Imperial College London

MRC Centre for Outbreak Analysis and Modelling

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ANNUAL REPORT 2013-14

Director's message

Neil Ferguson

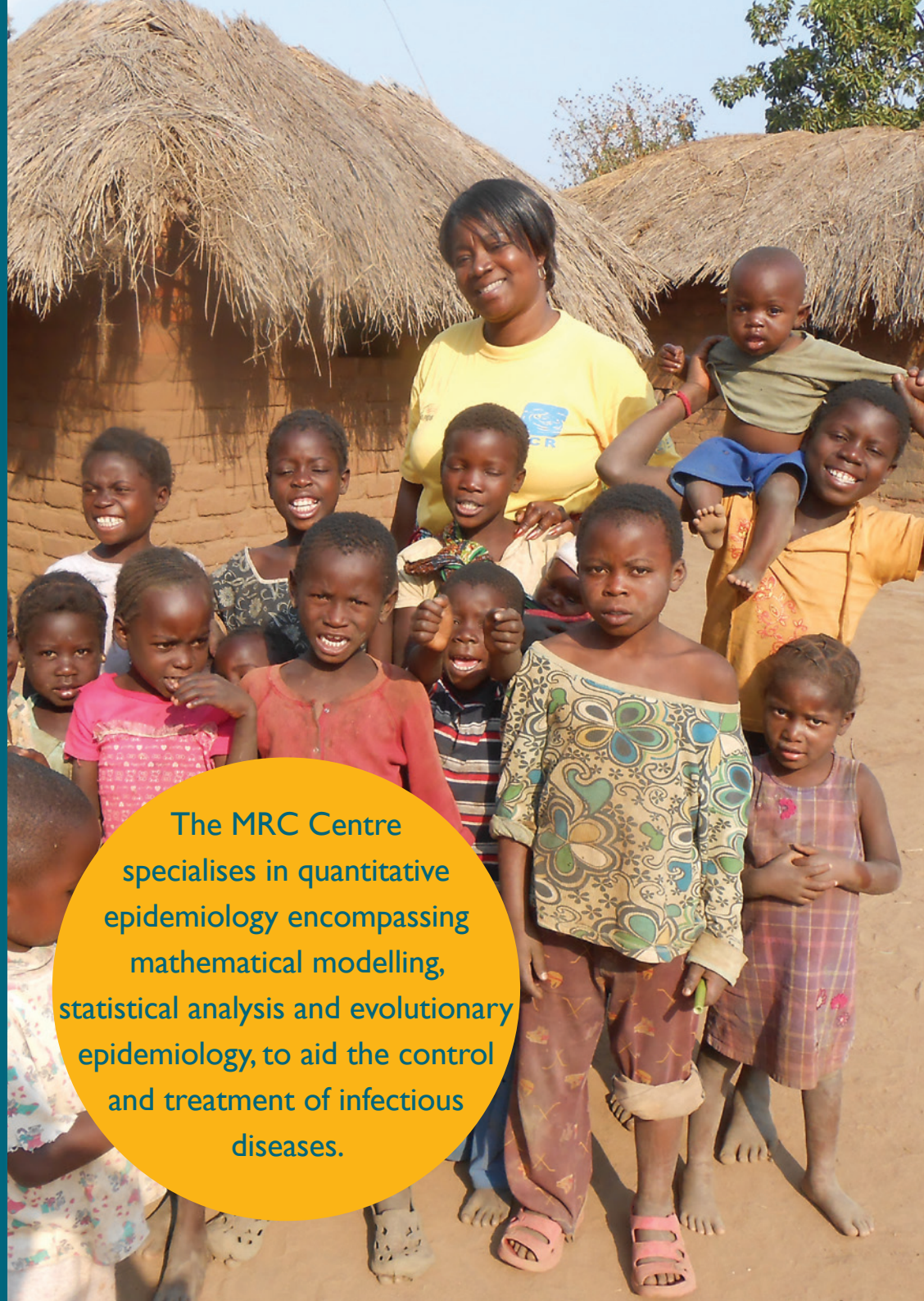
This report is being published a year later than planned – a delay resulting from the last twelve months being some of the busiest in the MRC Centre's now 6 year history. Following a very positive review of our progress by the MRC in late 2013, the Centre's funding was renewed for a further 5 years. The continuing relevance of the MRC Centre's mission was then underlined by events last year.

Within a month of our 5th anniversary we were approached by the Saudi Arabian government to assist them in risk analysis and modelling of the newly resurgent outbreak of Middle East respiratory syndrome (MERS) occurring in that country in spring 2014. Building on work completed the previous year, a team of 10 researchers was assembled to analyse the real-time data coming from Saudi Arabia to understand where transmission was occurring and to provide an assessment of the risk of large epidemics being triggered by the mass gatherings of pilgrims to Umrah and the Hajj. The MRC Centre continues to work closely with both the Saudi government and the World Health Organisation (WHO) in their efforts to monitor and control the ongoing threat posed by the MERS virus. Indeed, as I write this, case numbers are once again rising in Saudi Arabia and the MRC Centre and its collaborators are examining the latest data to try to understand the causes of the apparent seasonal variation in transmission this virus shows.

Just as MERS cases were declining in May of last year, international attention was turning to reports of increasing numbers of Ebola cases in an outbreak occurring in Guinea in West Africa. Within weeks, cases were detected in Liberia and Sierra Leone, and in August 2014, the MRC Centre dedicated a large team of researchers to providing real-time analytical support to WHO and country partners to analyse the case data being collected in the affected countries. The MRC Centre's work has provided insight into the epidemiology of the outbreak, improved situational awareness of transmission trends and assessed the effectiveness of the control measures being implemented. I would like to take the opportunity to recognise the huge commitment of time and effort made by the researchers involved – an effort more motivated by everyone's desire to do something to help rather than the usual academic drive to publish scientific papers.

While always remaining a core part of our mission, outbreaks have only been one element of the MRC Centre activities in the last two years. This annual report highlights the substantial progress made by MRC Centre researchers in improving understanding of the epidemiology, evolution and control of a broad range of major endemic pathogens, such as HIV, malaria, TB, dengue and polio. Much of this work is international in scope, but the MRC Centre is also strengthening its UK focus. Last year it became a key partner in a new initiative – the National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Modelling Methodology. This is a collaboration between Imperial College and Public Health England (PHE) funded by the NIHR. Its £3.5m programme of collaborative research aims to enhance UK capabilities to make best use of surveillance and health data to strengthen health protection and public health more generally.

Finally, improving the training of the next generation of researchers remains a key priority. As such, the MRC Centre was delighted to be successful in a bid for a Wellcome Trust Doctoral Training Programme award in 2013. The first intake of students arrived in the autumn of 2014 and (together with MRC-funded students) are currently benefitting from a new 1 year MRes programme created to enhance research training in the first year of a 4 year PhD award.



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

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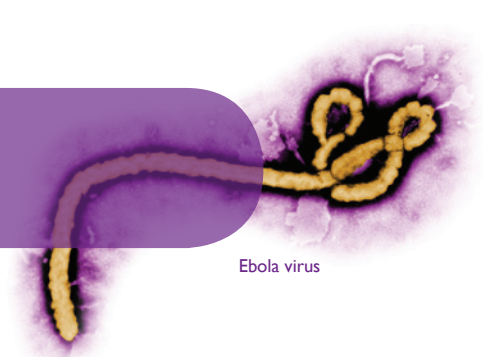


Ebola virus

The 2014 Ebola epidemic in West Africa – by far the largest Ebola outbreak seen to date – has been a catastrophe for the affected countries. As well as the immediate health impact (around 20,000 deaths, though the true toll is hard to assess), the epidemic led to the effective cessation of most other healthcare provision in those countries and major economic and societal disruption. Only now, with an enormous international effort, has control started to be achieved, though much remains to be done before the virus is eliminated from the human population.

Since August of last year, MRC Centre researchers have been working intensively to provide real-time support to WHO and countries in their efforts to control the epidemic. Within days of receiving detailed data from WHO on the outbreak, the team generated the first estimates of key epidemiological parameters, such as the case fatality rate and the incubation period distribution. The MRC Centre also tracked transmission intensity over time, generated projections of future case trends, (reproduction numbers), generated short-term projections of future case numbers and evaluated the impact of control measures over time based on case data collected in Guinea, Liberia, Nigeria, and Sierra Leone.

The fight against Ebola in West Africa

Social mobilisation being applied to curb Ebola in Sierra Leone

One focus has been to analyse the complex data provided by cases and their families on possible sources of exposure to gain insights into the key processes underlying transmission of the Ebola virus. This highlighted that exposure to dying and dead Ebola cases was responsible for the majority of transmission. More recent work which examined paediatric Ebola cases has shown that very young children have both quicker disease progression and a higher case fatality rate than older children and adults, highlighting their vulnerability to the disease.

The principal goal throughout has been to provide actionable information to WHO and its partners, to whom the MRC Centre has sent over 30 reports to date. However, in addition, the MRC Centre has made key epidemiological parameter estimates available to the wider community via three papers in the New England Journal of Medicine (NEJM) [1,2,3].

A new strain of bird flu in China: H7N9

Influenza virus

During March 2013, reports began to emerge from China that a new strain of influenza had started to infect humans. This strain returned in 2014 and again in 2015. Through a mixture of theoretical and empirical methods, Steven Riley and colleagues from the MRC Centre are helping to quantify important properties of the virus, such as its transmissibility and severity.

The outside of an influenza virus is covered in two types of protein: haemagglutinin (HA) and neuraminidase (NA). Because these are on the outside of the virus, they are the two proteins most easily recognised by our immune response. Therefore, when an influenza virus occasionally starts to spill over from poultry to humans with novel HA and NA types, it is cause for concern.

Rapid genetic analysis revealed that neither the HA type (H7) nor NA type (H9) had been seen before in humans. Cases were initially clustered around Shanghai but then spread to other cities, eventually causing large clusters in Zhejiang and Jiangsu. The rate of new cases declined quickly when live poultry markets were closed.

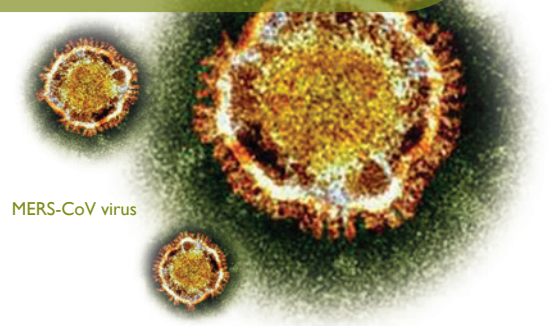
Researchers used the closure of the live bird markets as a natural experiment to estimate the transmissibility of the new human strain. A pathogen's transmissibility can be measured by the basic reproductive number R0, the average number of new infections generated by one typically infectious individual in an otherwise susceptible population. The absence of a sustained human epidemic after closing the markets was good evidence that R0 was less than 1. However, the degree to which R0 for a new infection is less than 1 is important: pathogens with R0=0.5 need to double their transmissibility to achieve take-off, whereas pathogens with R0=0.9 require only an 11% increase. Researchers estimated R0 for three clusters in 2013 to be: 0.19 in Shanghai, 0.29 in Jiangsu; and 0.03 in Zhejiang[1,2].

JONATHAN READ

Fluscape field team in Guangzhou

However, these analyses could not identify how many undetected or genuinely asymptomatic infections were occurring during these outbreaks. Therefore, more recently, when H7N9 infections started occurring in the same province as the FluScape study, researchers switched their focus to empirical methods, looking for H7N9 antibody prevalence in the study cohort of approximately 2000 individuals living in and near Guangzhou, China. By having a good estimate of the number of infected individuals, MRC Centre researchers hope to be able to also estimate the per infection severity of this new strain.

Middle East respiratory syndrome coronavirus (MERS-CoV)



MERS-CoV virus

In April 2012, a novel strain of coronavirus was identified in Saudi Arabia as the cause of Middle East respiratory syndrome (MERS), a severe lower respiratory tract infection in people. Since then over 1,000 cases have been reported, mainly affecting countries in the Middle East. MERS coronavirus (MERS-CoV) is a zoonotic virus and has been found in dromedary camels throughout the Middle East and Northern Africa.

From June 2013, a team of MRC Centre researchers worked intensively on trying to understand patterns of transmission of this new virus, most notably the relative contribution of exposure to the (as yet unidentified) animal reservoir and of human-to-human transmission. Under-reporting has been a major issue: the MRC Centre team estimated the number of symptomatic cases in the Middle East up to August 2013 as 940, three-fold higher than the reported number of cases up to that date. This analysis indicated that 74% of primary cases detected via routine surveillance had died, compared to 20% of secondary cases, suggesting that routine surveillance was more likely to miss less serious MERS-CoV cases.

Emergency department during MERS-CoV outbreak

A major surge in the MERS-CoV outbreak in March-April 2014 led to the MRC Centre being approached by the Saudi Arabian government to provide analysis and modelling support to their control efforts. The increase in cases was largely focussed on health-care facilities in Jeddah and Riyadh. The MRC Centre team provided risk assessments (for example on the risk of transmission at the Hajj pilgrimage) and epidemiological analysis (for example on the rate at which people were being exposed to infection from animals) to our Saudi partners. MRC Centre team members continue to engage with WHO and Saudi Arabia to better understand the transmission of MERS.

Throughout this period, the MRC Centre liaison to the WHO, Maria Van Kerkhove, worked as a member of the WHO Task Force for MERS-CoV; supporting WHO by providing technical epidemiologic and statistical support for the analysis and interpretation of MERS-CoV data for risk assessments, web-based summaries and communications, the development of epidemiologic and serologic investigation protocols for MERS-CoV, and other publications on related topics.

MERS-CoV was detected in nose swabs from three camels in 2013

Malaria: Planning for elimination

Over the past decade the burden of malaria has dropped dramatically, with an estimated 42% decline in cases between 2000-2012. As malaria continues to decline, several countries are now considering the prospect of local elimination, either country-wide or by province. Azra Ghani and the MRC Centre's malaria group is working in various areas to support elimination planning.

Mosquito nets used as preventative measures to reduce malaria transmission

The WHO Global Malaria Programme (WHO/GMP) is coordinating the development of a **Global Technical Strategy for Malaria (GTS)** for 2016-2025 to articulate the vision and goals for malaria over the next decade, and bring together current policy recommendations in a comprehensive, evidence-based strategy for WHO Member States to use in developing their own local strategies. MRC Centre researchers are working with the WHO/GMP to model potential scenarios for 2016-2025 worldwide. Using model outputs, researchers are evaluating the likelihood of achieving different goals, including reductions in mortality, burden, and the potential for countries to achieve elimination; the tools and implementation levels required to reach these goals; and the financial resources required to implement these strategies. This work has been presented to the WHO Malaria Policy Advisory Committee at a series of consultation meetings in 2014, and the final results will be used as the basis for setting GTS goals, to be endorsed by the World Health Assembly in 2015.

As an area approaches local elimination it becomes increasingly difficult to measure malaria accurately. Together with scientists from the Institut Pasteur, MRC Centre researchers have developed new epidemiological tools enabling countries to quantify their current transmission level from routine surveillance data. These methods can be used to determine whether endemic transmission has been halted, and where and when control programmes should target resources achieve elimination. Field tests are currently being conducted in partnership with the **Swaziland National Malaria Control Program (NMCP)** and the Clinton Health Access Initiative.

Elimination country case study: Swaziland

In 2008 Swaziland embarked on an elimination campaign and successfully reduced reported malaria cases to a few hundred a year. Many of these cases are imported from people travelling abroad making the current transmission level or whether the disease remains endemic unclear. Using 2010-2012 data, MRC Centre researchers developed new methods to estimate the current level of transmission. The raw data suggested that control measures needed to be improved as there were over 300 locally acquired cases during this period. However, the mathematical model showed that local transmission is sustained by continued case importation from outside Swaziland and hence that endemic transmission has been interrupted[1] the first time endemic transmission has been shown to be interrupted in a mainland sub-Saharan African country. The results of this work will inform the national malaria elimination strategy.

SWAZILAND NATIONAL MALARIA CONTROL PROGRAM

Malaria testing being conducted in Swaziland.

HIV: Pre-exposure prophylaxis

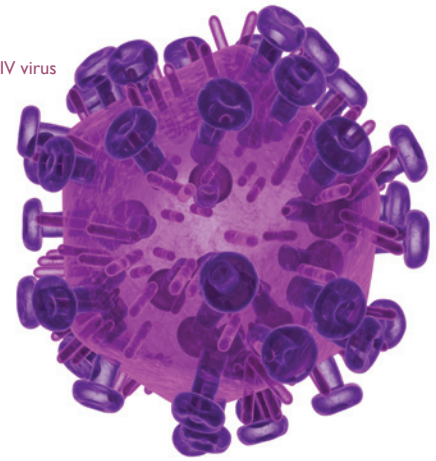
Pre-Exposure Prophylaxis (PrEP) is a promising new HIV prevention intervention. PrEP involves providing antiretroviral drugs to uninfected individuals who are likely to acquire HIV and has recently been shown to be effective in several clinical trials. Regulatory developments have been paving the way for eventual implementation. Several demonstration projects are getting underway to provide information regarding how best to provide PrEP in actual programmes rather than in clinical trials. These studies will inform future normative guidance regarding how best to safely and effectively deliver PrEP as part of combination HIV prevention.

Ide Cremin and Tim Hallett from the MRC Centre are working as part of a Bill and Melinda Gates Foundation (BGMF) funded consortium to support PrEP demonstration projects taking place in Kenya, South Africa, Nigeria and India. In 2013 they hosted a meeting to agree the design and implementation of these demonstration projects. In particular the group is working closely with a PrEP demonstration project in Kenya which aims to demonstrate the effective delivery of daily oral PrEP as part of an HIV combination prevention intervention among young women at high HIV risk, female sex workers and men who have sex with men (MSM). The study will be a prospective cohort design, assessing biological and behavioural outcomes through laboratory and survey assessments, and will also provide information regarding adherence monitoring, integration of services, task-shifting options and provider capacity.

Pre-Exposure Prophylaxis (PrEP)

The group has also been working closely with national HIV policy makers and implementers in Kenya. Modelling analyses regarding combination HIV prevention were presented at the National HIV Prevention Summit and have formed part of a recent national policy document which will be used to unify national and county level planning, financing and implementation of HIV prevention interventions in Kenya.

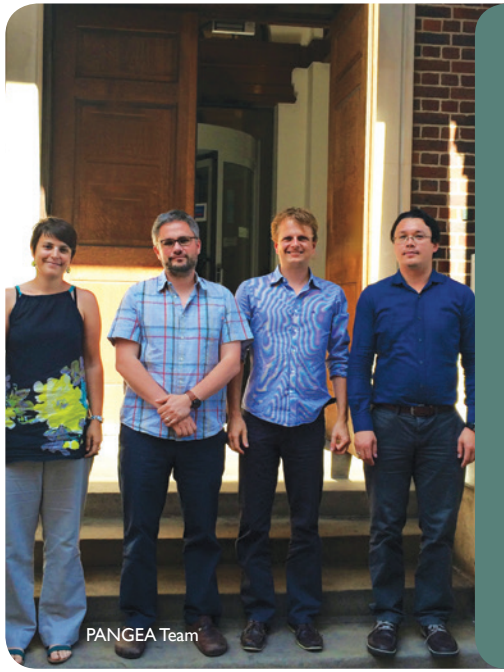
HIV virus



HIV: a targeted approach

In July 2014 Sarah-Jane Anderson and colleagues published the results of a modelling analysis for Kenya demonstrating that greater health gains could be achieved for a set budget when targeting a suite of interventions according to local epidemiology as opposed to uniform national coverage. Specifically they estimated an additional 100,000 infections averted (14% increase) over a 15-year period when implementing a targeted rather than uniform approach[1].

HIV-Genetics


PANGEA Team

Key questions:

- How does HIV-1 transmission in a generalised epidemic (where about 15-25% of the adult population is infected) differ to the transmission of the virus in concentrated HIV epidemics such as in Europe or the United States?
- Can we identify population groups at greater risk of onward transmission? Should these be prioritised for immediate testing, pre-exposure prophylaxis (PrEP) and/or immediate combination antiretroviral therapy?
- What can we learn from phylogenetic data about the underlying sexual network and the transmission dynamics along these networks?
- In which contexts should phylogenetic sequence analysis form part of a standard toolkit of epidemiological surveillance, inform trial design and form part of trial evaluation?

In November 2013, the Bill and Melinda Gates Foundation (BGMF) funded a major new global health initiative to provide a large volume of full genome HIV-1 sequences from infected individuals across sub-Saharan Africa. In recent years, phylogenetic analysis has played an increasing role in furthering understanding of HIV biology and epidemiology, with several MRC Centre researchers taking the lead. Based on this experience, Christophe Fraser from the MRC Centre was invited to join an international consortium involving researchers from the Africa Centre for Health and Population Science in South Africa, the Wellcome Trust Sanger Institute in the UK, and the University of Edinburgh in order to generate the sequences and develop tools for characterising HIV transmission sources and the impact of HIV prevention measures in sub-Saharan Africa.

The challenges ahead are plentiful, ranging from shipping plasma blood samples to the sequencing centres, to analysing full genome sequence data at an unprecedented scale. Within the MRC Centre Christophe Fraser is assisted by Anne Cori, Mike Pickles and Oliver Ratmann, drawing further support through collaborative partnerships with the African cohort sites that provide the samples. It is expected that first hand insights from the Rakai Health Sciences Program (RHSP) in Uganda, the HPTN071/PopART trial, and the Africa Centre in South Africa will be essential in making sense of the viral sequence data. The team is thus confident that this initiative, Phylogenetics and Networks for Generalized HIV Epidemics in Africa (PANGEA-HIV), will provide a major advance in monitoring and evaluating the impact of new interventions to bring HIV-1 transmission under control where it is highest.

Polio: New uses for old vaccines

In 1954 Jonas Salk was lauded for developing a polio vaccine, making the cover of Time magazine. He had successfully inactivated each of the 3 virus strains found in nature using formalin, and injected the resulting inactivated poliovirus vaccine (IPV) into monkeys and later, his family, to show this caused antibodies to the virus to be raised in the blood. In 1955 a field trial in over 1.3 million American children showed the vaccine to be safe and highly effective in preventing paralytic poliomyelitis. By 1960 IPV had reduced polio incidence in the USA by over 95% to about 1,300 reported cases, a tremendous public health success. Yet, by 1968 the USA no longer used IPV.

Following large field trials in the USSR, Albert Sabin had successfully lobbied for the adoption of his live-attenuated oral poliovirus vaccine (OPV) as the USA's vaccine of choice. He argued for its ease of administration, superior ability to induce effective immunity, and safety.

Importantly, in addition to the effectiveness of serum antibodies in preventing paralytic poliomyelitis, unlike IPV, OPV could also replicate in the intestine, inducing local immunity against virus replication and transmission[1]. IPV was no longer used by most countries worldwide, and in 1988 when the world committed to polio eradication, OPV was the vaccine of choice.


MRC Centre's Vaccine Epidemiology Research Group (VERG)


Polio Oral Vaccine

Led by Nick Grassly, the MRC Centre's Vaccine Epidemiology Research Group (VERG) recently documented some of OPV's limitations which severely hamper eradication efforts, including; poor efficacy in low income countries such as India, and the waning of intestinal immunity within a year of vaccination, such that vaccinated individuals can participate in transmission[2].

IPV does not induce intestinal immunity in naïve recipients, but it does boost local (secretory) antibody and gut-homing lymphocytes in individuals primed though previous exposure to live poliovirus (including OPV). In 2013, the VERG and colleagues at the Christian Medical College, Vellore, India, performed a clinical trial to see if children immunised with OPV were better protected against poliovirus replication and excretion in faeces when given an IPV boost, compared with no booster vaccine. They found that IPV-boosted children were between 40-70% less likely to have poliovirus in their faeces following OPV, compared with no booster[3]. In contrast, an additional dose of OPV had no significant effect on poliovirus excretion.

This work suggested that the **Global Polio Eradication Initiative (GPEI)** could use IPV to boost intestinal immunity to poliovirus and accelerate eradication by rapidly stopping transmission. Mass campaigns using this method have now begun in endemic countries, and their impact will soon be apparent.

Thus, the vaccines developed by Salk and Sabin are now both finding their place in the GPEI, a reconciliation that is sadly posthumous for these two warring scientists.

Dengue & Yellow Fever

Dengue mosquito

Dengue is the most common mosquito-borne viral infection of humans, responsible for a substantial burden of disease in most tropical and sub-tropical countries in the world.

MRC Centre research on dengue has expanded substantially in the last two years. The MRC Centre continues to collaborate with the international team of researchers developing Wolbachia – a bacterial infection of insects – as a novel biological control of dengue. Once established in an insect population, Wolbachia spreads via maternal transmission – from female mosquitoes to their eggs. It offers potential as a control measure for dengue since Wolbachia infection reduces the ability of dengue virus to infect and replicate in mosquitoes. MRC Centre researchers have recently published the first estimates of the potential impact of the most promising Wolbachia strain on dengue transmission. They concluded that established Wolbachia in mosquito populations would reduce dengue transmission intensity by two-thirds – sufficient to eliminate dengue in low to moderate transmission settings, and to have a major impact on disease even in high transmission areas.

Dengue vaccination

In addition, Neil Ferguson initiated a new collaboration – the Dengue Modelling Initiative – which brings together three of the leading academic groups modelling dengue with Sanofi Pasteur, the developer of the leading dengue vaccine candidate. The academic groups involved have been analysing Sanofi's clinical trial data to better characterise the efficacy of the vaccine, and using that information to inform modelling of the potential impact of different designs of vaccination programmes on the burden of dengue disease.

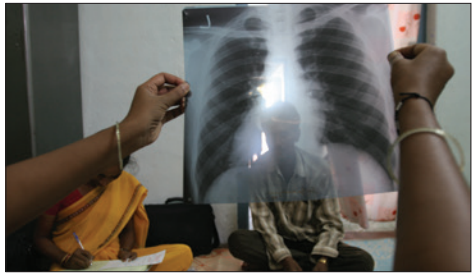
In all this work, MRC Centre staff have worked closely with stakeholders in the WHO and the Bill and Melinda Gates Foundation (BMGF), providing advice to both organisations on how these new interventions might help control dengue in the coming decade.

MRC Centre researchers also initiated new research on Yellow Fever in 2013. Yellow Fever is in the same family of viruses as dengue, and is another mosquito-borne infection. The MRC Centre was commissioned by WHO to update estimates of the number of deaths caused by Yellow Fever in Africa each year, and to evaluate the impact of recent vaccination campaigns in heavily affected countries. In a Plos Medicine paper published last year, it was estimated that Yellow Fever was responsible for 130 thousand deaths in Africa in 2013, but that vaccination had reduced mortality by over 80% in the countries targeted by recent campaigns. Work on Yellow Fever continues, informing the design of ongoing and future vaccination programmes.

Tuberculosis: improving control globally

A tuberculosis patient receiving medication

Tuberculosis (TB) as a global public health issue is a complex challenge. Despite most cases being curable with the availability of cost-effective drugs, TB causes nearly 2 million deaths worldwide each year. The global TB burden is concentrated in low- and middle-income countries, where substandard care can be a fundamental obstacle to the early diagnosis and appropriate treatment of active TB disease. In this context Nim Pathy from the MRC Centre and colleagues are working with a range of public health partners to explore strategies for improving TB control, emphasising interventions at a health systems level, and the potential implications of such interventions for TB transmission.



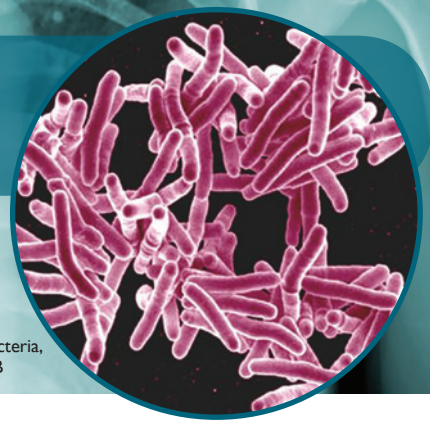
Patient being diagnosed for tuberculosis using a chest x-ray, a widely available tool in resource-constrained settings such as India

A prominent example is India, which has one of the largest public-sector TB programmes in the world, and yet continues to suffer the highest TB burden of any country. TB control in India is complicated by a vast and unregulated private healthcare sector, and commonplace substandard diagnosis and treatment. Such conditions also promote the emergence of multi-drug resistance, an increasing problem in India. To address these challenges, the BMGF is piloting innovative interventions to engage with private-sector physicians, providing training and incentives to improve provider behaviour while also encouraging patients to seek care early. Working with the Public Health Foundation of India (PHFI), MRC Centre research is integral in these efforts, providing analytical support to estimate the potential impact and cost-effectiveness of these interventions at scale. This analysis will form an important part of the evidence base used by the National TB Programme when adopting these interventions at a national scale.

Interview with a chemist in a Mumbai slum

Another important factor in access to care is the availability of affordable, quality-assured medicines. This problem is particularly acute in the case of multi-drug resistant (MDR) TB, where a patient treatment can cost a hundred times as much as a course of first-line treatment. Launched in 2001, the Global Drug Facility (GDF) assists high-burden, low-income countries in accessing essential TB medicines, with an emphasis on stringent drug quality standards. Today there is active discussion about the GDF's future role, and that of financing mechanisms like it. Funded by the Stop TB Partnership, Nim Pathy and colleagues are providing analytical expertise for the GDF, to estimate the impact their operations have been having. In related work, MRC Centre researchers are also collaborating with colleagues at the University of Michigan on the potential epidemiological and economic implications of alternative approaches for procuring second-line TB drugs.

Tuberculosis: in the UK



Mycobacterium tuberculosis Bacteria, the Cause of TB

TB has been increasing in the UK for the last two decades, and reducing TB infection rates is a key priority for Public Health England (PHE). In an era of constrained budgets, interventions must be both effective and cost-effective.

Peter White and colleagues in the MRC Centre are working with PHE to assess the effectiveness and cost-effectiveness of approaches to case-finding and treatment. A systematic review of pre-entry screening of migrants, conducted with collaborators at UCL, has been published in Lancet Infectious Diseases[1], and work has recently been completed on assessment of the cost-effectiveness of molecular diagnostics in the UK[2] An important part of assessing the benefit of interventions is using mathematical modelling to predict numbers of future infections averted by effective control measures implemented in the present. Averting infections not only improves population health, but also reduces future costs of treatment, so assessing these benefits requires integrating health economic analysis with transmission-dynamic modelling.

Most TB infections remain latent, not progressing to harmful, potentially transmissible, active disease. Therefore, most patients treated for latent infection will not benefit. MRC Centre and PHE colleagues are developing improved cost-effectiveness estimates of screening and treatment for latent TB using currently-available technology. To enable latent TB treatment to be targeted more cost-effectively, researchers are also working with collaborators who are attempting to identify biomarkers to ascertain those patients most at risk of progressing from latent infection to active disease.

TB treatment is particularly challenging for people with chaotic and disorganised lives. For latent TB, treatment typically takes several months, and for active TB, 6-18 months. The standard approach to supporting patients is Directly Observed Therapy, where patients take treatment in the presence of a healthcare worker. This is costly and inconvenient, both for providers and patients. With collaborators at UCL, MRC Centre researchers are assessing the effectiveness and cost-effectiveness of Video Observed Therapy, where patients use smartphones to upload videos of themselves taking treatment.

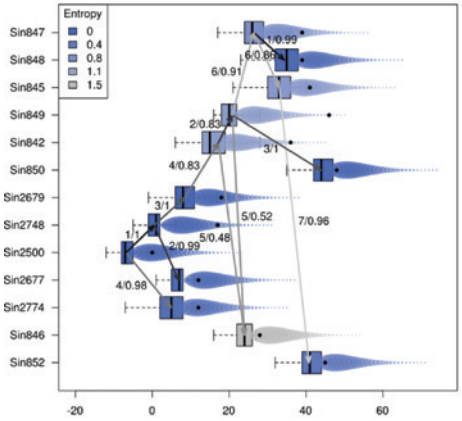
Drug resistance is a global problem, requiring international cooperation. A key component of control is rapid diagnosis and appropriate treatment. With collaborators at UCL, and in Bulgaria, Estonia, Latvia, and Romania, Peter White has been looking at how multi-drug resistant (MDR) TB diagnosis and treatment could be strengthened.

Improved targeting of interventions and assessment of their cost-effectiveness using mathematical modelling also requires a better understanding of TB transmission patterns. Whole-genome sequencing is providing valuable insights, and MRC Centre researchers will be working with colleagues at Imperial College and elsewhere to analyse the data.

Tracking transmission from genetic data

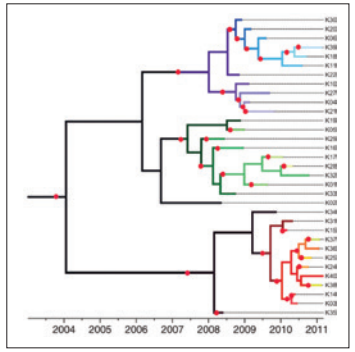
Many infectious diseases spread by direct host to host transmission. Reconstructing who infected whom in outbreaks is difficult, but would reveal many important epidemiological properties, like the presence of super-spreaders in the population or the relative importance of different contact types, which could directly inform public health strategies for limitation and prevention. A new genetic approach is however becoming increasingly possible due to sequencing technology developments; pathogens evolve as they spread, so the accumulated mutations can be used to deduce transmission events. MRC Centre researchers are developing the statistical methodologies to perform such genetic epidemiology investigations.

Outbreaker: Thibaut Jombart and colleagues[1] developed outbreaker, a software tool combining genetic and epidemiological data to reconstruct a transmission tree. It can be applied to a range of pathogens and scenarios, including the presence of missing transmission links and multiple introductions of infection. The 2003 Severe Acute Respiratory Syndrome (SARS) epidemic was amongst the first to apply pathogen sequencing, and reanalysing these data with **outbreaker** enabled reconstruction of person-to-person transmission during the outbreak's first stages.



Transmission tree of the Singaporean SARS outbreak computed using outbreaker

Phylogenetics: Xavier Didelot and colleagues[2] focused on pathogens that can be carried asymptomatically for extended periods; so significant within host evolution occurs, which must be accounted for when reconstructing transmission. This is relevant to many bacterial (e.g. MRSA, TB, gonococci) and viral (e.g. HIV, HCV) infections. A new model enabled transmission events to be reconstructed in a recent Canadian TB outbreak. The within-host evolutionary process and the between-host transmission network are combined; a phylogeny is estimated from the data, and the phylogeny branches are painted a unique colour for each host, with a colour change representing transmission from one individual to another.



Phylogenetic tree of a Canadian tuberculosis outbreak, coloured according to hosts to reveal the underlying transmission event (red dots).

Transmission chains: Erik Volz and colleagues[3] have studied HIV transmission chains using sequences routinely collected post-diagnosis to test for drug resistant strains. However researchers found genetic data quality is usually insufficient to confidently tell who infected whom. As not all infected individuals are diagnosed thus providing an HIV sequence, it's impossible to ascertain if closely related pathogens were directly transmitted or originated from unsampled hosts. Incomplete sampling limits genetic data's predictive power, but doesn't eliminate its role in understanding HIV's epidemiology. Researchers found that by examining a large number of potential transmission events, genetic data reveals much about factors making it more likely someone will transmit HIV, such as viral load, behaviour, and other clinical factors.

IN BRIEF

POLICY ENGAGEMENT

2014's World Health Day highlighted the threat of malaria.

To engage parliamentarians for a critical year in the malaria campaign, the MRC Centre's malaria group participated in an interactive awareness event at the Houses of Parliament, coordinated by Malaria No More. Parliamentarians, including the All-Party Parliamentary Group on Malaria and Neglected Tropical Diseases (APPMG), were encouraged to investigate the implications of future malaria investment using custom-built modelling games, challenging them to determine the best way to spend the global malaria budget and explore the implications of changing the global level of investment in malaria control.

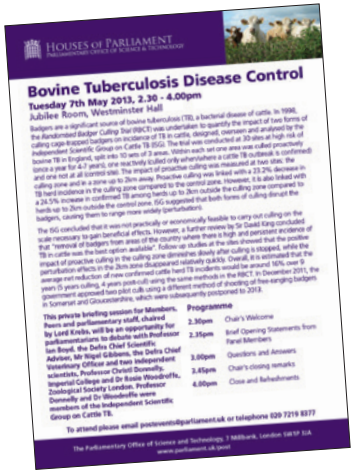
MRC Centre researchers at the Houses of Parliament

MRC Centre malaria researchers in working groups and policy liaison:

- Jamie Griffin, Bob Verity and Azra Ghani are participating in a WHO-coordinated modelling exercise to evaluate the public health impact and cost-effectiveness of the RTS,S vaccine.
- Lucy Okell participated in a WHO review of diagnostics in elimination, culminating in a revision to WHO guidelines, as well as being a scientific advisor to the Program for Appropriate Technology in Health (PATH) Diagnostics for Malaria Elimination Toward Eradication (DIAMETER), on developing target product profiles for diagnostics in elimination settings.
- Tom Churcher and Azra Ghani participated in a series of Malaria Vaccine Initiative (MVI)/PATH technical advisory group meetings to design Phase II and Phase III trials to evaluate the public health significance of novel transmission reducing vaccines.
- Azra Ghani teamed with Malaria No More, a major UK charity working with government, businesses, other organisations and the British public to raise awareness of and funds for malaria, as a policy advisor.
- Michael White has contributed to the work of the WHO's Global Strategic Plan on Plasmodium vivax Malaria Control and Elimination Committee. A report entitled 'Costs and cost-effectiveness of Plasmodium vivax control' will be published in the American Journal of Tropical Medicine & Hygiene in September 2015.
- The BMGF backed Diagnostics Modelling Consortium was established with the aim of utilising modelling to guide the effective use of diagnostics technologies across disease areas in resource-poor settings. To find out more visit: **www.dxmodelling.org/**

TB in cattle – is culling badgers the way forward?

On 7 May 2013, the MRC Centre's Christl Donnelly and Rosie Woodroffe from the Zoological Society London (members of the Independent Scientific Group on Cattle TB) took part in a private briefing session with MPs, Peers and parliamentary staff. In January 2014, Christl Donnelly presented results of the Randomised Badger Culling Trial (RBCT) to the Parliamentary and Scientific Committee, highlighting how two pilot culls conducted in England in 2013 differed from culling undertaken in the Trial. Pilot culls included shooting free-ranging badgers and cage-trapping, and occurred over an annual 6-week period (instead of the intensive 11 consecutive nights of the Trial). Following the finding that the pilot culls raised further concerns about animal welfare, and health and safety, and removed too few badgers (risking increased risks to nearby cattle), in April 2014 the government announced annual culling would resume in the pilot areas, but no new cull licences would be granted for the time being. Follow-up culls were undertaken in late 2014 in both areas subjected to culls in late 2013, but no wider policy has yet been announced.



HOUSES OF PARLIAMENT

Bovine Tuberculosis Disease Control

Tuesday 7th May 2013, 2.30 - 4.00pm
Jubilee Room, Westminster Hall

Badgers are a significant source of bovine tuberculosis (TB), a bacterial disease of cattle. In 1998, the Randomised Badger Culling Trial (RBCT) was undertaken to quantify the impact of two forms of culling cage-trapped badgers on incidence of TB in cattle, designed, overseen and analysed by the independent Scientific Group on Cattle TB (ISG). The trial was conducted at 30 sites at high risk of bovine TB in England, split into 10 sets of 3 areas. Within each set one area was culled proactively since a year for 4-7 years, one was reactively culled only when/where a cattle TB outbreak is confirmed and one not at all control sites. The impact of proactive culling was measured at two sites: the culling zone and in a zone up to 2km away. Proactive culling was linked with a 23.2% decrease in TB herd incidence in the culling zone compared to the control zone. However, it is also linked with a 24.5% increase in confirmed TB among herds up to 2km outside the culling zone compared to herds up to 2km outside the control zone. ISG suggested that both forms of culling disrupt the badgers, causing them to range more widely (perturbation).

The ISG concluded that it was not practically or economically feasible to carry out culling on the scale necessary to gain beneficial effects. However, a further review by Sir David King concluded that "removal of badgers from areas of the country where there is high and persistent incidence of TB in cattle was the best option available". Follow up studies at the sites showed that the positive impact of proactive culling in the culling zone diminishes slowly after culling is stopped, while the perturbation effects in the 2km zone disappeared relatively quickly. Overall, it is estimated that the average net reduction of new confirmed cattle herd TB incidents would be around 16% over 9 years (5 years culling, 4 years post-cull) using the same methods in the RBCT. In December 2011, the government approved two pilot culls using a different method of shooting of free-ranging badgers in Somerset and Gloucestershire, which were subsequently postponed to 2013.

This private briefing session for Members, Peers and parliamentary staff, chaired by Lord Krebs, will be an opportunity for parliamentarians to debate with Professor Ian Boyd, the Defra Chief Scientific Adviser, Mr Nigel Gibbens, the Defra Chief Veterinary Officer and two independent scientists, Professor Christl Donnelly, Imperial College and Dr Rosie Woodroffe, Zoological Society London. Professor Donnelly and Dr Woodroffe were members of the Independent Scientific Group on Cattle TB.

Programme	
2.30pm	Chair's Welcome
2.35pm	Brief Opening Statements from Panel Members
3.00pm	Questions and Answers
3.45pm	Chair's closing remarks
4.00pm	Close and Refreshments

To attend please email postevents@parliament.uk or telephone 020 7219 8377

The Parliamentary Office of Science and Technology, 7 Millbank, London SW1P 3JA
www.parliament.uk/post

7 May 2013 post event flyer

PUBLIC ENGAGEMENT

'Bacterial Games' at the Big Bang Fair:

In March 2013 the MRC Centre hosted a stand at the largest celebration of science, technology, engineering and maths for young people in the UK. Over twenty staff and students headed to London ExCel to start an epidemic, "infecting" and "vaccinating" children with fun stickers to teach the basics of epidemiology. The exhibit also featured a zombie outbreak game where visitors could seed their own outbreak throughout the UK using zombies, witches, werewolves or vampires. Over a thousand people visited the stand to take part in the outbreak and be inspired by the Centre's scientists.

The Big Bang Fair

STI group stand at the Imperial Festival, May 2014:

Visitors could learn the truth about common STI myths, hear how STIs are controlled around the world, and see the results of an anonymous live sexual behaviour survey of festival goers.

IN BRIEF

'LIFE: a healthy game of chance and choice' at the Science Museum:

The MRC Centre joined several London-based MRC Centres to collaborate with theatre company Non Zero One and the Science Museum to launch the MRC Centenary Open Week in June 2013. Visitors created an avatar (a 'pal') and participated in activities to learn how chance and choice could impact their pal's health. The MRC Centre demonstrated concepts of disease transmission and vaccination in the 'pal flu outbreak', where unvaccinated 'pals' were 'at risk' of infection if anyone gave them an infection sticker. Infected 'pals' received infection stickers to infect others, with 'Agent Grimes' encouraging visitors to become 'Disease Agents'. Hundreds of 'pals' were infected, and the transmission path tracked and plotted to a giant network projection. Visitors could identify their location in the outbreak via unique identifiers. Visitors could also experiment with disease scenarios, deciding how infectious a disease would be and how much of the population to vaccinate. Balls bounced around a screen simulating people moving around in a population; as 'infected' balls came into contact with unvaccinated balls their colour changed to indicate infection passing between them. Visitors could compare simulation outcomes, demonstrating the concept of conferred benefit from herd immunity against a disease.

MRC Centre lecturer Pierre Nouvellet interacting with visitors to the Science Museum

Café Scientifique Summer Science Exhibition:

In July 2013, Nim Pathy led a debate to discuss whether increasing globalisation and population migration mean viruses are poised to cause a pandemic, factors determining the spread of viruses in space and time, the anticipation of new strains and outbreaks, and the implications for vaccine control.

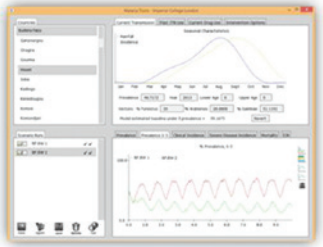
DEVELOPING TOOLS

'Malaria Tools' to aid malaria elimination scenario planning

25 April 2014
Invest in the future, defeat malaria

WORLD MALARIA DAY

To coincide with the **2014 World Malaria Day,** the MRC Centre's malaria team launched version 3.1 of their **Malaria Tools software.** This user-friendly malaria transmission model package is designed to allow National Malaria Control Programmes to explore the impact of a range of intervention combinations on malaria transmission, morbidity and mortality. The launch accompanied the release of the **WHO Elimination Scenario Planning Manual** which aims to provide countries with a framework to assess different scenarios and timelines for moving towards elimination, depending on programme coverage and available funding.



Malaria Tools 3.1

Hackathon for the analysis of disease outbreaks in R

Researchers participating in Hackathon

Identifying the spatio-temporal dynamics of disease outbreaks is essential to understanding how infectious diseases evolve and spread, and therefore to designing adapted containment strategies and prophylaxis. Advances in sequencing techniques mean pathogen genetic data can now be obtained in near real-time alongside epidemiological data, opening an avenue to reconstruct transmission trees ("who infected whom"). However, basic tools are lacking to analyse genetically sampled disease outbreaks. In 2013 the MRC Centre hosted a hackathon to fill this gap; to design, initiate and develop software implementing basic yet essential tools to represent, handle, visualise and analyse disease outbreaks. A further event is planned in 2015.

New MRes Course

In conjunction with other PhD programmes in the department, there is now an opportunity for Centre funded PhD students to begin their 4 year programme with a 1 year specialist MRes course. Students receive core taught training one day each week, but also undertake two 5-month attachments in the research groups of potential PhD supervisors working on research projects including extended systematic literature reviews, primary field data collection, secondary data analysis, laboratory-based analysis and mathematical modelling. During these placements, students will be full members of the research group, attending group meetings and participating in internal seminars in the same manner as PhD students and postdoctoral staff.

SHORT COURSES

As infectious-disease modelling becomes more mainstream, it is increasingly important for public health professionals to understand what modelling can do, what its data requirements are, and how to critically appraise models. The MRC Centre works with collaborators worldwide to deliver a programme of short courses catering for researchers, health economists, mathematicians, policy-makers, public-health and disease-control professionals.

Short course participants

The MRC Centre runs regular **WHO funded practical short courses**, attended by participants from countries worldwide. 'An Introduction to Influenza and Other Infectious Disease Modelling' was held in London in May 2013, and in Dubai in October 2014, the Centre ran 'An Introduction to Mathematical Modelling in Infectious Disease Epidemiology' for participants from countries in the Eastern Mediterranean Region and from Aga Khan University, Pakistan.

In September each year MRC Centre researchers contribute to the annual **Department for Infectious Diseases Epidemiology** interactive short course, Introduction to Mathematical Models of the Epidemiology & Control of Infectious Diseases **www.infectiousdiseasemodels.org**

In April 2014, in collaboration with the **Infectious Disease Research Network (IDRN)**, the MRC Centre hosted a one day beginner level Introduction to Infectious Disease Modelling course.

In November 2013, MRC Centre members ran a modelling course in Delhi in collaboration with the **Public Health Foundation India.**

IN BRIEF

MEDIA

'Swine flu infected 'fifth of people'. At least 20% of people, including half of schoolchildren, were infected with swine flu during the first year of the pandemic in 2009, according to data from 19 countries. January 2013
www.bbc.co.uk/news/health-21194090

Double vaccines 'could hasten the end of polio'
www.bbc.co.uk/news/health-28872763

FELLOWSHIP AWARDS 2013-2014

Michael White

Michael White – MRC Fellowship: Contribution of relapse infections to the epidemiology and control of Plasmodium vivax malaria. Working alongside Azra Ghani from the MRC Centre and Ivo Mueller and Stephan Karl from The Walter and Eliza Hall Institute, Melbourne, Australia, Michael White will be utilising mathematical models to investigate the contribution of relapse infections to the epidemiology and control of *Plasmodium vivax* malaria.

Patrick Walker

Patrick Walker – MRC Population Health Scientist Fellowship: Developing methods to assess the impact of malaria interventions upon transmission and the progress towards elimination in Western Kenya. In collaboration with colleagues at the Kisumu-based Centre for Global Health Research (CGHR), part of KEMRI, the study will take place in conjunction with the US Centers for Disease Control and Prevention (CDC) and other local partners including the Kenyan Malaria Control Unit, country health authorities and the Malaria Control and Elimination Partnership in Africa (MACEPA) and international collaborators from the UK (LSTM) and USA (PATH, BMGF).

Marga Pons-Salort

Marga Pons-Salort – Sir Henry Wellcome Fellowship: Epidemic dynamics of pathogenic human enteroviruses. Marga Pons-Salort will focus on identifying the epidemiological and evolutionary determinants of Human Enterovirus diseases patterns, using surveillance data from the UK and the USA. Marga Pons-Salort will work with MRC Centre researcher Nick Grassly and Professor Bryan Grenfell in Princeton University; collaborators include researchers at the University of Liverpool, PHE and the US and the US CDC.

Nick Croucher

Nick Croucher – Sir Henry Dale Fellowship: Evolutionary dynamics underlying pneumococcal genomic diversity. This project is designed to combine experimental microbiology, mathematical modelling and population genomic analyses to study genetic variation in the bacterial pathogen Streptococcus pneumoniae as it evolves in response to antibiotic use and the introduction of partial coverage vaccines.

Key publications/references

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(2) WHO Ebola Response Team. West African Ebola Epidemic after One Year – Slowing but Not Yet under Control. *N Engl J Med*, 372:584-587. 24 December 2014.

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HIV: Pre-exposure prophylaxis

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Malaria Vaccine Initiative (MVI)

Program for Appropriate Technology in Health (PATH)

Marie Curie

MRC

Medicines for Malaria Venture (MMV)

NIHR

National Institutes for Health (NIH)

Office of the United States Global AIDS Coordinator (OGAC)

Royal Society

Wellcome Trust

WHO

PUBLIC HEALTH PARTNERS:

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

World Health Organisation (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, yellow fever, polio, HIV/AIDS, hepatitis, and malaria.

OTHER COLLABORATORS: Amsterdam Medical Centre (AMC), AMPATH Partnership, MOI University, Animal and Plant Health Agency (APHA)-UK Government, Boston University, Botswana CPP, Brighton and Sussex Medical School, Brown University, Brunel University, Centers for Disease Control and Prevention (CDC), Chinese CDC, Christian Medical College-India, Christian Michelsen Institute (CMI), Clinton Health Access Initiative (CHAI), CNRS Montpellier, Desmond Tutu TB Centre-South Africa, East-West Center-Hawaii, Ecole Polytechnique Fédérale de Lausanne (EPFL), Emory University, Erasmus Medical Centre, ETH Zurich, Fred Hutchinson Cancer Research Center, Futures Institute, Georgetown University, GlaxoSmithKiline (GSK), Guangzhou People's Hospital Number 12, Hannover Medical School (MHH), Harvard University, Harvard School of Public Health, HIV Prevention Trials Network (HPTN), IeDEA Network-East African Region, IeDEA Network-South African Region, Imperial College Healthcare NHS Trust, Indiana University, Innovative Vector Control Consortium-LSTM, Institut national de la santé de la research medical (INSERM), Institut Pasteur, Institute for Disease Modelling (IDM), Johns Hopkins University, Kinshasha School of Public Health, L'Institut de recherche pour le développement (IRD), Liverpool School of Tropical Medicine (LSTM), London School of Hygiene and Tropical Medicine (LSHTM), Los Alamos National Laboratory, Makerere University, Malaria Control and Elimination Partnership in Africa (MACEPA), MRC Clinical Trials Unit (MRC CTU), MRC Uganda Virus research Institute (MRC UVRI), Medical University of South Carolina, Ministry of Health-Saudi Arabia, Monash University, National Heart and Lung Institute (NHLI), Imperial College London, National Institute for Biological Standards and Control (NIBSC), Princeton University, Public Health Foundation of India (PHFI), Queen Mary University of London, Radboud University Nijmegen, Rakai Health Sciences Program (RHSP), Results for Development, Robert Koch Institute, Sanofi Pasteur MSD LTD, Social Science Research Council, Stellenbosch University, Stop TB Partnership, Swansea University, Swiss Cohort Studies, Swiss Tropical and Public Health Institute (Swiss TPH), TB Modelling and Analysis Consortium (TB-Mac), The Centre for Global Health Research (CGHR), The Dutch HIV Monitoring Foundation, The Global Fund, The Kenya Medical Research Institute (KEMRI), The Mahidol Oxford Tropical Medicine Research Unit (MORU), The Pennsylvania State University, The Royal Free London NHS Foundation Trust, The South African Centre for Epidemiological Modelling and Analysis (SACEMA), The Zambia AIDS Related Tuberculosis Project (ZAMBART), University College London (UCL), University of Amsterdam, University of Bergen, University of Bern, University of Birmingham, University of Bristol, University of California, University of Cambridge, University of Edinburgh, University of Florida, University of Ghent, University of Helsinki, University of Hong Kong, University of KwaZulu-Natal, University of Liverpool, University of Lusaka, University of Malawi, University of Melbourne, University of Minnesota, University of North Carolina, University of Oslo, University of Oxford, University of Oxford Map Group, University of Oxford Spatial, Ecology and Epidemiology Group (SEEG), University of Pittsburgh, University of Stockholm, University of Tulane, University of Warwick, University of Washington, University of York, Walter and Elisa Hall Institute, Wellcome Trust Africa Centre, Wellcome Trust, Sanger Institute, William Davidson Institute, University of Michigan, Zoological Society of London (ZSL).

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www.imperial.ac.uk/medicine/outbreaks

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

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

MRC Centre researchers and external collaborators

MRC Outbreak Centre participating in LIFE: a healthy game of chance and choice' at the Science Museum as part of the MRC Centenary Week

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