and run on hundreds of whole genomes within hours. The illustration shows the application of ClonalFrameML to a species-wide genomic dataset of Staphylococcus aureus.



Health economics

The Centre now hosts the Health Economics group, led by Lesong Conteh and Katharina Hauck. The group works with mathematical modellers, epidemiologists, clinicians, in-country partners, national and international institutions, to generate analyses to support evidence-based health policy and decision-making worldwide.

Multidisciplinary research compares alternative uses of resources to improve health and understand the impact of incentives in health systems.

Healthcare systems performance to control infectious disease: how to organise, pay for and monitor health systems, reward workforces, and patient and public roles. E.g. investigating excess demands on secondary care in the H1N1 influenza pandemic, Accident and Emergency performance determinants, and the economic burden of infections and medical errors.

Complex interventions and prevention policies to reduce infectious disease burdens: using econometric methods, in-country studies, and integration of economic evaluations into dynamic (rather than static) disease progression models. E.g. with the Centre's modelling team, the group is evaluating PopART/HPTN071, a sub-Saharan African trial to analyse the impact of universal test and treat and combination prevention on HIV incidence. The group is also investigating the cost-effectiveness of several trials designed to combat malaria by improving access to treatment, prevention and innovative housing strategies across West Africa.

Health Economics Group. From left to right, back row: Jo Mulligan, Katharina Hauck, Laetitia Duval, Rocco Friebel; middle row: Christa Hansen, Lesong Conteh, Surya Singh, Zulma Cucunubá Perez; front row: Ranjeeta Thomas, Krystal Lau, Elisa Sicuri, Shevanthi Nayagam

Resource allocation and priority setting: integrating quantitative data on welfare-maximising interventions, epidemiological incidence, prevalence projections, qualitative insights, and the group budgets. E.g. with the Centre's Timothy Hallett, WHO, national and global policy makers, the group is developing an investment case for Hepatitis B, to assist in decision-making. It also contributed to the international support initiative with a range of theoretical and in-country studies.

Economic approaches to controlling epidemics: incorporating economic models of individuals' behaviour within infectious disease models, to understand how this changes transmission dynamic predictions and the design of optimal public health interventions. E.g. the role of risk and social preferences in an individual's decision to receive an influenza vaccination.

IN BRIEF

PUBLIC ENGAGEMENT EVENTS

Imperial Festival, 2015 & 2016
The Imperial Festival shares the best of Imperial College's science and arts, attracting over 15,000 visitors annually from all walks of life. Since its inception in 2012, the Centre has been engaging with audiences through activities developed specifically to showcase the breadth of its research.

In 2015 the Centre focused on addressing media "myths" about infectious disease spread, using visualisations and simple activities as a platform for discussion on realistic infectious diseases risks.

In the sticker epidemic individuals received Quick Response (QR) code stickers as a marker of "being infected", with "infected" individuals being given additional stickers to "spread the disease" throughout the crowd. When the newly "infected" individuals visited the stall, their barcode stickers were scanned and they were added to the growing infection network, visualised on a screen representing the epidemic outbreak in real time.

In 2016, the sticker epidemic again proved a hit, along with some newly developed games, such as Pandemic Potential based on the familiar Top Trumps but focusing on infectious diseases' facts. Adults and children compared information on different cards, and players with the worst diseases won. Many of the "worst" Pandemic Potential cards were zoonotic diseases, which cross from animals to humans, such as influenza, HIV and Ebola.

The Imperial Festival is an exciting opportunity to share the Centre's work with the public and will continue to be a core public engagement event in future.

Public Lecture Highlights

NOV 2014
"Ethical issues in international clinical research: understanding, respecting and addressing local cultural patterns." Institute of Tropical Medicine Colloquium: Human Factor through the Social Determinants of Health. Lesong Conteh

MAR 2015
"Ebola: Inside an Epidemic". Public Lecture at the Royal Society, London. Neil Ferguson

MAY 2015
"Epidemiology of the 2014 Ebola outbreak in West Africa". University of Pavia, Italy. Tini Garske

MAY 2015
"Tackling Public Health Priorities through the Social Determinants of Health". University of Newcastle. Katharina Hauck

JUNE 2015
"Mobile pathogens in a changing world: impacts on ecosystem, human and wildlife health". Grantham Institute, Imperial College. Tom Churcher

OCT 2015
Infectious Disease Genomics Symposium Beer & Pizza Science Evening. University College London. Xavier Didelot

DEC 2015
"Pricing and market impact of new TB medicines and regimens" International Union Against Tuberculosis and Lung Disease (The Union) World Conference on Lung Health in Cape Town, South Africa. Nimalan Arinaminpathy

Centre staff at the Imperial Festival in 2015 and 2016

Researchers participating in Hackout 2

Hackout 2, February 2015

In 2013, Hackout developed basic tools to represent, handle, visualise and analyse disease outbreaks, resulting in the R package OutbreakTools. In February 2015, Hackout returned focussing on developing new visualisation tools for outbreak data using leading-edge static and dynamic graphics. 25 international participants created various new packages for visualising incidence, time series, geographic distribution of cases, contact networks, and phylogenetic trees with reduced genetic diversity. A new universal format for epidemiological data, EpiJSON, was also created, and implemented in the R package REpiJSON. Hackout 3 was in June 2016 co-hosted with the University of California, Berkeley.

Annual Modelling Methodology Short Course, September 2015

Imperial College's "Introduction to mathematical models of the epidemiology and control of infectious diseases" two-week course is designed for public-health professionals, policy makers and infectious disease researchers. Each year Centre researchers are highly involved in preparing and leading the course.

Using lectures and practical sessions, the course provides a thorough grounding in dynamic transmission models for infectious diseases. Participants are expected to leave with the ability to understand transmission patterns, interpret and critically evaluate epidemiological data and the findings of mathematical modelling studies, as well as design and implement their own simple mathematical models.

Infectious Disease Epidemiology Short Course 2015 participants

Peter White presenting in September 2015

An Introduction to Infectious Disease Modelling to Inform Policy-Making, September 2015 and March 2016

In September 2015, the Centre, in collaboration with the NIHR Health Protection Research Unit (NIHR HPRU) in Modelling Methodology, ran a one-day course introducing basic concepts in infectious-disease modelling, illustrated using disease-specific examples. Topics included economic evaluation models, evidence synthesis, real-time outbreak analysis, scenario analysis, and informing policy; why infectious diseases are fundamentally different from non-infectious diseases and require specialised analysis; and how different types of models represent the natural history of infections and heterogeneities in population risk.

The course was positively received and made available in 2016 to a broader audience with a new emphasis on health policy.

Microbial Source Attribution using Genomic Data, May 2016

Inference of who infected whom is a fundamental problem in infectious disease epidemiology, with applications to surveillance, control, and outbreak investigations. Microbial source attribution (MSA) has attracted resurging interest from statisticians and mathematical modellers, coinciding with rapidly expanding availability of pathogen genomic data.

In May 2016, Erik Volz led a workshop focussing on the latest MSA advances and approaches, particularly novel applications of genomic data. Participants worked towards consensus regarding the advantages and disadvantages of numerous recently developed methods. Special attention was paid to the availability and applicability of implementation software, and to making these latest methods available to a broader community of epidemiologists and outbreak investigators.

Xavier Didelot presenting on converting a phylogeny into a transmission tree in partially sampled and ongoing outbreaks

Erik Volz opening the workshop and welcoming participants

Advising on using infectious disease modelling to inform policy-making, August 2015

Organised by the Office of Science and Technology Policy, Centre members Peter White and Steven Riley contributed to discussions in the US White House complex on "Integrating Forecasting Models for Decision-making: A National Strategy". They shared insights from work in pandemic preparedness and response; real-time analysis of outbreaks and epidemics including SARS, pandemic influenza, MERS and Ebola; and discussed how to achieve effective collaborative working between public health agencies and academic institutions to inform policy. There was great interest in how the UK integrates surveillance, microbiology, modelling and policy-making.

Tour of the West Wing of the White House.
From left to right: Larry Brilliant (Skoll Global Threats Fund) Jeremy Farrar (Director, Wellcome Trust), Steven Riley (MRC Centre), Peter White (MRC Centre and PHE), Mark Smolinski (Skoll Global Threats Fund), and Simon Hay (Institute for Health Metrics and Evaluation, and Oxford University).

Advising on malaria strategy in Papua New Guinea, June 2016

Workshop to support malaria strategy development.
From left to right: Dr Richard Cibulskis (WHO), Dr Jan Kolacksinski (The Global Fund), Patrick Walker (MRC Centre), Dr Paison Dakulala (Deputy secretary for Health), Dr Leo Makita (National Malaria Control Programme Manager), Alison Reynolds and Michael White (MRC Centre).

IN THE NEWS

Ebola Death Rates Vary Widely by Age Group – Live Science – Christl Donnelly

Study co-author, the Centre's Christl Donnelly, said in a statement "The study shows that Ebola affects young children differently from adults." Therefore, "it's especially important that we get them [children] into treatment quickly. We also need to look at whether young children are getting treatment that's appropriate for their age."

The Grim Prospect – The Economist – Nimalan Arinaminpathy, Pierre Nouvellet and Neil Ferguson (AMR Review)

"… 700,000 people die each year from infection by drug-resistant pathogens and parasites. And they say that if things carry on as they are that figure will rise to 10m by 2050, knocking 2-3.5% off global GDP."
See: Antimicrobial resistance (AMR) page 9.

Zika Epidemic – The Guardian – Neil Ferguson

According to a recently published paper co-authored by several Centre PIs, the findings suggest that the current Zika epidemic is likely to last for three years in total. Centre Director, Neil Ferguson, said that further large-scale epidemics are unlikely to occur for at least decade as a large proportion of the population will be left immune to the virus in the wake of the current epidemic.

Christl Donnelly elected a Fellow of The Royal Society in April 2016. This prestigious title comes in addition to her titles as Fellow of the Academy of Medical Sciences (FMedSci) and Honorary Fellow of the Zoological Society of London (ZSL) Institute of Zoology.

Steven Riley awarded a Wellcome Trust Investigator Award: "The life course of human immune responses to influenza infection and vaccination" is designed to answer questions relating to the lifetime development of the human immune state in response to influenza infection and vaccination.

NEW FELLOWSHIPS

Francois Blanquart: awarded a Marie Skłodowska-Curie Individual Fellowship (IF-EF) on "Predicting the Evolution of Antibiotic Resistance in Streptococcus Pneumoniae"

Rafal Mostowy: awarded an Imperial College Junior Research Fellowship on "Understanding the contribution of horizontal exchange of genes to the evolution of antigenic diversity in bacteria"

Ilaria Dorigatti: awarded an Imperial College Junior Research Fellowship on "Within-host dynamics of dengue virus pathogenesis and the human antibody response"

Bob Verity: awarded a Medical Research Council (MRC) Population Health Scientist Fellowship on "Genetic data as a signal of changing malaria transmission"

Hannah Slater: awarded an Imperial College Junior Research Fellowship on "Modelling the spatial heterogeneity of malaria transmission and the impact of spatially targeted interventions to eliminate malaria"

Lucy Okell: awarded a Royal Society Dorothy Hodgkin Fellowship on "Modelling the spatial heterogeneity of malaria transmission and the impact of spatially targeted interventions to eliminate malaria"

Rich FitzJohn – Senior R Application Developer – working with Centre researchers to remove computational research barriers. Currently he is working on open source tools to use the high performance computing cluster more efficiently, on new approaches for modelling dynamical systems, and on general strategies for cleaning messy data. He is also working with researchers to improve and distribute code that implements particular models and methods. Rich's background is in ecological and evolutionary modelling, using similar phylogenetic and dynamic modelling approaches to the Centre.

Annual Centre Away Day, October 2015

The 2015 Centre Away Day saw staff at all levels present their work via a series of excellent research talks. Staff contributed to discussions and workshops aimed at further developing the Centre's capacity through its training and mentoring schemes, further improving its excellent public engagement activities; and aimed at expanding its health economics capacity.

In addition, over 80 Centre staff took part in a team building activity. Teams were pre-selected with the intention of connecting newer and more established staff. Teams competed in a geocaching / trivial pursuit hybrid activity, planning a walking route around the Paddington area, to discover question locations. Questions on infectious diseases, statistical modelling, and the Centre itself led to 'pie wedges' and points being awarded. Bonus points were awarded for completing photo challenges (see below).

80

Centre staff took part in a team building activity.

Arinaminpathy N., Batra D., Khaparde S.,Vualnam T., Maheshwari N., Sharma L., Nair S.,Dewan P. *How many tuberculosis cases are treated outside the public health sector in India? An approach using private-sector drug sales data.* Lancet Infectious Diseases. In press.

Arinaminpathy N, Dowdy D. *Understanding the incremental value of novel diagnostic tests for tuberculosis*. Nature. 2015;528(7580):S60-7.

Bourhy H, Nakoune E, Hall M, Nouvellet P, Lepelletier A, Talbi C, et al. *Revealing the Micro-scale Signature of Endemic Zoonotic Disease Transmission in an African Urban Setting.* PLoS pathogens. 2016;12(4):e1005525.

Carvalho DO, McKemey AR, Garziera L, Lacroix R, Donnelly CA, Alphey L, et al. *Suppression of a Field Population of Aedes aegypti in Brazil by Sustained Release of Transgenic Male Mosquitoes*. PLoS neglected tropical diseases. 2015;9(7):e0003864.

Cauchemez S, Nouvellet P, Cori A, Jombart T, Garske T, Clapham H, et al. *Unraveling the drivers of MERS-CoV transmission. Proceedings of the National Academy of Sciences of the United States of America.* 2016.

Churcher TS, Trape JF, Cohuet A. *Human-to-mosquito transmission efficiency increases as malaria is controlled.* Nature communications. 2015;6.

Didelot X, Pang B, Zhou ZM, McCann A, Ni PX, Li DF, et al. *The Role of China in the Global Spread of the Current Cholera Pandemic*. Plos Genet. 2015;11(3).

Didelot X, Wilson DJ. ClonalFrameML: *Efficient Inference of Recombination in Whole Bacterial Genomes.* PLoS computational biology. 2015;11(2).

Ferguson NM, Cucunuba ZM, Dorigatti I, Nedjati-Gilani GL, Donnelly CA, Basanez MG, et al. *Countering the Zika epidemic in Latin America.* Science. 2016;353(6297):353-4.

Ferguson NM, Kien DT, Clapham H, Aguas R, Trung VT, Chau TN, et al. *Modeling the impact on virus transmission of Wolbachia-mediated blocking of dengue virus infection of Aedes aegypti.* Sci Transl Med. 2015;7(279):279ra37.

Ferguson NM, Rodríguez-Barraquer I, Dorigatti I, Mier-y-Teran-Romero L, Laydon DJ, Cummings DAT. *Benefits and risks of the Sanofi-Pasteur dengue vaccine: Modelling optimal deployment.* Science. 2016

Grassly NC, Praharaj I, Babji S, Kaliappan SP, Giri S, Venugopal S, et al. *The effect of azithromycin on the immunogenicity of oral poliovirus vaccine: a double-blind randomised placebo-controlled trial in seronegative Indian infants*. Lancet Infect Dis. 2016.

Griffin JT, Bhatt S, Sinka ME, Gething PW, Lynch M, Patouillard E, et al. *Potential for reduction of burden and local elimination of malaria by reducing Plasmodium falciparum malaria transmission: a mathematical modelling study.* Lancet Infect Dis. 2016;16(4):465-72.

Hauck, K., Thomas, R., Smith P. C. Departures from Cost-Effectiveness Recommendations: *The Impact of Health System Constraints on Priority Setting, Health Systems & Reform*. 2016:2:1, 61-70.
Hauck K, Zhang X. *Heterogeneity in the Effect of Common Shocks on Healthcare Expenditure Growth. Health economics*. 2016.

Kucharski AJ, Lessler J, Read JM, Zhu HC, Jiang CQ, Guan Y, et al. *Estimating the Life Course of Influenza A (H3N2) Antibody Responses from Cross-Sectional Data*. Plos Biology. 2015;13(3).

Lau MSY, Cowling BJ, Cook AR, Riley S. *Inferring influenza dynamics and control in households*. Proceedings of the National Academy of Sciences of the United States of America. 2015;112(29):9094-9.

Nouvellet P, Garske T, Mills HL, Nedjati-Gilani G, Hinsley W, Blake IM, et al. *The role of rapid diagnostics in managing Ebola epidemics*. Nature. 2015;528(7580):S109-S16.

Penny MA, Verity R, Bever CA, Sauboin C, Galactionova K, Flasche S, et al. *Public health impact and cost-effectiveness of the RTS,S/AS01 malaria vaccine: a systematic comparison of predictions from four mathematical models*. Lancet. 2016;387(10016):367-75.

Slater HC, Ross A, Ouedraogo AL, White LJ, Nguon C, Walker PG, et al. *Assessing the impact of next-generation rapid diagnostic tests on Plasmodium falciparum malaria elimination strategies*. Nature. 2015;528(7580):S94-101.

Smit M, Brinkman K, Geerlings S, Cohort AO. *Future challenges for clinical care of an ageing population infected with HIV: a modelling study* (vol 15, pg 810, 2015). Lancet Infect Dis. 2015;15(9):998-.

Volz E, Pond S. *Phylodynamic analysis of ebola virus in the 2014 sierra leone epidemic*. PLoS currents. 2014;6.

Volz EM, Frost SDW. *Sampling through time and phylodynamic inference with coalescent and birth-death models*. Journal of the Royal Society Interface. 2014;11(101).

Walker PG, White MT, Griffin JT, Reynolds A, Ferguson NM, Ghani AC. *Malaria morbidity and mortality in Ebola-affected countries caused by decreased health-care capacity, and the potential effect of mitigation strategies: a modelling analysis*. Lancet Infect Dis. 2015;15(7):825-32.

White MT, Verity R, Griffin JT, Asante KP, Owusu-Agyei S, Greenwood B, et al. *Immunogenicity of the RTS,S/AS01 malaria vaccine and implications for duration of vaccine efficacy: secondary analysis of data from a phase 3 randomised controlled trial*. Lancet Infect Dis. 2015;15(12):1450-8.

White PJ, Fox J, Weber J, Fidler S, Ward H. *How Many HIV infections may be averted by targeting primary infection in men who have sex with men? Quantification of changes in transmission-risk behavior, using an individual-based model. The Journal of infectious diseases*. 2014;210 Suppl 2:S594-9.

Woodroffe R, Donnelly CA, Ham C, Jackson SY, Moyes K, Chapman K, et al. *Badgers prefer cattle pasture but avoid cattle: implications for bovine tuberculosis control*. Ecol Lett. 2016.

Wu L, van den Hoogen LL, Slater H, Walker PG, Ghani AC, Drakeley CJ, et al. *Comparison of diagnostics for the detection of asymptomatic Plasmodium falciparum infections to inform control and elimination strategies*. Nature. 2015;528(7580):S86-93.

WITH THANKS TO OUR FUNDERS

Bill & Melinda Gates Foundation (BMGF)

Biotechnology and Biological Sciences Research (BBSRC)

Commission of the European Communities (EU)

Department for Environment Food and Rural Affairs (Defra)

Department of Health (England)

Department for International Development (DFID)

Engineering and Physical Sciences Research Council (EPSRC)

European and Developing Countries Clinical Trial Partnership (EDCTP)

Family Health International (FHI)

Gilead Sciences Ltd

HIV Prevention Trials Network (HPTN)

Imperial College Trust

Innovative Vector Control Consortium (IVCC), Liverpool School of Tropical Medicine

The Joint United Nations Programme on HIV/AIDS (UNAIDS)

Liverpool School of Tropical Medicine (intermediate funder)

Medicines for Malaria Venture (MMV)

Program for Appropriate Technology in Health (PATH)

Malaria Vaccine Initiative (MVI)

Jhpiego Corporation

Marie Curie

Medical Research Council (MRC)

National Institute for Health Research (NIHR)

National Institutes for Health (NIH)

Office of the United States Global AIDS Coordinator (OGAC)

Program for Appropriate Technology in Health (PATH)

The Royal Society

RUSH Foundation

The World Bank Group

Wellcome Trust

World Health Organization (WHO)

PUBLIC HEALTH PARTNERS:

Public Health England (PHE): Already close links between the MRC Centre and PHE have been further strengthened through the establishment of the NIHR HPRU in Modelling Methodology.

World Health Organization (WHO): As an official WHO Collaborating Centre for Infectious Disease Modelling since 2010, the MRC Centre is committed to supporting WHO activities and policy making in the areas of influenza, MERS-CoV, Ebola, Zika, yellow fever, polio, HIV/AIDS, hepatitis, and malaria

OTHER COLLABORATORS: Aalto University; Amsterdam Medical Centre (AMC); AMPATH Partnership; MOI University; Animal and Plant Health Agency (APHA); Boston University; Botswana Combination Prevention Project (BCPP); Brighton and Sussex Medical School; Brown University; Brunel University; Center for Global Development (CGD); Centers for Disease Control and Prevention (CDC); Centre de Recherches Entomologiques de Cotonou (CREC); Centre National de Recherche et de Formation sur le Paludisme (CNRFP); Chinese CDC; Christian Medical College-India; Christian Michelsen Institute (CMI); Clinical Research Unit of Nanoro (CRUN); Clinton Health Access Initiative (CHAI); CNRS Montpellier; Desmond Tutu TB Centre; East-West Center-Hawaii; Ecole Polytechnique Fédérale de Lausanne (EPFL); Emory University; Erasmus University Medical Centre; ETH Zurich; Foundation for Innovative and New Diagnostics (FIND); Fred Hutchinson Cancer Research Center; Futures Institute; Georgetown University; GlaxoSmithKline (GSK); Global Polio Eradication Initiative (GPEI); Global Vaccine Alliance (GAVI); Guangzhou People's Hospital Number 12; Hannover Medical School (MHH); Harvard University; HIV Prevention Trials Network (HPTN); IeDEA Network-East African Region and South African Region; Imperial College Healthcare NHS Trust; Indiana University; Innovative Vector Control Consortium (IVCC); Institut de Recherche en Sciences de la Sante (IRSS); Institut de recherche pour le développement (IRD); Institut national de la santé de la research medical (INSERM); Institut Pasteur; Institute of Tropical Medicine (ITM); Institute for Disease Modelling (IDM); Institute for Health Metrics and Evaluation (IHME); Institute of Human Virology Nigeria (IHVN); Johns Hopkins University; Karolinska Institutet; Kings College London; Lancaster University; Liverpool School of Tropical Medicine (LSTM); London School of Hygiene and Tropical Medicine (LSHTM); Los Alamos National Laboratory (LANL); Mahidol Vivax Research Unit; Makerere University; Malaria Control and Elimination Partnership in Africa (MACEPA); Malaria Research and Training Center (MRTC); Malawi-Liverpool-Wellcome Trust Clinical Research Programme; MERS-CoV Scenario Modelling Working Group; MRC Centre for Genomics and Global Health; MRC Clinical Trials Unit (MRC CTU); MRC Unit The Gambia; MRC Uganda Virus Research Institute (MRC UVRI); Medical University of South Carolina; Ministry of Health-Saudi Arabia; Monash University; Murdoch University; National Heart and Lung Institute (NHLI); National Institute for Biological Standards and Control (NIBSC); National Tuberculosis Institute India (NTIB); National Institute for Research in Tuberculosis India (NIRT); National Institute of General Medical Sciences (NIGMS); Operation ASHA (OpASHA); Oxford University Clinical Research Unit, Hospital for Tropical Diseases, Vietnam; Oxitec; PANGEA HIV Consortium; Pennsylvania State University; Polo d'Innovazione di Genomica Genetica e Biologia SCaRL (Polo-GGB); Princeton University; Public Health Foundation of India (PHFI); Queen Mary University of London; Radboud University Nijmegen Medical Centre; Rakai Health Sciences Program (RHSP); Research Council of Norway; Results for Development; Revised National TB Control Program, India (RNTCP); Robert Koch Institute; Sanofi Pasteur MSD LTD; Seattle Children's Research Institute; Shantou University; Social Science Research Council (SSRC); Stellenbosch University; Stichting HIV Monitoring (SHM); Royal Tropical Institute (KIT); Stop TB Partnership; Swansea University; Swiss HIV Cohort Study (SHCS); Swiss Tropical and Public Health Institute (STPH); TB Modelling and Analysis Consortium (TB-Mac); The Centre for Global Health Research (CGHR); The Dutch HIV Monitoring Foundation; The Global Fund to Fight Aids, TB and Malaria; The Kenya Medical Research Institute (KEMRI); The Mahidol Oxford Tropical Medicine Research Unit (MORU); The Royal Free London NHS Foundation Trust; The South African Centre for Epidemiological Modelling and Analysis (SACEMA); The Zambia AIDS Related Tuberculosis Project (ZAMBART); Tulane University; University College London (UCL); Universidad Industrial de Santander; University of Amsterdam; University of Antioquia; University of Bergen; University of Bern; University of Birmingham; University of Bristol; University of California San Diego; University of California Berkeley; University of Cambridge; University of Durham; University of Edinburgh; University of Florida; University of Ghent; University of Glasgow; University of Helsinki; University of Hong Kong; University of Iowa; University of Keele; University of Kinshasha; University of KwaZulu-Natal; University of Liverpool; University of Lusaka; University of Malawi; University of Maryland; University of Melbourne; University of Michigan; University of Minnesota; University of North Carolina; University of Notre Dame; University of Oslo; University of Oxford; University of Perugia; University of Pittsburgh; University of Sciences, Techniques and Technologies of Bamako (USTTB); University of Stockholm; University of Toronto; University of Warwick; University of Washington; University of Wisconsin; University of York; Walter and Eliza Hall Institute of Medical Research; Wellcome Trust Africa Centre; Wellcome Trust Research Programme-Kilifi; Wellcome Trust Sanger Institute; Wildlife Conservation Society (WCS); Worldwide Antimalarial Resistance Network (WWARN); Yale University; Zoological Society of London (ZSL).

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MRC Centre for Outbreak Analysis and Modelling
Department of Infectious Disease Epidemiology
School of Public Health
Imperial College London
St Mary's Campus, Norfolk Place
London W2 1PG

mrc.outbreak@imperial.ac.uk

@MRC_Outbreak